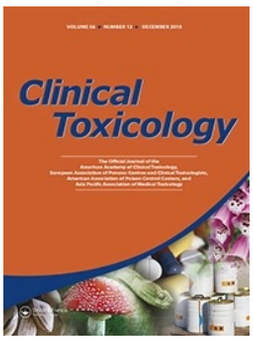

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CLINICAL RESEARCH

Buproprion associated seizures following acute overdose: who develops late seizures

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ABSTRACT

Objectives: Bupropion is an antidepressant that is commonly known to cause seizures in overdose. Because of concern for delayed onset of seizures, patients are frequently observed for prolonged periods after overdose. The primary objective is to evaluate the incidence and clinical parameters associated with late seizures following bupropion overdose.

Methods: This retrospective study of acute bupropion overdose who presented to 26 different hospitals in California and Arizona during an 8 year time period.

Results: 437 patients were identified. Tachycardia and altered mental status were common. A total of 122 (27.9%) patients had seizures following their overdose. Only eight patients (1.8%) had a seizure more than 8 h after hospital arrival. None of these patients were asymptomatic on arrival. Among patients with tachycardia on arrival, the odds of having a seizure was 6.7 (95% CI 3.7–10.9); the odds of a seizure more than 8 h after arrival was 5.24 (95% CI 1.2–23.5). Similarly, altered mental status on arrival was significantly associated with the risk of a seizure; OR 3.93 (95% CI 2.21–7.0).

Conclusion: Seizures are relatively common, and are associated with antecedent tachycardia or altered mental status.

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KEYWORDS
Bupropion; overdose; seizure; suicide; toxicity

Background

As a monocyclic aminoketone compound, bupropion is a unique antidepressant, belonging to its own class [1–5]. It is commonly prescribed for the treatment of major depressive disorder, and can be used as adjunctive treatment for smoking cessation [3].

In the United States, bupropion is available in three different formulations: immediate release (IR) which is dosed three times daily, sustained release (SR) which is dosed twice daily, and extended release (XL) which is dosed once daily [3]. In volunteer studies, the time to peak plasma concentrations were longer for the SR and XL products. Time to peak concentrations were 1 h for IR versus 3 h for SR and 5 h for XL [4]. Bupropion is extensively metabolized *via* several enzymes, including CYP2B6 to three different metabolites [4]. While the metabolites have pharmacologic activity, they are not as potent as the parent compound.

Bupropion overdoses are a common source of toxicity. In 2018, nearly 15,000 overdoses involving bupropion were reported to US Poison Control Centers [6]. Furthermore, bupropion is the most commonly ingested antidepressant per the Toxicology Investigators Consortium case registry [7]. Bupropion toxicity is commonly characterized by tachycardia and seizures, which may be delayed [1,8]. At therapeutic dosing, bupropion causes seizures in approximately 0.1% of patients [2,3,9]. However, in overdose, seizures are much more common, occurring in 11–37% of patients [6–9]. The seizures are clearly dose dependent [10,11,12], and may be more common with certain preparations. Other than some suggestion that seizures occur less frequently in pediatric patients [13–14], and concurrent ingestion of a benzodiazepine may be somewhat protective against seizures [15], there is little additional information to aid in identifying which patients are at higher risk for developing seizures after overdose. The primary purpose of this study is to evaluate the incidence and clinical parameters associated with late seizures following bupropion overdose, which may aid in the identification of high-risk individuals.

Methods

This multi-center, retrospective cohort study included patients presenting with bupropion overdose between January 2011 and December 2018. Patients were identified *via* search of medical toxicology service logs. As a secondary search strategy, a search of ICD9 and ICD10 codes were

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The work was performed at the Kaiser Northern California system, the University of Southern California, and the Banner University Medical Center, Phoenix
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utilized to ensure no patients were missed. The study received approval from the institutional review board at each of the participating sites.

Settings

The study included patients from a single integrated healthcare system incorporating 20 hospitals located throughout Northern California, a toxicology practice group covering 5 hospitals located throughout the Los Angeles region, and a single tertiary care toxicology referral center located in Phoenix, AZ. Cumulatively, these toxicology practice groups provide admitting or consultative services for approximately 6500 patients annually. Geographically, there are two poison control systems in the areas where the hospitals are located. However, the poison control systems are not routinely involved in the direct management of these patients.

Outcome parameters

The primary outcome parameter was the incidence of seizures following bupropion overdose. Secondary outcomes included the characteristics of these ingestions, observed signs and symptoms, timing of late seizures, use of mechanical ventilation, hospital admission, and death. The primary goal involves being able to identify clinical features that are associated with delayed seizures, thereby ultimately aiding clinicians to develop a tool to help risk stratify which patients may be at risk for delayed seizures.

Data collection

Data was abstracted using a pre-designed data abstraction form created using an Excel spreadsheet. Before performing data abstraction, each reviewer received a standardized training in systematic chart review. Following abstraction, ten percent of the charts from each site were subsequently abstracted by a second investigator to ensure accuracy of abstraction and assess inter rater reliability.

The data abstracted included demographic information (age, sex), ingestion details (amount and type of product ingested, timing of ingestion, reason for ingestion), clinical characteristics (presence or absence of a seizure, location and timing of seizure, history of baseline seizure disorder, presence or absence of tachycardia or hypotension, presence or absence of documented altered mental status, etc.), treatment rendered (decontamination, use of vasopressors, mechanical ventilation, etc.), length of stay, return visits within 24 h, and outcome.

All participating medical centers utilize a commercially available electronic medical record (EMR). Data points were abstracted from the EMR. Whenever possible automated, objective data was used. Narrative chart review was used for collection of more subjective data.

Study definitions

Initial tachycardia was defined as any heart rate above 100 beats per minute documented at the time of first medical contact. Sustained tachycardia was any heart rate documented above 100 beats per minute for two or more consecutive hours. Among pediatric patients, tachycardia was defined as any heart rate documented above the upper limit of normal per age, as per pediatric advanced life support (PALS) guidelines. Based on author consensus, we defined marked tachycardia as a heart rate above 120 beats per minute for adults, and more than 20 beats per minute above the upper limit of the age-adjusted normal for pediatric patients. Late seizure was defined as any seizure occurring more than 8 h after hospital arrival, regardless of the presence or absence of a seizure occurring earlier. Hypotension was defined in adults as a systolic blood pressure under 90 mmHg. Length of stay was calculated from the initial hospital arrival time until discharge orders were placed in the computer. If a patient was transferred from one emergency department to another hospital for admission, the length of stay time included the time in the emergency department at the first hospital plus the time admitted at the second hospital. Any subsequent psychiatric admission was not included in the length of stay calculation. Pediatric patients were defined as age 14 years and younger. The diagnosis of bupropion overdose was based on the discharge diagnosis.

Data analysis

For categorical data, descriptive statistics included proportions. Confidence intervals were calculated from proportions of interest using binomial exact methods. For continuous data which were demonstrated to be non-normally distributed by Shapiro-Wilk testing, central tendency was reported as median with dispersion reported as interquartile range (IQR). Associations between categorical variables were evaluated by Chi-squared testing or Fisher's exact test, as appropriate. Associations involving continuous data were assessed using non parametric Kruskal-Wallis testing. Univariate logistic regression was used to calculate odds ratio and confidence intervals. Multivariate analysis was used for two primary endpoints – any seizure and late seizures. After identifying features on univariate analysis that may be statistically significant, modeling used a step-wise approach per Hosmer and Lemeshow's standard logistic regression [16]. A C-statistic was calculated to assess the goodness of fit testing. All data was analyzed using Stata (version 15.1, StataCorp, College Station, TX). Significance was set at the $p < 0.05$ level and confidence intervals are reported at the 95% level.

Data sharing

De-identified data may be shared with outside qualified investigators following completion of data sharing agreements through local institutional review board policies.

Table 1. Detailed information on the five cases with cardiac arrest.

Age, sex*	Bupropion ingestion**	Co-ingestants	Seizures	Tachycardic on arrival	Sustained tachycardia	Cardiac arrest	Treatment***
20 F	4.5 g; XL	Acetaminophen, oxycodone	Prehospital and hospital	Yes	Yes	Yes	AC, BZD, ETT ILE Vaso
20 M	Unknown	clonazepam	Prehospital	Yes	Yes	Yes	Barb, ETT, ILE
16 F	18g; XL	None	Prehospital and hospital	Yes	Yes	Yes	AC, BZD, ECMO, ETT, ILE, Vaso
15 F	15g; ER	None	Prehospital and hospital	Yes	Yes	Yes	BZD, ECMO, ETT, Vaso
32 M	27g; ER	None	Prehospital	Yes	Yes	Yes	AC, BZD, ETT, Vaso

*Sex: F: female; M: male.
**Ingestion: XL and ER refer to the preparation of bupropion.
***Treatment rendered: AC: activated charcoal; Barb: barbiturates; BZD: benzodiazepines; ECMO: Extracorporeal membrane oxygenation; ETT: endotracheal intubation/mechanical ventilation; ILE: Intravenous lipid emulsion therapy; Vaso: vasopressors.

Table 2. Breakdown of individual patients with late seizures.

Age (years)	Sex	Amount ingested (gram)	Formulation	Co-ingestants	Seizures	Time to seizure* (hours)	Clinical
50	M	Unknown	XL	Olanzapine	Single seizure in hospital	19.6	Tachycardic with altered mental status upon arrival
18	M	Unknown	XL	Quetiapine, Fluoxetine	Single seizure in hospital	12.8	Tachycardic with altered mental status upon arrival
20	F	4.5	XL	Acetaminophen	Single seizure in hospital	12.1	Tachycardic with altered mental status upon arrival
37	F	7.5	XL		Single seizure in hospital	10.1	Tachycardic, but normal mental status on arrival
43	F	6.75	XL	Sertraline	Multiple seizures in hospital	9.9	Altered mental status with normal HR upon arrival. Developed sustained tachycardia shortly after arrival
24	M	Unknown	XL	Lorazepam, Risperidone, Diphenhydramine, Olanzapine	Multiple seizures in hospital	9.8	Tachycardic with altered mental status upon arrival
15	F	Unknown	XL	methylphenidate	Single seizure in hospital	8.5	Tachycardic with normal mental status upon arrival
32	F	3.75	SR	Trazadone	Multiple seizures in hospital	8.3	Tachycardic with altered mental status upon arrival

*Time in hours from arrival in the hospital until first seizure.

Table 3. Characteristics of patients with late seizures.

Group based on timing of seizure	Arrival Tachycardia	Arrival AMS	Sustained tachycardia	AMS prior to seizure
Sz >8 h ($N = 8$)	7	6	8	6
Sz 8–12 h ($N = 5$)	4	3	5	3
Sz >12 h ($N = 3$)	3	3	3	3

AMS: altered mental status.

Results

A total of 437 patients were included in the study. The majority (63%) were female, and involved intentional ingestions (78%). The median (IQR) age was 29 (18–43) years. Pediatric patients accounted for 9.6% of all patients. Co-ingestants (other than ethanol) were common, with 232 (53.1%) patients having a coingestion in addition to the bupropion. The formulation of bupropion was known in 388 (88.8%) patients; among patients with a known formulation, immediate release preparations accounted for 17 (4.7%), sustained release/extended release formulations accounted for 151 (38.9%), and XL preparations accounted for 220 (55.7%) patients. Thirty-nine (8.9%) patients involved an unintentional double dose exposure. Cardiac arrests occurred in five patients, all of whom were symptomatic on arrival. Two of these patients required extra-corporeal membrane oxygenation (ECMO). Detailed information on the cardiac arrests with cardiac arrest including those who received ECMO are listed on Table 1. There were no deaths in this series.

The amount ingested was reported in 279 patients. Among these, the median (IQR) dose ingested was 1.5 (0.6–3.6) g, with an overall range being 0.1–27 g. The time from ingestion to ED presentation was known in 205 patients. Among these patients, the median (IQR) time from ingestion to ED presentation was 105 (60–303) min.

The median (IQR) length of stay was 1.5 (0.5–3) days. There were four patients who returned within 24 h post ingestion. One patient who crushed and insufflated bupropion returned in less than 24 h with an additional seizure, but had admitted to re-insufflating bupropion shortly before his second seizure. One patient returned with aspiration pneumonia, possibly the result of the first seizure. The other two visits were not related to the ingestion.

Tachycardia was present upon arrival in the emergency department in 246 (56.5%) of individuals. Sustained tachycardia was observed in 220 (50.6%) individuals. Altered mental status was present upon arrival in 181 (41.2%) bupropion overdoses. Sixty-six (15.1%) patients were intubated.

In total, 122 (27.9%) patients had any seizure; seizures occurred in the prehospital setting in 68 (55.7%) patients, and in the hospital in 75 (61.5%) patients. Twenty-one patients (17.2%) had both pre-hospital and in-hospital seizures. A total of 8 patients had late seizures (Tables 2 and 3). Details on these eight patients are presented in Table 2. None of these patients had pre hospital seizures. Each patient who had a late seizure also had sustained tachycardia prior to the seizure. No patient who was asymptomatic

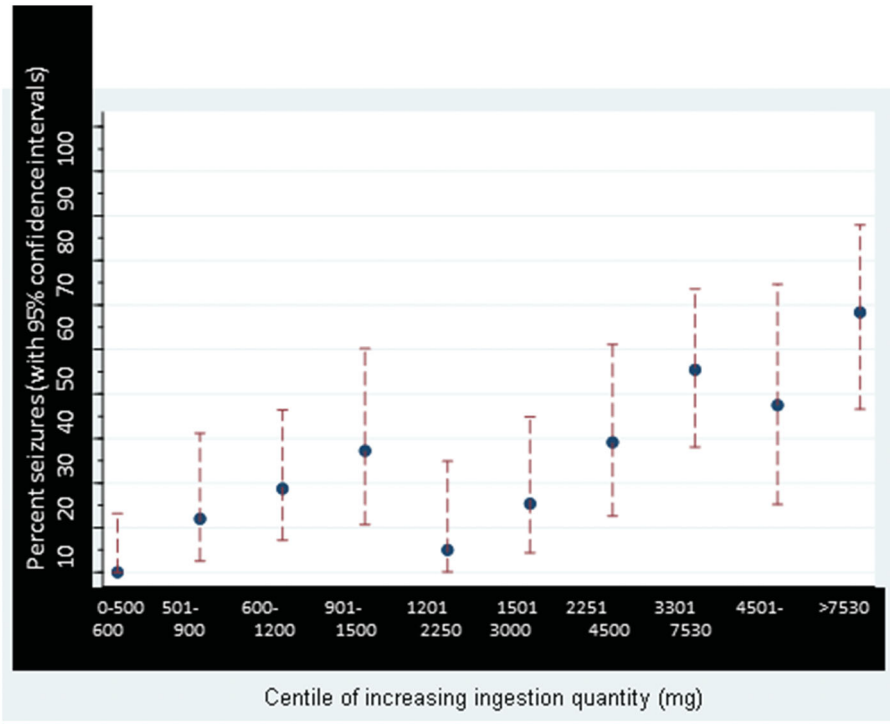

Figure 1. Dose dependent risk of seizures.

on arrival had their first seizure more than 8 h after arrival. The risk of seizures was dose dependent (Figure 1). The median dose for those who had a seizure was 3.75 (IQR 1.2–6.75) g, where as the median dose for those who did not have a seizure was 1.2 (0.6–1.2) g ($p = 0.0001$).

Among patients with tachycardia on arrival, the odds of the patient having a seizure at any point (prehospital or in hospital) or late seizure was 6.7 (95% CI 3.72–10.9) and 5.24 (95% CI 1.16–23.5), respectively. Marked tachycardia also predicted seizure, with an odds ratio of 2.93 (1.9–4.54). In addition, altered mental status on arrival was strongly associated with the risk of having a seizure (OR 5.84 (95% CI 3.7–9.3). Hypotension was noted in 14 adult patients. The development of hypotension at any time during the hospitalization was associated with an increased risk of seizure (OR 2.36; 95% CI 1.04–5.34), but was not associated with an increased risk of delayed seizures.

Using logistic regression, arrival tachycardia, arrival altered mental status, and adult status were all significantly associated with the development of a seizure; OR 4.4 (95% CI 3.9–5.0), 3.93 (95% CI 2.2–7.0), and 1.47 (95% CI 1.1–2.0), respectively. The discrimination of the model was good (c-statistic 0.79; 95% CI 0.74–0.83). Utilizing logistic regression for the 395 adult patients, sustained tachycardia was associated with an increased odds of seizure (OR 4.08; 95% CI 2.99–5.57). Similarly, unintentional double dose and measurable ethanol levels were associated with lower risk of seizures (OR 0.42; 95% CI 0.35–0.51; OR 0.50; 95% CI 0.30–0.83, respectively). The Hosmer Lemeshow goodness of fit test indicated acceptable calibration ($p = 0.82$) with good discrimination model (c statistic 0.79; 95% CI 0.74–0.83).

There were 75 patients involving double-dose ingestion, in which patients consumed twice the normal dose of their medication. Among these 75 patients, seizures occurred in two patients (2.7%; 95% CI 0.3–9.3%). One patient had ingested 600 mg and the other ingested 800 mg. Both patients seized prior to arrival in the emergency department. One had an additional seizure 60 min after arrival in the emergency department. Thus, none of the 73 patients with double dose ingestions who did not seize in the pre-hospital setting had an in hospital seizure (97.5% CI 0–4.9%).

The kappa statistic was greater than 0.8 for each variable abstracted.

Discussion

This study sought to determine the prevalence of seizures following bupropion overdose, and to attempt to determine features that may predict late seizures. Overall, late seizures were uncommon, and when they did occur, never occurred in asymptomatic individuals. While the results should be validated prospectively to increase external validity, it should be noted that this study is the largest non-poison center study to address this topic to date, and thus, contains the most detailed case data available to provide insight into this topic.

Based on previous studies, the vast majority of patients who develop seizures following bupropion overdose do so within 8 h [1,11,12]. When looking at the patients with bupropion XL overdose specifically, seizures occur more commonly and may be presenting late. In this series, it should be noted that the absence of tachycardia or altered mental status was associated with the absence of late seizures. It is possible this may serve as a useful measure for determining the optimal time of observation for patients with bupropion ingestions. Starr et al. in their study looking at bupropion XL overdose, reported that 32% of patients (12/37) with seizures

had their initial seizure at greater than 9 h from the time of ingestion [1]. One of these patients had an initial seizure at 24 h. Because of these findings, many poison centers routinely recommend 24 h observation after overdose of bupropion XL or unknown preparations of bupropion. In Starr's paper, however, there was no description of the clinical appearance of those patients having initial seizures after 9 h. It has been our clinical experience that patients with late seizures generally have clinical clues such as tachycardia and/or altered mental status prior to the seizure. This study supported our clinical experience by demonstrating tachycardia and/or altered mental status were universally present in cases of late seizures.

In the current study, 27.9% of bupropion overdose patients had seizures. Late seizures after a prolonged period of observation were unusual, occurring in 6.6% of patients who experienced a seizure and 1.8% of the overall overdose population. Seizures beyond 12 h were rare, occurring in 2.5% of patients with seizure and 0.7% of the overall overdose population.

This study observed seven of the eight patients with late seizures had ingested the XL preparation. The one patient who did not consume an XL preparation took an SR preparation and experienced a seizure just beyond the pre-defined 8 h time span (8.3 h – see Table 2). This finding is consistent with known pharmacokinetic data, in which the time to peak plasma levels (Tmax) is 1.5 h for IR, 3 h for SR, and 5 h for the XL product [2–4].

Shepherd and colleagues examined bupropion toxicity in a poison center model [7]. In their study, seizures occurred in approximately 11% of their patients, and typically occurred within 6 h of ingestion. Similar to this study, while seizures did occur in a delayed fashion, tachycardia and altered mental status were typically present in scenarios involving late seizures. The current study had a higher rate of seizures than reported in Shepherd's paper. It is possible that the difference relates to Shepherd's paper being a poison center study, and thus reliance on notes entered by the poison center, rather than reviewing the medical record in its entirity. More likely, however, is that Shepherd's study included patients reported to the Texas Poison Center Network in 1998 and 1999. The once daily XL preparation, which seems to induce seizures at higher rates than the twice daily SR formulation, was not available at the time of Shepherd's study.

In this study, we found a dose-dependent effect on the risk of seizures, which has been previously reported [2,3,5]. Correia and colleagues examined unintentional double dose ingestions reported to the California Poison Control System [17]. Similar to this study, seizures following double dose ingestions were uncommon, and did not occur with doses under 600 mg.

Lewis reviewed 67 patients with bupropion insufflation reported to the California Poison Control System [18]. Similar to this study most patients with bupropion toxicity had antecedent tachycardia before a seizure. However, Lewis's paper involved insufflation of bupropion, which involves crushing the tablet prior to snorting. Thus, rapid peak concentrations would likely be achieved, thus likely explaining why no patient had late seizures.

In this study, we found adult status was associated with increased risk of seizure. This study did not specifically adjust the reason for an intentional ingestion (e.g. suicidal vs. recreational abuse to get "high)" but did account for those who accidentally took a double dose of their medications, vs. those who took the bupropion intentionally. Most of the intentional ingestions were suicidal. After adjusting for accidental double dose ingestions versus intentional ingestion, we found age remained associated with an increased risk of seizure. It is possible that those who abused bupropion recreationally consumed less than those who took it as part of a suicide attempt. Similarly, we cannot exclude the possibility thatsuicidal adults ingest more drug than suicidal adolescents. Nonetheless, we did find a positive correlation between age and risk of seizure.

This study raises an important, provocative question: is routine 24-h observation of asymptomatic patients following bupropion overdose warranted. It is possible that a period of 8 h of observation in the emergency department may be sufficient for patients with bupropion IR and SR preparations who remain asymptomatic throughout the observation period. Eight hours observation also appears to be sufficient for the majority of patients following bupropion XL overdose. Those patients with altered mental status and/or tachycardia will require longer periods of observation, beyond the 8 h time period. Those with continued symptoms should be observed for at least 24 h.

Limitations

This study is limited primarily by its retrospective nature. Retrospective studies are limited by the potential for recall and recording bias. In our study, many of the variables of interest (such as event times) were recorded electronically in the EMR which tends to improve accuracy. Other more subjective variables were, by necessity, taken from the narrative notes within the EMR. It would be very difficult to perform prospective research in this area as it was necessary to include many medical centers (over a wide geographic area) in order to accumulate the numbers of patients needed to draw conclusions. Furthermore, the use of multiple reviewers for data abstraction can be problematic. It is possible that there could have been differences in how data points were collected and/or interpreted. However, the weighted kappa was consistent with excellent inter-observer reliability. As a retrospective study, the study is limited by the accuracy and completion of the medical record. By focusing on categorical variables with dichotomous outcomes (e.g. prehospital seizure or no), and limited continuous data that is easily ascertainable on an electronic medical record (e.g. time of seizure), we feel that we have reduced some of the limitations associated with a retrospective review [19].

Because of the retrospective and purely observational nature of this study, patient observation times were at the discretion of the attending physician and consultant. Therefore, patients may have been discharged prior to 24 h observation.

It is conceivable that delayed seizure may have been missed in patients released early. All medical records were reviewed for return visits within 24 h of discharge. However, if the patient presented to another hospital system, it is possible that repeat presentation may have been missed. It is also conceivably possible a seizure was not documented in the records, but we feel that is highly unlikely as all nursing notes and physician notes were reviewed during the extraction, to ensure all in-hospital seizure events were collected.

This study also is limited by reported ingestion histories from patients, family members, or other witnesses, which is a problem inherent in most clinical toxicology research. It is possible histories may be inaccurate. To reduce some of the limitation of unknown time of ingestion, we opted to define late seizures as being more than 8 h after emergency department arrival, rather than from the time of ingestion. It is likely the length of time from ingestion to ED arrival may vary. However, clinically, we feel that having a clear time of observation in the emergency department is not only more clinically useful to the practicing provider, but also reduces the inherent difficulty associated with ambiguous or inaccurate histories. Lastly, confirmatory testing, which is not routinely available at most centers, was not an inclusion criterion. Thus, it is possible a patient reported taking bupropion but actually took a different medication. If this happened, it could underestimate the number of patients with seizures, including late seizures. However, given the relatively high percentage of patients who exhibited toxicity consistent with bupropion ingestion, we feel this is unlikely to have significantly altered our findings.

In this study, more than half of all patients had co-ingestants. We opted to include these patients, however, to maximize external validity. The exclusion of patients with co-ingestants would limit the generalizability of this study. If a patient had a co-ingestant such as a benzodiazepine, there could be a theoretical concern that the seizure occurred after the metabolism of the protective effect of the benzodiazepine. Given only a single patient who had a delayed seizure had reported a co-ingestant of a benzodiazepine, we feel it is unlikely that the co-ingestant was the result of the delayed seizure. Non-benzodiazepine co-ingestants would increase the likelihood of causing symptoms, not decrease the likelihood of symptoms. Again, no patient who had a late seizure, regardless of co-ingestants, was asymptomatic during the first eight hours in the hospital and then had a seizure. Furthermore, even if a patient had consumed a co-ingestant which could cause tachycardia, we nonetheless still demonstrated the lack of tachycardia to be predictive. It is possible that co-ingestants delayed absorption of bupropion, but again, given no patient who had a late seizure was asymptomatic during the first eight hours, we feel the use of co-ingestants is not a limitation.

Many of these patients were transferred from outside hospitals specifically for toxicology services. It is possible that sicker patients were more likely to be transferred, thus falsely elevating the rate of seizure. However, because the rate of seizures were consistent with what was previously reported, we feel this is relatively unlikely.

Conclusion

In this large multi-center study involving bupropion overdose, seizures were common and tended to occur within 8 h of presentation to healthcare. While some patients did have late seizures, such scenarios were associated with antecedent symptoms, most notably sustained tachycardia or altered mental status. The absence of altered mental status or sustained tachycardia may serve as a marker for which patients are at risk for delayed seizures. Unintentional double dose ingestions, age under 14 years, and concurrent ethanol ingestion may be associated with a reduced rate of seizures. If these findings are validated with external data, patients who remain asymptomatic may be safe for medical clearance after 8 h of emergency department observation.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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