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ORIGINAL ARTICLE

Pediatric Bupropion Ingestions in Adolescents vs. Younger Children—a Tale of Two Populations

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Abstract

Background Bupropion is a unique class of antidepressant. In overdose, it is associated with tachycardia, altered mental status, and a dose-dependent risk of seizures, which can be delayed. Despite being a common medication, there is a paucity of data comparing toxicity in younger versus older children with bupropion exposures. The primary purpose of this study is to examine bupropion toxicity in pediatric patients and assess for toxicity differences between younger and older (teenaged) groups.

Methods This single-center, observational cohort study reviewed pediatric patients presenting to a toxicology service between 2011 and 2018. The primary outcome measures evaluated were the presence of any seizure, delayed seizure (defined as occurring at least 6 hours after hospital arrival), and a composite endpoint of seizure, hypotension, or need for endotracheal intubation. Patients were subdivided into two groups—those 12 years and under, compared with those 13–17 years.

Results A total of 80 unique pediatric cases were identified. Overall, the median (IQR) age was 14 (2.4–16) years. Patients under 13 years accounted for 31 (39%) of cases, whereas the remaining 49 cases were adolescents. Compared with the adolescents, the younger patients were less likely to be female (41.9% vs. 71.4%; $p = 0.009$) and more likely to have an unintentional ingestion (100% vs. 10.2%; $p < 0.001$). The younger group was more likely to present to health care earlier after the ingestion (median 61 (IQR 39–103) min vs. 139 (67–399) min; $p = 0.002$). The older group was more likely to be tachycardic (73.5% vs. 19.4%; $p < 0.001$), have sustained tachycardia (71.4% vs. 29% $p < 0.001$), and more likely to have altered mental status on arrival (38.8% vs. 6.5%; $p < 0.001$). Seizures were also much more likely in the older group (40.8% vs. 3.2%; $p < 0.001$). Adolescents were much more likely than younger children to reach the pre-defined composite endpoint (42.9% vs. 6.5%; $p < 0.001$), but this was largely driven by the seizures.

Conclusion Bupropion ingestions are relatively common among pediatric patients. However, adolescents are much more likely to present with more severe toxicity. Seizures are uncommon among younger children with exploratory ingestions.

Keywords Seizure · Tachycardia · Bupropion · Adolescent · Pediatric

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Introduction

Bupropion is an aminoketone class of antidepressant that is commonly used for both depression and smoking cessation [1, 2]. Shortly after its introduction in the late 1980s, the drug was withdrawn from the market due to the dose-related risk of seizures. However, it was reintroduced in the 1990s as both an antidepressant and to provide pharmacologic aid for smoking cessation [3]. In part to optimize compliance and in part because toxicity is related to C_{max} (with concomitant risk reduction with fewer daily doses), the drug has evolved over the years from its initial formulation's dosing frequency of three times per day (immediate release or IR) to twice-daily (SR or ER) and then once-daily (XL) forms [2].

Intentional and unintentional ingestion of bupropion (in all forms) is well described in the emergency medicine literature. With regard to pediatric bupropion ingestion, it has been known for decades that younger pediatric patients manifest clinical effects from bupropion in only 8% of cases, whereas adolescents showed symptoms in 46% of cases [1]. While there are case reports of severe toxicity in young children [3, 4], such case reports are rare, emphasizing the relatively uncommon nature of severe toxicity in children with unintentional ingestions. In contrast, intentional ingestions may result in a range of serious toxicities that are usually neurological but also occasionally cardiac [5–7]. Manifestations of such toxicity include altered mental status, seizures, and tachycardia [8]. While tachycardia following bupropion overdose is common, serious cardiac dysrhythmias that may be occasionally seen in adults [9] are very infrequent in children [8]. Because seizures may be delayed, it is commonly recommended that patients with an overdose of bupropion should be admitted and/or observed for prolonged periods.

Informative data on bupropion's general toxicity characteristics across all age groups is known. However, there are relatively few data characterizing bupropion toxicity in children from single-center or single system studies, in which the investigators have access to the entire medical record. In particular, despite an understanding of some of the risk factors (e.g., dose) for toxicity in pediatric bupropion exposure, there is little evidence addressing specific predictors and their associated relative risks for seizures in children.

The purpose of the current study was two-fold. The first aim was to evaluate a large group of pediatric bupropion cases in order to characterize patient presentations and assess for predictors (with associated relative risks) involving the main toxicity manifestation of seizure. The second study aim was to assess for differences in bupropion ingestion characteristics (including toxicity) in younger children (aged up to 12 years) versus adolescents (aged 13–17).

Methods

This retrospective, observational cohort study was drawn from a database of bupropion ingestions presenting to a single toxicology service during an 8-year period (2011–2018). Patients were identified via a search of the medical toxicology service logs. The study service encompasses 20 hospitals in Northern California. The study was approved by the institutional review board.

Data was abstracted on pre-designed data abstraction sheets and subsequently entered into a Microsoft Excel spreadsheet. Prior to abstraction, the reviewer received a standardized training in systematic chart review. Following abstraction, 10% of records were abstracted by a second reviewer to ensure accuracy of abstraction and assess inter-rater reliability.

The study's analytic plan was set up to align with the project's twin aims of (1) examining bupropion ingestion in the overall pediatric population and (2) assessing for toxicity differences between older (teenaged) and younger age groups. The first part of the analysis consisted largely of descriptive summary of pediatric bupropion ingestion as assessed over all pediatric cases. The second part of the analysis focused on the comparison of characteristics and predictors of seizure between the study's two age groups: adolescents and younger patients. The cutoff of 13 years of age to characterize "older" pediatric patients was made based on both clinical experience and existing bupropion-exposure literature [1]. The older age group, therefore, encompassed patients age 13 through 17 years, inclusive.

All analysis was performed with Stata (version 15.1, StataCorp, College Station, TX). Significance was defined at the $p < 0.05$ level.

Categorical variables were reported as proportions with binominal exact 95% confidence intervals (CIs). Assessment of association between categorical variables was performed with chi-square testing or Fisher's exact test, as appropriate. Among the major categorical variables of interest were the study's main clinical endpoints: (1) any seizure, either prehospital or in the hospital, (2) delayed seizure, which was defined as a seizure occurring at least 6 hours after hospital arrival, and (3) a composite endpoint of seizure, hypotension, or need for endotracheal intubation. Tachycardia was defined as any heart rate exceeding the upper limit of normal per age, as defined in the Pediatric Advanced Life Support (PALS) guidelines. "Sustained tachycardia" refers to persistent elevation in (age-corrected) heart rate for at least 2 hours after ED arrival.

Continuous variables, all of which were demonstrated by the Shapiro-Wilk testing to have non-normal distribution, were reported as medians and interquartile ranges (IQRs). Associations involving continuous variables were assessed using the non-parametric Kruskal-Wallis testing or its extension for non-parametric trend testing [10].

For dichotomous variables (e.g., occurrence of seizure) with demonstrated univariate associations of statistical significance, relative risks were estimated as odds ratios (ORs, with 95% CIs) using logistic regression. Study planning called for multivariate logistic regression modeling to allow investigation of predictor variables while simultaneously adjusting for other factors. Logistic regression model calibration was tested using the Hosmer-Lemeshow goodness-of-fit test. Model discrimination was assessed with the *c* statistic. For non-nested models, logistic regression models' comparative performance was assessed using the Akaike and Schwarz Bayesian information criteria (BIC) calculation in which a lower BIC indicates a preferable model [11].

Results

The study included 80 pediatric cases of known or probable bupropion ingestion. The median annual case number was 8 (IQR 7–14), and the overall case numbers did not significantly change over the study period (p for trend, 0.251). For the overall group, the median age (IQR) in years was 14 (2.4–16). Non-adolescents accounted for 31 (38.8%) of the cases whereas the remaining 49 cases (61.3%) were adolescents. Within the group of non-adolescents, the median (IQR) age was 2.1 (1.8–2.6) years, whereas the median age of the adolescents was 15 (IQR 14–16) years. Compared with non-adolescents, adolescents were much more likely to be female (OR 3.5; 95% CI 1.3–8.9), have co-ingestants (OR 3.4; 95% CI 1.2–9.7), and were suicidal. The non-adolescents were much more likely to have an accidental ingestion (100% vs. 10.2%; $p < 0.001$). Other exposure characteristics of the overall group are shown in Table 1.

Assessment for possible trends in case numbers over time yielded differing results for the two age groups. For cases in the teenage age group, findings mirrored the overall study result of no change in case numbers over the study's 8 years. For the younger age group, though, case numbers trended significantly upwards over the course of the study, from just a single annual case (in the first 2 years of the study) to 9 annual cases the last full year (2017) of data collection.

Tachycardia on arrival in the emergency department was present in 42 (52.5%) of all cases. Children under 13 were much less likely to be tachycardic on arrival in the emergency department or have sustained tachycardia (19.4% and 29.0%, respectively), compared with adolescents (73.5% and 71.4%, respectively ($p < 0.001$ for both; OR 11.5 (95% CI 3.9–34.4) and 6.1 (95% CI 2.3–16.5), respectively)). Altered mental status was also more likely to be documented in older children compared with younger children (38.8% vs. 6.5%, respectively; $p = 0.001$). There was no difference in the rates of hypotension between the two groups.

Seizures occurred in 21/80 (26.3%) cases. Adolescents were more likely to have a seizure than non-adolescents (40.8% vs. 3.2%; $p < 0.001$; OR 20.1 (95% CI 2.6–164.3)). Prehospital seizures were more likely to occur in adolescents compared with non-adolescents (11/49; 22.5% vs. 1/31; 3.2%; $p = 0.024$; OR 8.7 (95% CI 1.1–71.1)). Multiple seizures occurred in 12 (15%) of cases. All of these cases were in adolescents (12/49; 25.5%). Seizures were more common with the XL preparation compared with the SR or ER preparation. The reported OR for bupropion formulation is thus interpreted as indicating an approximately 3.4-fold increase in seizure odds in moving from IR to SR, and another 3.4-fold increase in seizure odds characterizing XL to SR/ER (Table 2). A total of 6 (12.2%) adolescents had seizures occurring beyond 2 h after arrival. A single patient had seizures occurring more than

Table 1 Overall characteristics of ingestions, with p for comparison between age groups.

Variable	Overall ($N = 80$)	Age < 13 ($N = 31$)	Adolescents ($N = 49$)	p
Proportion female	48 (60%)	13 (41.9%)	35 (71.4%)	*0.009*
Drug formulation ingested				*0.394*
IR	5	3	2	
SR or ER (twice-daily form)	24	7	17	
XL (once-daily form)	44	17	27	
Unknown	7	4	3	
Unintentional ingestion	36 (45.0%)	31 (100%)	5 (10.2%)	*< 0.001*
Known time of ingestion	63 (78.9%)	28 (90.3%)	35 (71.4%)	*0.053*
Median (IQR) ingestion-to-ED time in minutes	93 (IQR 52–244)	61 (39–103)	139 (67–399)	*0.002*
Known ingestion quantity	59 (73.8%)	24 (77.1%)	35 (71.4%)	*0.553*
Median (IQR) grams ingested	0.6 (0.225–2.0)	0.175 (0.15–0.3)	1.5 (0.7–2.7)	*0.0001*
Any co-ingestants**	28 (35%)	6 (19.4%)	22 (44.9%)	*0.02*

IQR interquartile range

**Specific co-ingestants are recorded in the supplementary appendix

Table 2 Univariate analyses of factors associated with seizure occurrence in the overall group of cases ($N = 80$).

Variable	No seizure ($N = 59$)	Seizure ($N = 21$)	p	Relative risk (95% CI)*
Bupropion formulation			0.026	OR 3.4 (1.1–10.5)**
IR	5 (8.5%)	0 (0%)		
SR or ER	20 (33.9%)	4 (19.1%)		
XL	28 (47.5%)	16 (76.2%)		
Unknown	6 (10.2%)	1 (4.8%)		
Ingested gram median, interquartile range (IQR); known $N = 59$	0.425 (IQR 0.15-1.375)	2.3 (1.2-4.5)	0.016	OR 2.4 (1.3–4.3)
Emergency Department (ED) arrival tachycardia	23 (39.0%)	19 (90.5%)	< 0.001	OR 14.9 (3.2–69.9)
ED arrival altered mental status	7 (11.9%)	14 (66.7%)	< 0.001	OR 14.9 (4.5–49.4)
Sustained tachycardia	25 (42.4%)	19 (90.5%)	< 0.001	OR 12.9 (2.8–60.6)

*Relative risk as univariate odds ratio (OR) with its 95% confidence interval (CI)

**OR for bupropion formulation represents incremental seizure odds moving from IR to SR/ER to XL formulations

6 hours after presentation. That case was a 15-year old who ingested an unknown quantity of bupropion XL. This patient presented to the emergency department 1.8 hours after ingestion and had a first seizure 8.5 hours after presentation.

Only one non-adolescent had a seizure. This case involved a 2-year old who had ingested 300 mg of XL bupropion. The patient presented approximately 5 hours after ingestion, following a prehospital seizure.

Tachycardia on arrival in the emergency department was highly associated with seizures (OR 7.1; 95% CI 1.2–43.1). Similarly, documentation of altered mental status on arrival in the emergency department was highly associated with the development of a seizure (OR 8.6 95% CI 2.3–32.6).

The pre-specified composite endpoint of any seizure, endotracheal intubation, or hypotension did not serve to capture many bupropion-toxic patients who were not already captured by the seizure endpoint. In fact, only one patient met the composite endpoint without also meeting the seizure endpoint. Therefore, to maintain simplicity in endpoint analysis, the univariate p for adolescents' higher incidence of the composite endpoint is reported here ($p < 0.001$), but this endpoint was not evaluated in further analysis.

Among the six (7.5%) cases requiring endotracheal intubation, all were in adolescents. Hospital admission was more common in adolescents compared with non-adolescents (65.3% vs. 35.5%; $p = 0.009$; OR 3.4 (95% CI 1.3–8.8)). The median (IQR) length of stay was significantly longer in adolescents compared with non-adolescents (31.1 (15.6–58.5) vs. 9.5 (3.8–14.6) h; $p = 0.0001$)).

None of the patients in either age group died. No cases returned with unexpected visits related to the index ED visit (i.e., no cases of delayed post-discharge bupropion complications were seen). For all of these outcomes with an incidence of 0 of 80 cases, the one-sided 97.5% CI for the 0% point estimate was 0–4.5% (Table 3).

The quantity ingested was known in 59 of 80 cases (73.8%). For each additional gram of bupropion ingested, the odds of a seizure increased by 2.3 (95% CI 1.1–4.9).

Discussion

This manuscript evaluated bupropion exposures in younger and older children. Toxicity was much more common in older children compared with younger children. In addition, severe toxicity, including tachycardia and seizures, was much more commonly encountered in older, rather than in younger children.

A 14-year review of nationwide (USA) data for patients aged 13 through adulthood with intentional abuse for psychoactive effects found that use of bupropion generally rose through 2000–2012, with a leveling in cases in 2013 [12]. In the current study, there was no statistically significant trend upwards in bupropion case numbers in adolescents, but this may have been due to a mixture of intentional and non-intentional cases in adolescents. The current study's analysis period did see an increase in the number of bupropion cases seen in younger pediatric patients. One possible explanation for this finding is bupropion's increasing availability due to more frequent prescription. Referral bias is another possibility, but given the nature of the system where the study was performed, we feel that is less likely.

In a national analysis of adolescents and adults with non-accidental bupropion exposure, tachycardia occurred in half of the cases and one-third seized [12]. This study had results that were similar in some respects, but the current data also added a juxtaposition of teenage versus younger children. In older children, the current study found a high rate of ED arrival tachycardia—nearly 3 out of 4 adolescents—but in the under-13 age group, the finding was present in only 1 in 5 cases. The 11-fold increase in odds of ED arrival tachycardia was not the only important physical finding distinguishing teenage from younger cases with bupropion exposure; both

Table 3 Seizure-related findings, with *p* for comparison between age groups.

Variable	Overall (*N* = 80)	Age < 13 (*N* = 31)	Teenage (*N* = 49)	*p*
Any seizure	21 (26.3%)	1 (3.2%)	20 (40.8%)	*< 0.001*
Seizure prior to ED* arrival	12 (15%)	1 (3.2%)	11 (22.5%)	*0.024*
ED arrival-to-seizure time (minutes)*	89 (IQR 60–183)	No ED seizures	89 (IQR 60–183)	
Initial seizure > 2 h after ED arrival	6 (7.5%)	No ED seizures	6 (12.2%)	
Multiple seizures	12 (15%)	0 (0%)	12 (24.5%)	*0.002*

**ED* Emergency Department

*Assessed for the 14 cases with seizure in hospital

sustained tachycardia and altered mental status were far more likely in the older children.

The ingestion characteristics portray a marked contrast between the under-13 and teenage groups. Compared with younger patients, adolescents were 3.5 times more likely female, 3.4 times more likely to have taken co-ingestants, and approximately 10 times more likely to have intentional exposures. Adolescents presented, on average, 68 minutes longer after bupropion ingestion, and ingestions involved 1350 mg more bupropion.

The ingestion characteristics' difference between younger and older children translated into differences in toxicity rates. This difference likely represents different reasons for ingestion. While the overall seizure rate in the current study of just over 1 in 4 cases is not inconsistent with the broader adult and teenage bupropion literature [12], the seizure rates were near zero (just 1 of 31 cases) in this data set's under-13 group. In this study, over 95% of post-bupropion seizures occurred in patients at least 13 years of age.

The composite endpoint generated during study planning included seizure, endotracheal intubation, or hypotension. It was thought that the mixed-outcome endpoint would potentially capture multiple forms of bupropion toxicity in children. In fact, with seizures seen in just over a quarter of all cases (21 of overall *N* = 80) and only one additional case picked up by application of the composite endpoint, there was no need to add multifaceted composite endpoints to capture instances of significant bupropion toxicity. The low rate of death is consistent with that previously reported in the literature [13].

The low rates of non-seizure outcome endpoints (e.g., death) led to the remaining analysis' focus on the seizure endpoint. All seizures were counted in this endpoint, but it is noteworthy that in nearly a third of cases with seizure (6 of 20 in-hospital seizures), the initial seizure occurred after at least 2 h in the ED. Study numbers were insufficient to explore specific predictors of delayed versus early seizures, so further work in this arena will be necessary to generate precise guidelines for required observation periods.

Univariate predictors of seizure that were identified in this analysis allowed calculation of specific seizure risks attendant to these factors. It should be noted, however, that the low rate of seizures in the under-13 age group results in low precision for estimates in these cases.

It is possible that the higher bupropion-associated seizure rate seen in adolescents is attributable to co-ingestants. Some co-ingestants seen in the current study (see appendix) could be related to seizure activity. The overall rate of co-ingestant presence was just over 1 in 3 cases in the overall group, but as compared with the younger age group, teenage cases were more than three times as likely to have co-ingestants. Bupropion has toxicity synergism with certain co-ingestants such as cocaine (not known to be encountered in this study), so clinicians should consider the possibility of multiple-drug exposure when refractory complications are seen after bupropion use [13]. However, more likely, the higher rates of seizures in the older population likely represent a difference in intent (unintentional vs. intentional ingestion) and the inherent difference in dose consumed.

To the literature's well-established fact that bupropion-induced seizures are dose-related, the current data add a specific estimate for effect magnitude: each additional gram of bupropion increases seizure likelihood by 2.4-fold. Unfortunately, one of the study limitations is that there were insufficient data for robust exploration of non-linear associations between ingestion quantity and seizure.

Related to the quantity of ingested bupropion is the finding that different formulations of the drug were identified in univariate analysis to have differing seizure risks. Each incremental step toward a more sustained-release formulation (e.g., IR to SR) is associated with more than trebling of seizure risk (OR 3.4). The study was not powered to adjust for ingestion quantity while assessing the release-timing formulation, so definitive conclusions about the risks attendant to different formulations of bupropion could not be drawn from the current analysis.

Perhaps more compelling than the confirmation of dose-related seizure risk were the findings that either ED arrival tachycardia or ED arrival altered mental status (both had the same univariate OR) increased seizure risk nearly 15-fold. The estimates for risk associated with presentation tachycardia or altered mental status remained in multivariate modeling simultaneously adjusting for both of these physical findings and ingestion quantity.

The study is limited by its retrospective nature and reliance on the completeness and accuracy of data presented in the medical record. By relying on dichotomous outcomes (e.g., seizure or no seizure, intubation or no intubation), we feel we have minimized the effect of this limitation [14]. In addition, because comprehensive drug testing was not performed routinely, it is possible additional medications were ingested, or no bupropion was actually ingested. Lastly, overall, there were relatively few patients in this study, and very few non-adolescents who had seizures. While the findings are unlikely to be significantly altered by small numbers, the exact magnitude of this effect may be altered. In addition, we did not collect the weight of each of the pediatric patients, so it is impossible to determine the amount ingested on a milligram-per-kilogram basis.

Tachycardia as a risk factor for bupropion-associated seizure is well known, much of the available evidence focuses on adults [15]. This paper is one of the first to focus strictly on pediatrics and attempt to quantify this risk in pediatric patients. Unintentional ingestions in young children are rarely associated with significant toxicity. The predictors of the risk of seizure in adolescent patients include tachycardia and altered mental status, and are similar to that described in adult populations.

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Compliance with ethical standards

Conflicts of Interest The authors declare that they have no conflicts of interest.

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