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Epidemiology of severe buprenorphine exposures reported to the U.S. Poison Centers

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ABSTRACT

Objective: This study aims to evaluate the trends and risk factors of severe buprenorphine outcomes (SBO) reported to the U.S. Poison Centers (PCs).

Methods: We queried the National Poison Data System for exposures to buprenorphine from 2011 to 2016. SBO cases were defined as exposures that resulted in either a death or major clinical outcomes. Trends were tested using Poisson regression. Characteristics of the exposures were descriptively assessed. Logistic regression was used to evaluate the risk factors of SBO.

Results: SBO cases (967) reported to the PCs increased by 66.6% during this period (114–190, $p < 0.001$). While adults between 20 and 39 years were more frequent in the SBO group (50.4%) compared to the non-SBO group (38.7%), cases under 6 years (29.6% vs 13.8%) were more common among the non-SBO group. Intentional abuse (20.1% vs 24.9%) and suspected suicides (13.7% vs 37.5%) were significantly higher among the SBO group. Multisubstance exposures were more frequent among the SBO cases (36.4% vs 71.4%). SBO risk increased with age, with cases above 60 years (AOR: 1.66, 95% CI: 1.14–2.42) demonstrating significantly increased odds. Suspected suicide (AOR: 1.87, 95% CI: 1.53–2.28) and abuse (AOR: 1.40, 95% CI: 1.13–1.73) cases were more likely to result in a SBO. Multisubstance exposures significantly increased the risk of a SBO.

Conclusions: This study reflected an increase in the cases of SBO paralleling the rise in the buprenorphine prescriptions. Age, reasons for exposure and multi-substance exposures significantly increased the risk of SBO.

1. Introduction

Misuse of prescription opioids continues to be a significant public health crisis globally. The number of patients with opioid dependence worldwide was estimated to be 15.5 million in 2010 (Sordo et al., 2017). In 2015, there were approximately 2.6 million patients with an opioid use disorder in the United States (U.S.) (Roberts et al., 2018). The estimated that there were 70,237 drug overdose-related fatalities in the U.S. in 2017, with 67.8% of these attributed to an opioid. The age-adjusted rate of overdose increased by 9.6% from 2016 (19.8 per 100,000) to 2017 (21.7 per 100,000) (Seth et al., 2018; Vivolo-Kantor et al., 2018). In 2015, there were approximately 1.3 million high-risk opioid users in Europe, and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) estimated that there were 7,585 overdose fatalities, an increase of 6% from the previous year. In Australia, while the use of prescription opioids increased 15-fold over the last two decades, the prescription opioid-related mortality rates approximately doubled between 2007 and 2016 (3.8 to 6.6 deaths per 100,000) (Larance et al., 2018; Roxburgh et al., 2017, 2018).

Buprenorphine, often used in combination with naloxone, is effective in recovery and reduces the risk of remission and overdose deaths (Lin et al., 2018; Volkow et al., 2014). Buprenorphine maintenance therapy has shown benefits in the treatment of patients with heroin dependence while reducing drug-related risky behaviors and sexually transmitted diseases (Bentzley et al., 2015). Additionally, this medication has demonstrated utility in decreasing the utilization of emergency department (ED) visits while increasing the quality of life in patients (Li et al., 2016; Parran et al., 2010; Schwarz et al., 2012).

Buprenorphine can be easily dispensed through office-based prescribers as well as community pharmacies and has been a key measure globally to respond to the opioid crisis since its approval (Li et al., 2016; Roberts et al., 2018). For example, the number of patients receiving a

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buprenorphine prescription in the U.S. exceeded 800,000 in 2010, while there were more than 2.1 million ambulatory treatment visits involving buprenorphine in 2013 (Post et al., 2018; Turner et al., 2015). In Europe, the access to opioid substitution therapies (OST) has grown substantially with a reported 628,000 patients receiving OST in 2016. Buprenorphine was utilized by approximately 28% of patients on OST (Vasilev et al., 2016). Recent studies have shown that the use of OST increased five-fold in the United Kingdom (U.K.) since 2000 with 35% of patients utilizing such therapies being prescribed buprenorphine (Hickman et al., 2018; Mravcik et al., 2018). Although buprenorphine is considered to have a low misuse potential, several studies have previously indicated substantial diversion and misuse of buprenorphine in Europe, Australia, and Asian countries, with some studies estimating misuse in up to 20% patients (Lofwall and Walsh, 2014; Soyka, 2014). Prior research has identified several factors including lower costs, management of withdrawal symptoms, unavailability of other drugs and sub-optimal dosing as potential reasons for buprenorphine misuse and diversion (Yokell et al., 2011).

As the availability of buprenorphine continues to increase due to changes in regulation including waivers that allow physicians to prescribe buprenorphine more freely in response to the increasing opioid-related deaths, it is critical to monitor the trends in reports of the related adverse events. A greater understanding of the patient and drug use characteristics that may increase the risk of severe outcomes associated with buprenorphine is key to ensuring the optimal and safe use (Roberts et al., 2018). Due to lack of extensive literature, the present study sought to evaluate the recent trends in the exposures to buprenorphine and predictors of severe outcomes to such exposures reported to the U.S. Poison Centers (PCs). PCs are in a unique position to track the trends of buprenorphine and the related outcomes due to the extensive and near real-time nature of case reporting from a variety of sources, including healthcare professionals and the general public.

2. Methods

2.1. Study population and data sources

We conducted a retrospective, cross-sectional study utilizing the National Poison Data System (NPDS), a robust surveillance system containing de-identified data of toxic exposures reported to the network of 55 PCs within the American Association of Poison Control Centers (AAPCC) (Appendix A in Supplementary) (Centers for Disease Control and Prevention, 2005). Trained specialists within the PCs manage the poisoning cases while also logging detailed case information including demographics, therapeutic management, and clinical outcomes. These data are auto-uploaded to the national system approximately every eight minutes by individual PCs (Mowry et al., 2016). The NPDS received information regarding approximately 2.1 million human exposures in 2017. The NPDS is a validated tool that has been widely used in surveillance of poisonings (Naun et al., 2011; Wolkin et al., 2012).

All human exposures to buprenorphine from January 1, 2011 to December 31, 2016 were included for the analyses. Buprenorphine exposure cases were further classified into two categories based on the medical outcomes documented during either the initial or follow-up call: severe outcomes (SBO) and non-severe outcomes (Non-SBO). SBO were defined as exposures that resulted in major medical outcomes or death (Appendix B in Supplementary). Major medical outcomes are defined as life-threatening symptoms resulting in significant residual disability or disfigurement. Death is defined as when the patient dies as a result of the exposure or as a direct complication of the exposure with the fatalities verified clinically (Allen et al., 2017; American Association of Poison Control Centers, 2012, 2014). Non-SBO included cases where the medical outcome reported was broadly classified into none, minor, moderate, or other medical outcomes including instances where follow-up was not possible. Cases which were confirmed as non-exposures during the follow-up were excluded from the analysis.

2.2. Demographic and clinical variables

Sociodemographic variables analyzed included age, gender, and exposure site. The exposure reasons were segmented into specific categories including suspected suicides, intentional abuse and misuse of substances, and unintentional reasons such as therapeutic errors and adverse reactions (American Association of Poison Control Centers, 2012, 2014; Mowry et al., 2016). Intentional exposures are those resulting from the inappropriate use of a substance for self-harm, psychotropic effects including recreational use, or other reasons, while unintentional exposures are those not appropriately defined by any other pre-defined category (American Association of Poison Control Centers, 2012, 2014; Mowry et al., 2016). The level of healthcare received by the patients was categorized into treated and released from a healthcare facility (HCF), admission to a critical care unit (CCU), admission to a non − CCU, and others including admission to a psychiatric facility (American Association of Poison Control Centers Centers, 2012, 2014). Additional substances reported in polysubstance exposures were identified using the AAPCC generic codes. In addition to the broad generic codes, the substances are also coded by the AAPCC using POISINDEX (Micromedex, Denver, CO) database for specific product identification. The specific buprenorphine product types were examined to evaluate the patterns in exposure to buprenorphine films or tablets. Other clinical variables considered in the analysis included the route of exposure, the number of exposure agents reported for cases, and number and type of additional opioids reported as exposure agents.

2.3. Statistical analysis

Temporal trends in the frequency of buprenorphine reports were evaluated using a Poisson regression model comparing the change in the annual number of cases during the study period (2011–2016). The cumulative incidence rates of buprenorphine reports at the national level were obtained by utilizing the July 1st intercensal and postcensal population estimates for 2011–2016 obtained from the U.S. Census annual estimates of the resident population (Allen et al., 2017; United States Census Bureau, 2014).

We first outlined the demographic and clinical characteristics of buprenorphine exposure cases descriptively. We further conducted bivariate analyses to assess comparability between severe and non-severe cases utilizing the Pearson's chi-sq statistic for categorical variables. We then selected all the variables with a p-value of less than 0.25 in these preliminary analyses. We developed a predictive logistic regression model using the variables identified in the above process, initially fitting a preliminary model containing all of the selected variables and further refining it using a manual iterative process. During this process, we sequentially excluded variables that were not significantly associated with SBO through Wald p-value assessment, with confirmation of removal through likelihood ratio testing. Multivariable (adjusted) ORs, with their respective 95% Confidence Intervals (CIs), were reported.

All statistical tests were conducted with a 2-tailed α of 0.05. Data were analyzed using SAS 9.4 Software (SAS Institute Inc., Cary, NC). This study was deemed exempt by our university's institutional review board.

3. Results

3.1. Trends in buprenorphine exposures

Overall, there were 13 million human exposures reported to the PCs during the study period. Among the 506,405 opioid exposures during this period, 21,516 involved buprenorphine (Appendix C in Supplementary). During the follow-up, 152 buprenorphine cases were confirmed to be non-exposures and hence were excluded. The final sample included 21,364 buprenorphine exposures (Appendix C in Supplementary). Of these, 967 cases (4.5%) demonstrated SBOs, with

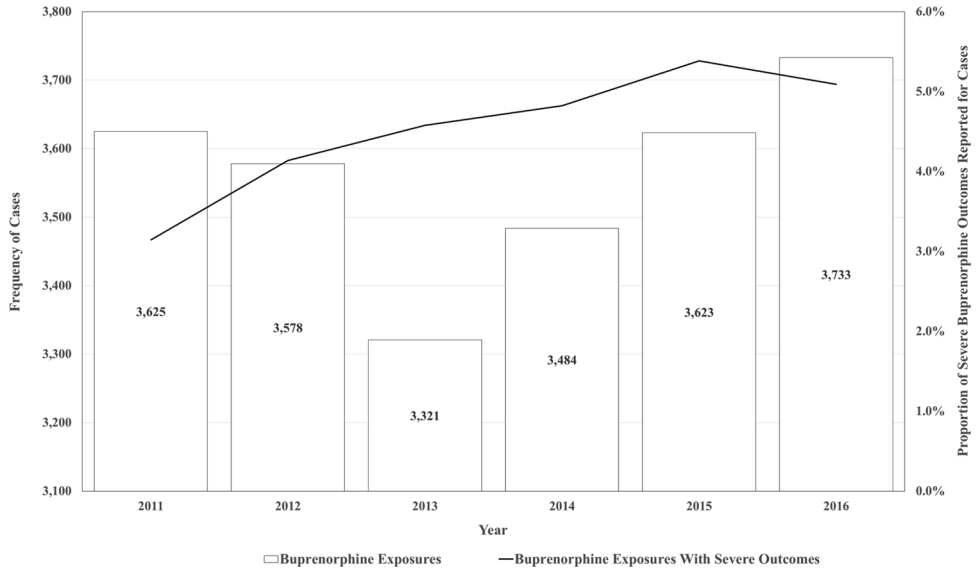

Fig. 1. Trends in buprenorphine exposures reported to the U.S. Poison Centers.

the frequency of such exposures increasing by 66.6% during this period (114–190, $p < 0.001$) (Fig. 1). The national cumulative incidence rate of overall buprenorphine cases and SBO cases during the study period were 1.12 cases and 0.05 per 100,000 population, respectively.

From 2011 to 2016, buprenorphine exposures significantly increased by 3% from 3625 to 3733 ($p < 0.001$) (Fig. 1). However, specifically from 2013 to 2016, there was a significant increase (12.4%) in exposures from 3321 to 3733 ($p < 0.001$). The proportion of SBOs increased from 3.1% to 5.1% during the study period (Fig. 1).

3.2. Characteristics of buprenorphine exposures

Overall, the most common age group observed among exposures was children under 6 years (28.9%), followed by adults between 20 and 29 years (22.7%) (Table 1). Males (53.4%) were predominant in this overall sample. The majority of exposures were unintentional (56.4%), followed by abuse (20.2%). More than half of the total cases resulted from single substance exposures (62.0%). While the number of exposure products ranged from 1 to 18, approximately 11% cases involved an additional opioid. The most common route of exposure was ingestion (91.6%). One-fifth (20.8%) of the cases were admitted to the critical care unit. Naloxone therapy was administered to 19.4% cases. Most exposures occurred at the residence of the patient (90.8%), and the proportion of cases that sought care at acute care hospitals and EDs increased from 39.9% to 51.1% during the study period (results not shown). The most common buprenorphine formulation reported for exposures was the film (35.9%) (Table 1).

3.3. Comparison of SBO and non-SBO case characteristics

Table 1 also compares the demographic and clinical characteristics for the SBO and non-SBO group. Cases between ages 20–39 years were more common among the SBO group (50.4%) as compared to the non-SBO group (38.7%), whereas the proportion of pediatric cases under 6 years was significantly higher among the non-SBO group vs SBO group, respectively (29.6% vs 13.8%) (Table 1). The most common reason for exposure among SBO cases was suspected suicides (37.5%) followed by intentional abuse (24.9%). The proportion of these reasons of exposure were lower in the non-SBO group (13.7% and 20.1%, respectively). Multi-substance exposures were frequent among the SBO (71.4%), while non-SBO cases demonstrated a higher proportion of single-substance exposures (63.6%). Additional co-occurring opioids were reported in 21.3% of the SBO cases and 10.7% of non-SBO cases.

The majority of the SBO cases were en route to a healthcare facility when the PC was called (results not shown). A benzodiazepine class drug was the most commonly reported co-occurring substance in both groups (Table 1). While vomiting and tachycardia were commonly seen clinical effects in the non-SBO group, coma and respiratory depression were frequent in the SBO group (Fig. 2).

3.4. Risk factors for severe outcomes with buprenorphine exposures

Table 2 outlines the risk factors associated with buprenorphine cases resulting in SBO. This risk of severe outcomes in buprenorphine exposures was significantly associated with age. For example, children under 6 years of age had a 35% higher risk of such outcomes (AOR: 1.35, 95% CI: 1.02–1.78) (Reference: 20–29 years), while cases between 50–59 years (AOR: 1.62, 95% CI: 1.25–2.09) and adults above 60 years (AOR: 1.66, 95% CI: 1.14–2.42) demonstrated significantly increased odds of such outcomes. Cases of suspected suicide (AOR: 1.87, 95% CI: 1.53–2.28) and abuse (AOR: 1.40, 95% CI: 1.13–1.73) were significantly more likely to result in an SBO (reference: unintentional reasons). Conversely, misuse cases had lower odds of severe outcomes (AOR: 0.56, 95% CI: 0.38 – 0.82). Involvement of one additional co-occurring substance increased the risk of an SBO by 125% (AOR: 2.25, 95% CI: 1.81–2.70), while more than three co-occuring substances increased the SBO risk 6-fold (AOR: 5.92, 95% CI: 4.71–7.45) (reference: single substance exposures). Non-oral routes, including nasal exposures (AOR: 1.96, 95% CI: 1.21–3.20) and parenteral exposures (AOR: 1.80, 95% CI: 1.25–2.59) (reference: ingestion) demonstrated a higher risk of such outcomes. Acute on chronic and chronic exposures were significantly more likely to result in an SBO (AOR: 1.45, 95% CI: 1.25–1.68) (reference: acute exposures).

4. Discussion

Our study extends the literature by highlighting the key indicators for severe outcomes associated with buprenorphine exposures by utilizing a national poison database. Previous studies have largely assessed severe outcomes to opioids as a comprehensive group, buprenorphine cases among specific demographic groups, or cases reported to public health surveillance system by specific health-care settings like the ED (Allen et al., 2017; Crane, 2013; Sordo et al., 2017).

During our study period, buprenorphine exposures and the number of exposures resulting in severe medical outcomes reported to the PCs increased. These trends might in part be attributed to a substantial

Table 1
Characteristics of buprenorphine exposures reported to the U.S. poison center centers.

Characteristic, N (%)[a]	Buprenorphine Cases (N = 21.364)	Non-Severe Buprenorphine Cases N = 20,397	Severe Buprenorphine Cases (N = 967)
Age*			
0 - 5 Years	6,173 (28.9%)	6,040 (29.6%)	133 (13.8%)
6 – 19 Years	1,200 (5.6%)	1,149 (5.6%)	51 (5.3%)
20 – 29 Years	4,851 (22.7%)	4,595 (22.5%)	256 (26.5%)
30 – 39 Years	3,534 (16.5%)	3,303 (16.2%)	231 (23.9%)
40 – 49 Years	1,932 (9.0%)	1,788 (8.8%)	144 (14.9%)
50 – 59 Years	1,370 (6.4%)	1,266 (6.2%)	104 (10.8%)
> =60 Years	677 (3.2%)	636 (3.1%)	41 (4.2%)
Unknown	1,627 (7.6%)	1,621 (7.9%)	6 (0.6%)
Gender*			
Female	9,797 (45.9%)	9,346 (45.8%)	451 (46.6%)
Male	11,413 (53.4%)	10.898 (53.4%)	515 (53.2%)
Unknown	154 (0.7%)	153 (0.8%)	1 (0.1%)
Reason*.[b]			
Unintentional	12,065 (56.4%)	11,734 (57.5%)	331 (34.2%)
Suspected Suicide	3,159 (14.7%)	2,796 (13.7%)	363 (37.5%)
Abuse	4,332 (20.2%)	4,091 (20.1%)	241 (24.9%)
Misuse	1,808 (8.5%)	1,776 (8.7%)	32 (3.3%)
Number of Products*			
1	13,254 (62.0%)	12,977 (63.6%)	277 (28.6%)
2	4,074 (19.1%)	3,863 (18.9%)	211 (21.8%)
3	2,080 (9.7%)	1,911 (9.3%)	169 (17.5%)
> 3	1,956 (9.1%)	1,646 (8.1%)	310 (32.1%)
Exposure to Other Opioids*			
No	18,986 (88.8%)	18,225 (89.3%)	761 (78.6%)
Yes	2,378 (11.2%)	2,172 (10.7%)	206 (21.3%)
Route of Exposure*,[c,d]			
Ingestion	19,574 (91.6%)	18,715 (91.7%)	859 (88.8%)
Inhalation/Nasal	259 (1.2%)	239 (1.1%)	20 (2.1%)
Parenteral	787 (3.6%)	749 (3.7%)	38 (3.9%)
Others	744 (3.4%)	694 (3.5%)	50 (5.2%)
Chronicity*,[e]			
Acute	16,137 (75.5%)	15,596 (76.4%)	541 (55.9%)
Others	5,227 (24.5%)	4,801 (23.5%)	426 (44.1%)
Level of Healthcare Facility Care*,[f]			
Treated/evaluated and released	5,256 (24.6%)	5,145 (25.2%)	111 (11.5%)
Admitted to critical care unit	4,443 (20.8%)	3,772 (18.5%)	671 (69.4%)
Admitted to noncritical care unit	3,103 (14.5%)	2,977 (14.6%)	126 (13.1%)
Admitted to psychiatric care facility	779 (3.6%)	762 (3.7%)	17 (1.8%)
Others	7,783 (36.4%)	7.741 (37.9%)	42 (4.3%)
Buprenorphine Product Type*,[g]			
Film	7,683 (35.9%)	7,349 (36.0%)	334 (34.5%)
Tablet	7,011 (32.8%)	6,724 (33.0%)	287 (29.7%)
Others	6,670 (31.3%)	6,324 (31.0%)	346 (35.8%)
Co-Occurring Substances[h]			
Benzodiazepines*	3,316 (15.5%)	2,999 (14.7%)	317 (32.8%)
Ethanol (Beverage)*	1,106 (5.2%)	925 (4.5%)	91 (9.4%)
Gabapentin*	717 (3.3%)	615 (3.1%)	102 (10.5%)
Atypical Antipsychotics*	669 (3.1%)	559 (2.7%)	110 (11.3%)

*Statistically Significant differences observed at p-value = 0.05 as derived from the chi-sq test.

[a] Percentages may not add up to 100% due to rounding errors.

[b] Unintentional include: Unknown. Contamination / tampering, Malicious, Withdrawal, Bite / sting, Environmental, Food poisoning, Unintentional – Misuse, Occupational, Therapeutic error.

[c] Column percentages may sum to > 100.0% because each exposure can involve > 1 route of exposure.

[d] Others include Aspiration, ocular, dermal, bite/sting, unknown, otic, rectal, and vaginal.

[e] Others include: Acute-on-Chronic, Chronic, And Unknown.

[f] Others Includes: Patient refused referral/did not arrive at HCF, Patient lost to follow-up/left AMA.

[g] Others Includes: Injections, Non-specific product (e.g. Buprenorphine-Naloxone, Buprenorphine HCl), Unavailable/Unknown.

[h] Percentage denotes proportion of patients reporting a co-occurring exposure to the listed substance (Listed substances considered as individual categorical variables: Present vs Not present).

increase in buprenorphine prescribing in a short span of time, as it has been viewed as a safer alternative to other treatments for opioid use disorder such as methadone owing to its "ceiling effect" at higher doses (Li et al., 2016). In recent years, the number of U.S. substance use treatment facilities and office-based providers that prescribe take-home buprenorphine has dramatically increased (Mojtabai et al., 2019). Moreover, the license waiver privileges to nurse practitioners and physician assistants as well as Medicaid coverage have expanded in the U.S., highlighting a low-threshold approach to buprenorphine treatment (Saloner and Karthikeyan, 2015; Wen et al., 2019). According to data from the Automation of Reports and Consolidated Order Systems, buprenorphine prescriptions grew by more than 2000% from 2004 through 2011 (Schiller and Mechanic, 2019). Similarly, in European countries such as France, a large proportion of individuals receiving OST are being increasingly prescribed by general practitioners to better engage the patients and maximize the physician-patient interactions (Mravcik et al., 2018). The ease of access has undoubtedly provided benefits across multiple health outcome metrics, evident by a 79% reduction in mortality rates in France between 1995 and 1999 (Auriacombe et al., 2004). However, an increased incidence of adverse events due to the higher use may be inevitable, as seen in our study. Hence, the timely surveillance of such reports is key in informing critical public health interventions. Moreover, in countries where buprenorphine is readily prescribed across the spectrum of healthcare, development of uniform practice guidelines and induction protocols as well as novel approaches like telemedicine to train providers may be essential for risk reduction (Guillou Landreat et al., 2015; Huhn and Dunn, 2017).

Our findings support prior evidence demonstrating an increasing trend in severe clinical outcomes due to buprenorphine. For example, according to data from the Drug Abuse Warning Network (DAWN), ED visits associated with buprenorphine grew significantly from 3161 in 2005 to 30,135 visits in 2010 following the U.S. approval of this drug (Crane, 2013). In a recent Finnish study, there were 775 deaths where buprenorphine was found on toxicological post-mortem analysis (Kriikku et al., 2018). With the increased availability, there is potential for buprenorphine misuse and diversion resulting most notably from self-medication due to sub-optimal dosing, lower prices than heroin in some regions, or simply to seek euphoria (Yokell et al., 2011). Such use may contribute to the increased buprenorphine-related serious outcomes as shown by a study that concluded that 20% of overdose patients received prescriptions from multiple physicians (Hall et al., 2008). A Researched Abuse Diversion Addiction Related Surveillance (RADARS) study indicated that among the patients undergoing treatment for opioid use disorders, approximately 16–46% reported past month misuse of intravenous (IV) buprenorphine, while in Finland, buprenorphine was more prevalent than heroin as the most frequently abused opioid among patients seeking treatment for substance use disorder (Dart, 2011; Lofwall and Walsh, 2014; Uosukainen et al., 2013). Furthermore, there were an estimated 21,483 U.S. ED visits for non-medical use of buprenorphine in 2011 according to the Drug Enforcement Agency (DEA), highlighting the significantly increased risk of

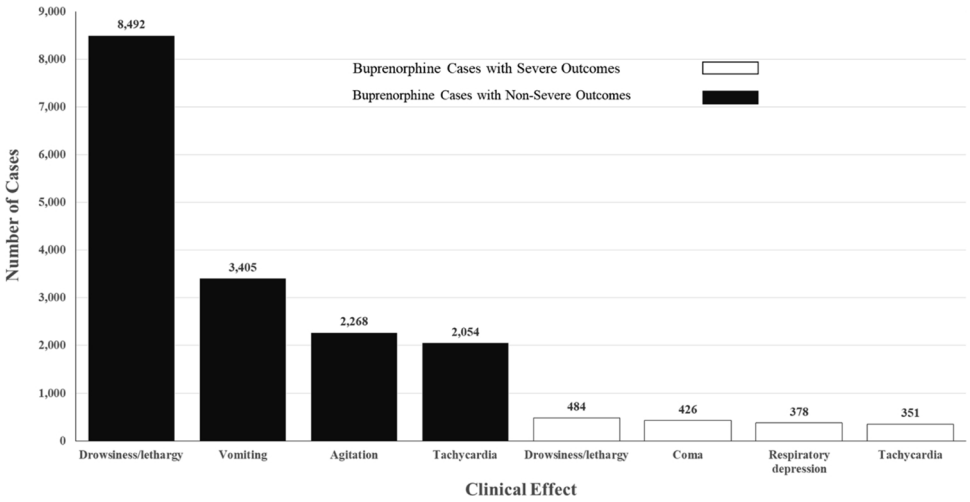

Fig. 2. Clinical effects for buprenorphine exposures.

Table 2
Independent predictors of severe buprenorphine outcomes reported to the U.S. poison center centers.

Age		
20 – 29 Years	Reference	Reference
0 - 5 Years	1.35	1.02 – 1.78
6 – 19 Years	1.17	0.89 – 1.53
30 – 39 Years	1.12	0.92 – 1.36
40 – 49 Years	1.45	1.16 – 1.80
50 – 59 Years	1.62	1.25 – 2.09
> =60 Years	1.66	1.14 – 2.42
Gender		
Female	Reference	Reference
Male	1.01	0.88 – 1.16
Reason[a]		
Unintentional	Reference	Reference
Suspected Suicide	1.87	1.53 – 2.28
Abuse	1.40	1.13 – 1.73
Misuse	0.56	0.38 – 0.82
Number of Products		
1	Reference	Reference
2	2.25	1.81 – 2.70
3	3.14	2.47 – 3.99
> 3	5.92	4.71 – 7.45
Exposure to Other Opioids		
No	Reference	Reference
Yes	0.95	0.79 – 1.14
Route of Exposure[b]		
Ingestion	Reference	Reference
Inhalation/Nasal	1.96	1.21 – 3.20
Parenteral	1.80	1.25 – 2.59
Others	2.59	1.88 – 3.55
Chronicity[c]		
Acute	Reference	Reference
Others	1.45	1.25 – 1.68

[a] Unintentional include: Unknown. Contamination / tampering, Malicious, Withdrawal, Bite / sting, Environmental, Food poisoning, Unintentional – Misuse, Occupational, Therapeutic error.
[b] Others include Aspiration, ocular, dermal, bite/sting, unknown, otic, rectal, and vaginal.
[c] Others include: Acute-on-Chronic, Chronic, And Unknown.

mortality and morbidity with such use (Drug Enforcement Administration, 2013).

However, despite perceivable concerns, evidence from several countries has demonstrated that limiting access has a mixed impact on misuse (Li et al., 2016; Lofwall and Walsh, 2014). For example, while inadequate access was a risk factor for buprenorphine diversion in Finland, a substantial supply of buprenorphine was associated with higher intravenous use in Malaysia. Considering the expanding substance use treatment services, it is necessary to outline concerted efforts to ensure that the increase in the utilization of this treatment is safe and effective. Approaches like unit dose packaging, medication monitoring measures like prescription drug monitoring programs, promoting incentive-based safe practices and drug use, and focusing on high-risk populations may help to mitigate the risk of diversion without limiting access (Li et al., 2016). Prior authorization of doses, improving provider capacity for addiction treatment and a greater role for the pharmacist are measures that have shown considerable promise in limiting diversion (Li et al., 2016).

A significant finding in our study was the higher risk of SBO in adolescents. Although mostly accidental, such exposures are common in children due to their "hand-to-mouth" behaviors and can have serious implications including respiratory depression due to the smaller body mass (Allen et al., 2017). Nevertheless, the prevalence of opioid exposures in children has declined as a result of several prevention initiatives including PC outreach efforts, CDC's Preventing Overdoses and Treatment Errors in Children Taskforce (PROTECT), the "Up and Away and Out of Sight" program and the development of child resistant unit dose packaging (Patel et al., 2019). Our study results further highlight the continued need for greater patient awareness regarding the safe storage and disposal of buprenorphine, as the majority of pediatric exposures are avoidable (Kennedy-Hendricks et al., 2016; Patel et al., 2019).

The risk of serious outcomes in adult buprenorphine exposure cases increased with age and was especially higher in adults above 60 years of age. Our results align with a recent study by Gomes and colleagues that highlighted the growing rate of overdose deaths among ages 55 to 64 years. Apart from physiological changes in these patients, multiple medication regimens, high doses, and the increased prevalence of opioid use disorder may increase the risk of synergistic adverse events (Gomes et al., 2018; Rose et al., 2019). For instance, hydrocodone and oxycodone were commonly reported opioids in misuse cases in our sample. Aging was also significantly associated with increased all-cause mortality in a study of primary care patients treated with buprenorphine or methadone in the U.K. (Hickman et al., 2018). Considering the increasing population size in older adults and the growing substance use in this population, it is conceivable that the demand for OST treatments like buprenorphine will undoubtedly increase further in the coming years (Carew and Comiskey, 2018; Han et al., 2009; Simoni-Wastila and Yang, 2006). As a result, it is key to limit such severe exposures utilizing a targeted multifaceted approach including policy

changes, patient education and support, and evidence-based treatments (Rose et al., 2019).

Our study did not find any statistically significant gender differences in the risk of SBO. However, it has been noted that women are more likely to suffer from conditions like pain and major depressive disorder, which has important implications on the patterns of prescription opioid use (LeResche et al., 2015; Serdarevic et al., 2017). There is also evidence that female cases utilizing substance abuse treatments like buprenorphine are generally more severe and exhibit other complex behavioral and psychological issues (Greenfield et al., 2010). Personalized gender-specific approaches including tailored medication regimens, counseling and other services like childcare are key in order to ensure better outcomes to buprenorphine therapy in women (Mazure and Fiellin, 2018).

Cases of suspected suicides and intentional abuse had a significantly elevated risk of severe outcomes in our study. Substance use disorder patients often suffer from chronic pain and mental health issues, both prominent makers of suicide attempts, and may be prescribed buprenorphine (Oquendo and Volkow, 2018). A recent study demonstrated that the deaths attributed to suicides in the U.S. significantly increased in recent years, with one-third of all overdose-related suicides involving an opioid (Bohnert and Ilgen, 2019; West et al., 2015). Similarly, 30% of opioid-related hospitalizations in Canada were due to self-inflicted harm (Chan et al., 2018). We observed a higher proportion of polysubstance exposures in cases where the exposure reason was noted as suspected suicide and intentional abuse. Previous studies have also demonstrated that individuals using opioids exhibited higher use of recreational substances like alcohol, non-opioid prescription medications and illicit substances which might exacerbate the severe outcomes including death (Winkelman et al., 2018). Therefore, it is essential to closely monitor the risk of suicide in patients being prescribed buprenorphine, for instance by developing risk-scoring algorithms using electronic health records and exploring an array of psychosocial treatment opportunities. Examples of harm reduction strategies that have proven useful in this population include detoxification, motivational interviewing, tapering of opioid dosage, and distribution of naloxone, a therapy that was commonly reported for our sample (Bohnert and Ilgen, 2019; Rege et al., 2018).

Our finding that the risk of SBO increased with a higher number of co-occurring substances is congruent with previous studies (Calcaterra et al., 2018; Kerr et al., 2005). A study using Global Drug Survey data from five countries concluded a higher degree of misuse and abuse in individuals using multiple substances including benzodiazepines and illicit drugs (Morley et al., 2017). Benzodiazepines, also the most common co-occurring substance in our analysis, have been increasingly used in combination with opioids for nonmedical purposes, increasing the risk of serious adverse events due to the cumulative central nervous system depression. Accidental injuries and ED visits attributed to this combination have increased significantly in recent years (Calcaterra et al., 2018; Jones et al., 2012; Schuman-Olivier et al., 2013). Some postulated reasons for polysubstance use include inappropriate self-medication for treating symptoms, including those associated with substance withdrawal, and the need for enhanced psychoactive effects (Liu et al., 2018). Emphasizing appropriate management of pain via management clinics, assessing the use of other medications, as well as early recognition of mental health issues may prove crucial in maintaining the appropriate level of buprenorphine prescribing (Jones et al., 2018).

Our results are in alignment with previous studies that demonstrated that non-oral routes of administration likely result in a higher risk of severe outcomes for opioid drugs including buprenorphine. This can be attributed to the immediate release, rapid absorption and the resulting higher systemic availability and central nervous system effects of such medications (Green et al., 2017). There is also prior evidence that the parenteral use of buprenorphine may result in serious cutaneous and pulmonary complications (Gasior et al., 2016). Development of alternative drug delivery systems like the abuse-deterrent buprenorphine films have proven effective in reducing the misuse of prescription drugs (Green et al., 2017). Our study also exhibited a strong association between non-acute exposures (chronic and acute on chronic) and SBO. Persistent substance use is known to increase the risk of severe outcomes (Chou et al., 2014).

Our study has several key limitations. Considering the passive self-reporting nature of the dataset, there is an underreporting of the true prevalence of exposures with patients seeking and receiving care directly without PC involvement. All the data are de-identified, and hence it is not possible to clearly delineate several factors associated with the cases that might be available in a detailed follow-up (Hoffman, 2007). The data are susceptible to issues of inaccuracy, incompleteness, miscoding, potential selection as well as reporting bias and limited ability for verification due to lack of prescribing and clinical information. The coding of therapies using the AAPCC coding system is not extensively validated, thereby increasing the possibility of miscoding (Naun et al., 2011). Despite these drawbacks, PC data are subject to standardized quality controls and have served as a vital public health surveillance tool to effectively track toxicity trends.

5. Conclusions

Our study focused on risk factors for severe outcomes associated with buprenorphine exposures reported to the U.S. PCs. We determined that age, the reason for exposure and presence of other co-occurring substances significantly increased the risk of such severe outcomes. A greater understanding of these factors is essential for the safe and effective use of buprenorphine as the prescriptions are expected to increase in the future. The results of our study can aid the clinicians in identifying patients with a higher risk for adverse outcomes. Buprenorphine remains an underutilized treatment option despite the increased prescribing and documented long-term health benefits. Developing early evidence-based intervention and recovery opportunities while addressing other practical barriers is key in the ongoing opioid crisis.

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Contributors

CH conceived the study objective. SR conceived the study design, performed the analyses, and drafted the manuscript. All authors contributed to interpretation of the results and writing the manuscript. All authors approved the final version of the manuscript before submission. None of the original material contained in this manuscript has been submitted for consideration nor will any of it be published elsewhere.

Declaration of Competing Interest

All authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

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