




CLINICAL RESEARCH



Factors associated with seizure development after bupropion overdose: a review of the toxicology investigators consortium

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ABSTRACT

Background: Bupropion is an aminoketone antidepressant. A major concern in bupropion toxicity is seizure activity, which can occur up to 24 h from ingestion. It is difficult to predict which patients will have seizures. The purpose of this study is to identify clinical features associate with seizure after bupropion overdose.

Methods: We searched the Toxicology Investigators Consortium registry for a cases of poisoning by bupropion between January 1, 2014 and January 1, 2017 in patients aged 13–65. Demographic variables and clinical features were compared between patients who did and did not experience a seizure and presented as unadjusted odds ratios (OR). Multivariable logistic regression was used to calculate adjusted odds ratios (aOR) between clinical features and seizures.

Results: There were 256 cases of bupropion overdose remaining after inclusion/exclusion criteria were applied. Clinical features associated with seizure were QTc >500 (OR = 3.4, 95% CI: 1.3–8.8, $p=0.012$), tachycardia ($p > 140$) (OR = 1.9, 95% CI: 1–3.561, $p=0.05$), and age 13–18 years (2.4, 95% CI: 1.3–4.3, $p=0.005$). The mean QTc value for patients experiencing a seizure was 482 ms ($N=95$ IQR: 59 ms) versus 454 ms ($N=103$, IQR: 43) in patients who did not experience seizure, however, it was not possible to identify a QTc cutoff with sensitivity or specificity to predict seizures.

Conclusion: Based on our analysis of data from the ToxIC registry, age (13–18), tachycardia ($p > 140$) and QTc >500 ms are associated with seizures in bupropion overdose; however, a specific QTc value may not be a useful predictor of seizures.

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Background

Bupropion is an antidepressant medication that is commonly prescribed for seasonal affective disorder, smoking cessation, and weight loss [1]. It was initially marketed in 1986 with dosing recommendations of up to 600 mg/day, however, subsequent reports of seizures in a small population of bulimic patients [2] resulted in its complete withdrawal from the market [3]. Further studies indicated that doses <450 mg/day provided an appropriate safety margin [4], and the drug was later reintroduced in 1989 as an immediate-release formulation. In 1996 and 2003, sustained-release and extended release formulations allowed for once daily dosing [5]. While it is currently only FDA approved for adults, there are an increasing number of off-label pediatric prescriptions¹.

Bupropion is both structurally and biochemically unique among antidepressants. It is an aminoketone medication structurally related to cathinones [6]. Bupropion inhibits the reuptake of dopamine and norepinephrine, though the exact mechanism of its antidepressant effect is unclear. In contrast to many other antidepressant medications, bupropion does not inhibit serotonin reuptake [5,7] but may increase

serotonergic neuronal firing [8,9] and has been implicated as a cause of serotonergic toxicity [10–12].

When taken in excess, bupropion results in a number of physiologic and neurologic changes. Sinus tachycardia and agitation are common [13,14], as are ECG changes, such as QRS widening and QTc prolongation [15–18]; however, malignant dysrhythmias are rarely reported [13]. Seizures are common with suprathreshold doses and are likely dose related [19]. Seizures occur in 8–40% of bupropion overdoses, which may depend on the formulation ingested, population, and dose ingested [6,14,18–22]. A major concern for medical providers caring for patients who have overdosed on bupropion is that seizures can be significantly delayed and may occur as late as 24 h after ingestion [6,23].

It is difficult to predict which patients are at highest risk for seizure, and many bupropion overdose patients are admitted to hospital intensive care units for 24 h or more for close monitoring. The purpose of this study is to investigate whether there are clinical signs and symptoms which may help identify patients who are at greater risk of developing seizure activity after bupropion overdose.

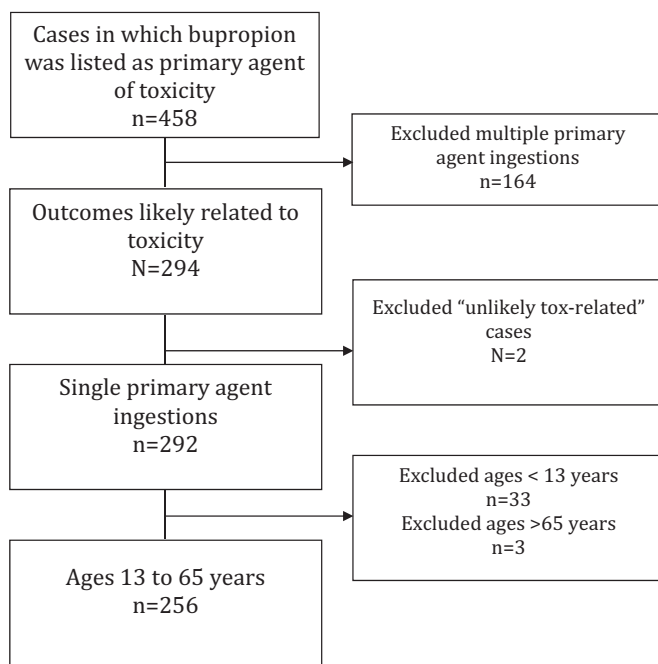


Figure 1. Inclusion and exclusion criteria.

Methods

Study design

The Toxicology Investigators Consortium (ToxIC) registry is a database of prospectively collected data from patients seen at the bedside by medical toxicologists. Deidentified patient data is entered in real-time at over 40 sites throughout the world [24,25]. Data are regularly reviewed by central monitoring by the American College of Medical Toxicology (ACMT) for completeness with directed questions to the ToxIC site investigators to fix any omissions and inconsistencies.

We performed a retrospective review of data collected and entered into the ToxIC registry between January 1, 2014 and January 1, 2017. This study was approved by the ACMT ToxIC research committee and participation in the ToxIC registry is approved by the Institutional Review Board at Oregon Health and Science University.

Inclusion/exclusion criteria

All cases involving patients who had bupropion exposure listed as a "primary agent" of toxicity were included for analysis. Patients were excluded from analysis if multiple agents were listed as a "primary agent" contributing to toxicity, the evaluating medical toxicologist deemed the patient's signs and symptoms to be "unlikely tox related," or patients were less than 13 years or greater than 66 years old. Cases involving co-ingestion of "secondary agents" were included for analysis, as "secondary agents" are not thought to be contributors to toxicity by evaluating toxicologists. Criteria are summarized in Figure 1.

Table 1. Demographics of patient population.

	N (%)
Total	256 (100)
Seizure	
Yes	92 (36)
No	164 (64)
Race	
Caucasian	134 (52)
Non-Caucasian	27 (11)
Unknown/not-identified	95 (37)
Age	
13–18	104 (41)
19–65	152 (59)
Gender	
Male	96 (38)
Female	160 (63)
Chronicity	
Acute	179 (70)
Acute on Chronic	63 (25)
Chronic/Unknown	14 (5)
Type of ingestion	
Intentional exposure	236 (92)
Unintentional exposure	15 (6)
Unknown	5 (2)

N: number; %: percentage of total.

Statistical analysis

Demographic variables and clinical features were compared between patients who did and did not experience a seizure and are presented as unadjusted odds ratios (OR) with corresponding 95% confidence intervals (CI). Multivariable logistic regression was used to calculate adjusted odds ratios (aOR) between clinical features and seizures and are presented as an OR with corresponding 95% CI.

QTc data were cleaned and any values recorded in seconds were converted to milliseconds (e.g., 0.52 s was converted to 520 ms), numbers that are not within human normal (e.g., 11.5 ms or 3538 ms) and cases with non-numerical terms ("long") were excluded. If more than one value was recorded, the higher value was used.

QTc values between patients who did and did not have a seizure during their clinical course were compared using independent *t*-tests. Receiver operator characteristics of QTc value in the setting of seizure were calculated and are reported as area under the curve (AUC).

Excluding QTc receiver operator curve (ROC) calculations, all statistics analysis was performed using SPSS v 25 (IBM, Armonk, NY). The QTc ROC was produced using SPSS v 26 (IBM, Armonk, NY).

Results

There were 458 cases that met inclusion criteria, with a total of 202 cases excluded due to multiple "primary substances" ($n = 164$), "unlikely tox-related" ($n = 2$), age < 13 years ($n = 33$), age > 65 years ($n = 3$), leaving 256 cases for review. Among the remaining cases, 36% ($n = 92$) experienced a seizure. The majority of patients were Caucasian (52%), female (63%), were aged 19–65 years (59%), and had an acute (70%) and intentional (92%) exposure (Table 1).

Clinical characteristics associated with seizure activity in bupropion ingestions in the initial evaluation were QTc > 500 (OR = 3.7, 95% CI: 1.6–8.4), QRS > 120 (OR = 7.6, 95% CI:

Table 2. Characteristics of patients who did and did not experience seizure.

	Total	Seizure (n = 92)	No seizure (n = 164)	OR ^a	95% CI
Cardiovascular					
QTc > 500	28	18	10	3.7	1.6–8.4
QRS > 120	10	8	2	7.6	1.6–36.7
Tachycardia	79	38	41	2.1	1.2–3.6
Hypotension	10	9	1	17.5	2.2–140.1
CNS					
Agitation	73	25	48	0.9	0.5–1.6
CNS depression	39	19	20	1.8	0.9–3.7
Hyperreflexia	58	21	37	1.0	0.5–1.8
Demographics					
Male sex	95	34	61	1.0	0.6–1.6
Age 13–18	104	50	54	2.4	1.4–4.0

OR: odds ratio; CI: confidence interval, CNS: central nervous system.

^aUnadjusted OR.

1.6–36.7), tachycardia ($p > 140$) (OR = 2.1, 95% CI: 1.2–3.6), hypotension (OR = 17.5, 95% CI: 2.2–140.1) and age (13–18) (OR = 2.4, 95% CI: 1.4–4.0). Sex, agitation, central nervous system (CNS) depression, and hyperreflexia were not associated with seizure (Table 2). After binary logistic regression, QTc > 500 (OR = 3.4, 95% CI: 1.3–8.8, $p = 0.012$) and age 13–18 years (2.4, 95% CI: 1.3–4.3, $p = 0.005$) remained statistically significant, while tachycardia ($p > 140$) bordered statistical significance (OR = 1.9, 95% CI: 1–3.561, $p = 0.05$). (Table 3)

To investigate QTc value as a possible predictor of seizure activity, we isolated cases where a specific QTc value was known. One hundred and sixty-five out of 256 total cases had a documented QTc value. Five were excluded because of inaccurate values (4 physiologically impossible; 1 approximation). Of the remaining 160 cases, 57 (31%) had a seizure, therefore, of the 92 cases resulting in seizure, 61.9% had available QTc data. Of the 162 cases that did not result in seizure, 103 cases had available QTc data (63.5%).

The mean QTc value for patients experiencing a seizure was 482 ms ($N = 95$ IQR: 59 ms) with a total range of 389–681 ms. By comparison, patients who did not experience seizures and had a mean QTc of 454 ms ($N = 103$, IQR: 43) and a total range of 252–624 ms (Figure 2). The difference in QTc values between patients who seized and those who did not seize was statistically significant ($p < 0.000$), however, it was not possible to identify a QTc cutoff with sensitivity or specificity to predict seizures. Overall, QTc as a lone factor appeared to be a poor predictor of seizures in isolation (AUROC 0.67) (Figure 3).

Discussion

In this study, we found a 36% prevalence of seizure after bupropion overdose, which is consistent with previously reported rates [6,19]. Additionally QTc prolongation (QTc > 500 ms), and age 13–18 years were all significantly associated with the development of seizures, while tachycardia ($p > 140$ bpm) approached statistical significance.

Tachycardia is a well-documented physiological response in bupropion overdose [18,19,21,22] and has been cited as the most common cardiovascular side effect of bupropion toxicity [15]. In this study, we found 31% of our cases had

Table 3. Adjusted odds ratios for predictors of seizure.

	Total	Seizure (n = 92)	No seizure (n = 164)	OR ^a	95% CI	p-value
Cardiovascular						
QTc > 500	28	18	10	3.4	1.3–8.8	0.012
QRS > 120	10	8	2	4.9	0.8–28.6	0.079
Tachycardia	79	38	41	1.9	1.0–3.6	0.05
Hypotension	10	9	1	6.3	0.7–56.9	0.1
CNS						
Agitation	73	25	48	0.7	0.4–1.4	0.3
CNS depression	39	19	20	1.0	0.4–2.3	1.0
Hyperreflexia	58	21	37	0.9	0.5–1.9	0.9
Demographics						
Male sex	95	34	61	1.2	0.6–2.2	0.6
Age 13–18	104	50	54	2.4	1.3–4.3	0.005

^aOR: adjusted odds ratio; CI: confidence interval, CNS: central nervous system.

tachycardia. The ability to predict seizure using heart rate was documented by Starr, who found tachycardia (>100 bpm) to be 91.2% sensitive in predicting seizure and have a 92.9% negative predictive value [6]. The ToxIC registry defines tachycardia as HR >140 bpm, making a direct comparison to Starr's data difficult. Nevertheless, current literature indicates that there is a clear association between tachycardia and seizures [6,18,21,22].

QTc prolongation in the setting of bupropion overdose has been documented previously [15–17]. There is *in vitro* evidence that bupropion is a weak I_{kr} channel blocker [15]. Additionally, hypokalemia, which may result in QTc prolongation, has also been documented in bupropion toxicity [26]. Bupropion antagonizes cardiac myocyte gap-junctions, which also plays a role in the QTc prolongation [15]. Previous authors have pointed out that many EKG machines use Bazett's formula to calculate QTc which is known to overestimate QTc prolongation in the setting of tachycardia. Therefore, it is possible that the tachycardia that is present in many bupropion overdoses results a significant overestimation of the QTc [16]. Despite this, in our analysis, both QTc > 500 ms and tachycardia > 140 bpm remained statistically significant after logistic regression. It should be noted that despite our data demonstrating a statistically significant increase in QTc prolongation among patients who experienced seizure, the clinical relevance of this prolongation is unclear. Ventricular dysrhythmias, which represent the most severe complication of QTc prolongation, are an uncommon occurrence in bupropion overdose [17,18]. In our data set, only one of our 28 (3.6%) patients with QTc prolongation greater than 500 ms had a ventricular dysrhythmia.

Lastly, we found age (13–18 years) to be strongly associated with seizure, with 47% of patients in this age group experiencing a seizure. This is higher than reported in previous studies of similar age groups [22,27,28]. Both Sheridan and Overberg documented a higher rate of severe physiological effects with regards to bupropion ingestion in this age group when compared to other antidepressants including SSRIs and tricyclic antidepressants. However, rates of seizure following bupropion overdose in these studies did not significantly differ from current literature (30.7% and 27%, respectively) [27,28]. Interestingly, in our data set, 82% of cases in the 13–18 age group were a result of intentional self-harm attempts versus 63% of adult ingestions, which

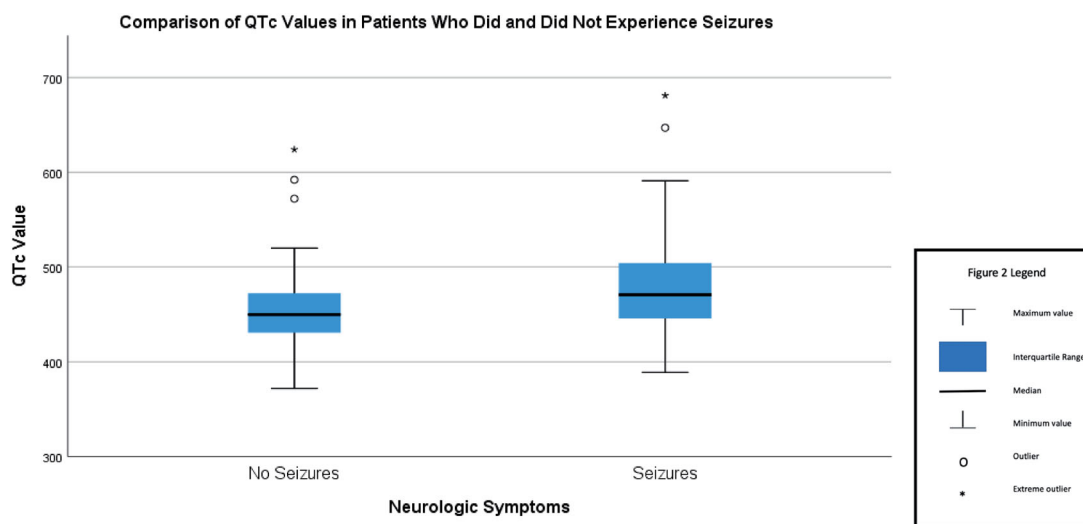


Figure 2. Comparison of QTc values in patients who did and did not experience seizures.

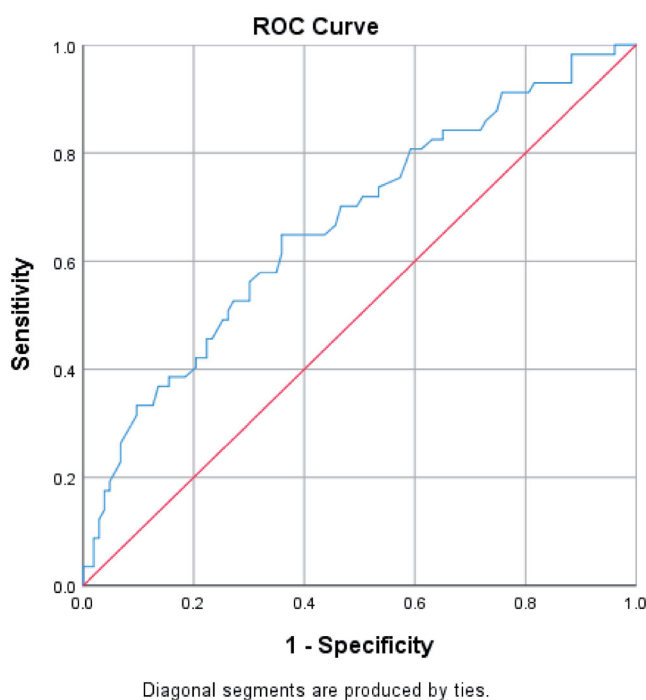


Figure 3. Receiver operator curve of QTc for seizures in bupropion overdose.

may indicate that intent plays a role in whether patients experience seizure activity.

Other studies have documented agitation as a key clinical feature that is potentially useful in predicting seizure [20]. Our data do not support this, and we found no statistical correlation between agitation and seizure.

Limitations

A strength of the ToxIC registry is that each patient entered into the database was evaluated at by a trained specialist in Medical Toxicology; however, there are a number of limitations inherent in this type of database.

While the ToxIC database contains a number of relevant clinical parameters to analyze there are often important data

absent. For instance, the timeline of events is not recorded in the registry data. Therefore, we are unable to determine if patients had tachycardia or QTc prolongation before or after a seizure, making these parameters difficult to suggest as predictors of seizure activity and limiting our ability to draw conclusions. Similarly, evaluation of clinical features may be limited to the time at which the patient was evaluated. For instance, a patient may have been agitated prior to evaluation by the toxicologist, but at the time of evaluation may have been sedated. This could potentially affect our analysis of agitation and seizure. A prospective analysis would better characterize relevant clinical features and their ability to predict seizure although as discussed by Offerman et al., prospective research on this topic is limited by a low number of cases [27].

Additionally, the dose ingested is rarely entered, which represents an important factor in comparing patients who seized to patients who did not.

Patients entered into the ToxIC registry have been seen at the bedside by medical toxicologists. Inpatient hospital teams and emergency department physicians may be more likely to consult medical toxicologists to assist with severe poisonings than with mild or moderate poisonings. Therefore, cases entered into the database may represent a more severely poisoned subset of patients, and selection bias likely exists in the registry data although the extent to which bias is present is not known. Overall, patients in our data set experienced seizures at rates similar to previous studies with the exception of patients aged 13–18 who seized at rates higher than previously reported in the literature.

While all the patients entered into the ToxIC database in this study were reported to have ingested bupropion, in the majority of cases, there is no confirmatory testing available and exposure was largely based on history, clinical exam, and clinician expertise.

Although we attempted to select ingestions where the toxidrome experienced by the patient was entirely related to bupropion alone by eliminating cases involving any other "primary agents," we did not eliminate cases involving "secondary agents" – as these are co-ingestants that the

evaluating medical toxicologist did not feel contributed to the toxicity of the patient.

Lastly, while it is requested that institutions participating the ToxIC registry enter all patients seen in consult into the database, there may be some variability between institutions that affects which patients are actually logged into the registry.

Conclusions

While this study is limited by our ability to interpret the timeline of events for each case, we demonstrate that QTc prolongation (QTc >500), tachycardia ($p > 140$), and age (13–18) are associated with seizure in bupropion overdose. Our data suggest that QTc values alone are unlikely to be helpful in predicting seizure. Further studies should aim to chronologically characterize clinical features in bupropion toxicity that predict seizures.

Disclosure statement

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

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