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ORIGINAL ARTICLE

Single-Agent Bupropion Exposures: Clinical Characteristics and an Atypical Cause of Serotonin Toxicity

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Abstract

Introduction Bupropion is the only Food and Drug Administration–approved synthetic cathinone. It increases the release of norepinephrine in the locus coeruleus and dorsal raphe nucleus, causing an increase in the frequency of serotonergic neuron firing. The diagnosis of serotonin toxicity (ST) from bupropion poisoning is controversial due to the lack of direct serotonergic activity. Nonetheless, there is one documented report of ST after single-agent bupropion overdose and multiple reports describing polypharmacy overdoses where bupropion may have contributed to ST.

Methods This is a retrospective analysis of data collected by the Toxicology Investigators Consortium (ToxIC), a prospective multi-center toxico-surveillance and research network registry, from 2014 to 2017. Cases were identified if ST was a clinical effect and bupropion was the single agent listed. Data is presented descriptively.

Results Of the 266 recorded single bupropion overdoses, the most common symptoms were seizures (47.1%), tachycardia (greater than 140 bpm) (33.9%), agitation (31.7%), toxic psychosis (20.4%), and myoclonus/tremor/hyperreflexia (19%). Benzodiazepines were the most common therapy (69.2%). Thirteen patients (5.9%) were diagnosed with ST by a medical toxicologist.

Conclusion Bupropion overdose is primarily associated with seizures, tachycardia, and agitation; bupropion may be an atypical cause of serotonin toxicity.

Keywords Bupropion · Abuse · Single-agent · Characteristics · Serotonin syndrome

Introduction

Bupropion, a monocyclic phenylethylamine antidepressant, is the only Food and Drug Administration–approved synthetic cathinone. It is labeled for use as monotherapy or as an adjunctive treatment for major depressive disorder, seasonal affective disorder, and smoking cessation. Bupropion exposures reported to the National Poison Data System (NPDS) increased by 75% from 2000 to 2013 [1], and even though it is considered an effective medication [2], it does have well-documented adverse effects such as seizures. The risk of seizure with the maximum daily therapeutic dose of 450 mg is 0.35–0.44% (similar to selective serotonin reuptake inhibitor (SSRI) antidepressants) [3], but increases significantly to 20–33% in overdose. [1, 4].

Bupropion also causes cardiac toxicity that results in a widened QRS interval, QTc prolongation, and hypotension [5]. The QRS widening is refractory to sodium bicarbonate administration as it is not sodium channel mediated, but rather is due to reduced cardiac intercellular coupling from gap-junction antagonism [6]. Additionally, tremors, lethargy, agitation, dry mouth, hallucinations, nausea and vomiting, confusion, dizziness, tachycardia, and conduction delays have also been reported [1, 4]. Non-epileptic myoclonus was also mentioned as a side effect in one case report [7].

The exact mechanism of action of bupropion is not completely understood. One theory is that bupropion works through norepinephrine (NE) and dopamine (DA) reuptake

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inhibition; however, the affinity for these reuptake transporters is not in the range of therapeutic use for antidepressants [8, 9]. Alternatively, bupropion has been shown to increase the release of NE, potentially through vesicular monoamine transporter-2 (VMAT-2) activation [2, 10] in the locus coeruleus and dorsal raphe nucleus [11–14]. This VMAT-2 activation is similar to the mechanism of action of amphetamines [15]. While controversial, concern exists as to whether bupropion has the ability to affect the activity of serotonergic neurons and lead to the development of serotonin toxicity [16, 17].

The objective of this study was to identify the clinical characteristics of single-agent bupropion exposures and to determine the prevalence of ST among these patients.

Methods

This study was a retrospective analysis of data collected by the American College of Medical Toxicology (ACMT) Toxicology Investigators Consortium (ToxIC), a prospective multi-center toxico-surveillance and research network registry comprised of physicians specifically qualified in the field of medical toxicology from 50 participating sites in the United States, Canada, Israel, and Thailand [18, 19]. Cases were included in the registry by a medical toxicologist after a bedside evaluation. This study was approved by the ToxIC Research Board and was determined to be exempt from review by our Institutional Review Board (IRB).

The electronic database was queried for all cases involving a bupropion ingestion from the beginning of 1/1/2015 through 12/31/2017. Only single-agent exposures were included for analysis. As an internal quality check, particularly important in the absence of definitive toxicologic testing, medical toxicologists are asked whether they feel the signs and symptoms are "TOX Related?", with answer options: "Most Likely", "Unlikely", and "Unknown". All cases where "Unlikely" was selected were excluded from analysis and "Unknown" cases were analyzed as missing data. Clinical outcomes and treatment information were recorded for each case. Cases were categorized as ST if that clinical outcome was selected in the "Toxidrome" category. Participating sites have the option to enter "None" under toxidrome or select all toxidromes that apply to a specific patient.

Statistics

Categorical variables were described using percentages and 95% confidence intervals (95% CIs). Continuous variables were described using medians and interquartile ranges. Across the data set, 5.4% of data points were missing and the pattern of these missing values was consistent with missing completely at random mechanisms ($p = 0.6$). Missing data were imputed using fully conditional specification, an iterative method that relies on Markov Chain Monte Carlo procedures. Analyses were conducted using SPSS v25 (IBM; Armonk, NY).

Results

In total, there were 266 single-agent bupropion exposures reported to ToxIC during the study period. The number of single-agent bupropion cases reported per 1000 ToxIC registry cases for each year was 9.9, 9.8, and 13.5 for 2015–2017, respectively [19]. Of these, 45 (17%) were excluded from analysis either because they did not have any signs or symptoms, or had signs and symptoms determined to be unrelated to their toxic exposure by the evaluating medical toxicologist. (Fig. 1) The remaining 221 cases were included in our analysis.

The demographic characteristics are described in Table 1. Of the included cases, 64% were female, 69% were white, 15% were Hispanic, and the median age was 19 years old (IQR = 15–30). The exposure was acute in 68% of the cases, acute-on-chronic in 29%, and chronic in 4%. Self-harm accounted for 64% of the cases. We were unable to accurately assess dosage or bupropion formulation as this dosage was not available in 84% cases and only 3% of cases specified the formulation. One patient insufflated the bupropion, the remaining 220 exposures were ingestions. One death was reported.

The predominant symptoms reported in these patients were seizures (47%), followed by tachycardia greater than 140 bpm (34%), agitation (32%), toxic psychosis (20.4%), prolonged QTc (15.8%), tremor/myoclonus/clonus/hyperreflexia (15.8%), central nervous system (CNS) depression (15.8%), and hallucinations (15.4%) (Table 2). Only 3.6% of patients developed a QRS longer than 120 ms. In 22.2% of cases, the medical toxicologist believed that the patient was exhibiting a sympathomimetic toxidrome and in 2.7% of patients, an anticholinergic toxidrome was identified.

Benzodiazepines were utilized for treatment in 69.2% of the cases. Likewise, sodium bicarbonate and lipid emulsion treatments, which are specifically used in severe bupropion toxicity, were used infrequently (4.5% and 1.8% respectively). Intubation was performed in 12.2% of the cases. ST was reported in 13 (5.9%) patients. There was one death reported; however, it was not in patients diagnosed with ST.

Discussion

In this investigation of bupropion overdoses reported to the ToxIC registry, we observed a 36% increase in single-agent bupropion cases per 1000 from 2015 to 2017. The majority of

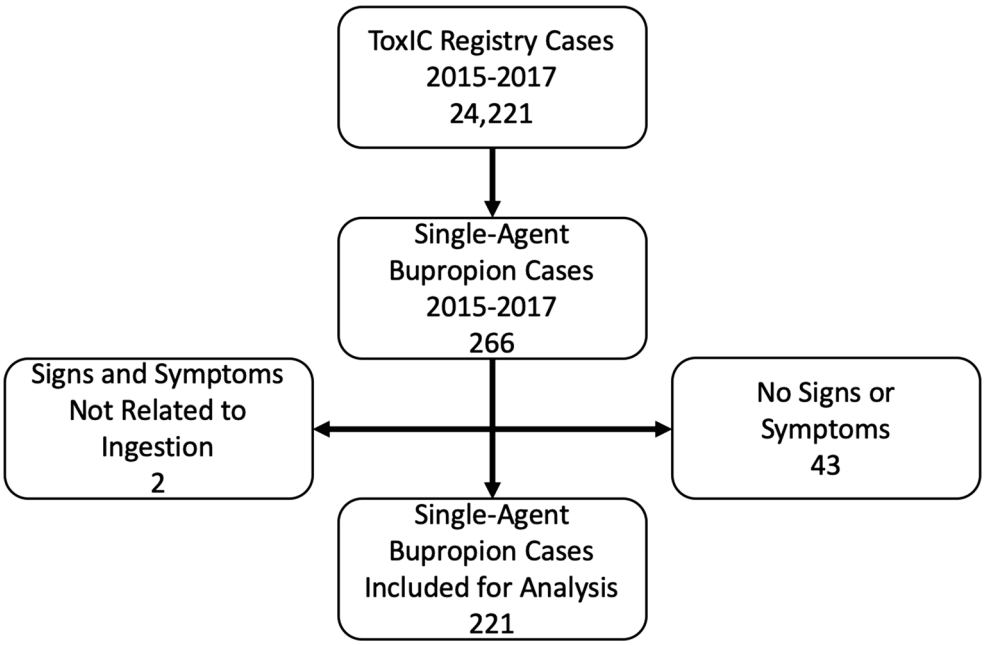

Fig. 1 Flow chart of bupropion overdoses reported to the Toxicology Investigators Consortium

exposures were ingestions with suicidal intent. However, 9% of the exposures were for abuse or misuse, likely because bupropion is a cathinone and acts as a stimulant which produces a cocaine-like "high" [20]. Among the abuse or misuse cases, 33% were for abuse with the intent to become high or intoxicated with their own medication or as use of medication that was not prescribed to the patient. This is higher than the rate of abuse found by Stassinos et al. [1] who found that 3.3% of the cases involving bupropion overdoses reported to the NPDS over a 14-year period were related to bupropion abuse. This difference may be related to the difference in coded data or a higher rate of abuse during the study period. Furthermore, in comparison with prior studies that included multiple-agent ingestions, we only evaluated single-agent bupropion ingestions.

The most common clinical effect in our population was seizures (47%). This is in contrast to Stassinos et al. [1], Shepherd et al. [21], and Spiller et al. [4] all of whom reported that tachycardia was the most common adverse effect. Stassinos et al. found a similar rate of seizures of 34%, while Shepherd et al. and Spiller et al. both found lower rates of seizures, with 11% and 20%, respectively. Our population exhibited tachycardia in 34% of the cases, whereas Stassinos et al., Shepherd et al., and Spiller et al. found tachycardia in 57%, 23%, and 43% of cases, respectively. In our study, the percentage of patients with tachycardia is likely underreported, as the prior studies utilized the NPDS definition of tachycardia (heart rate over 100 beats per minute), [22] whereas the ToxIC registry defines tachycardia as a heart rate over 140 beats per minute. As with the other studies, agitation, CNS depression, and hallucinations were all prominent clinical effects, with Shepherd et al. describing hallucinations as the sensation of formication [21]. Although the clinical endpoint of "hallucinations" is not further defined in the ToxIC registry data collection instrument, the assessment of clinical features was performed by medical toxicologists at the bedside and therefore should be a reliable field.

ST was diagnosed in 6% of the patients. Bupropion is not known to have direct serotonergic agonism [23] nor does it bind the serotonin reuptake transporter with sufficient affinity to cause reuptake inhibition [2]. However, ST has been reported when bupropion is used in combination with other serotonergic agents, such as SSRIs [24, 25], and in a case report that described ST after a single-agent overdose [16]. A rebuttal article in the same issue argued the implausibility of this finding as bupropion fails to meet the first of the Hunter Criteria [26], specifically that the xenobiotic be serotonergic [17]. Despite this fact, bedside evaluations of single-agent bupropion overdoses by medical toxicologists have resulted in diagnoses of ST.

The effect of bupropion on serotonin receptors is as controversial as its mechanism of action [4, 17]. Despite a lack of direct action, its effect on NE release leads to an increase in the frequency of serotoninergic neuronal firing, likely by direct agonism, without regulation by 5-HT_{1A} attenuation [11–14]. Therefore, although it has no direct effect on serotonin, it does appear to have an indirect effect on serotonergic cells, which may be the mechanism of ST.

Limitations

The limitations of this study include the post hoc analysis of previously prospectively collected data and the depth and limited number of variables recorded in the registry. We were

Table 1 Demographic characteristics.

	Full sample	Serotonin toxicity
Age, M (IQR)	19 (15–30)	17 (15–25)
Gender, *N* (%, 95% CI)		
Male	78 (35.3; 29.2–41.8)	6 (46.2; 22.1–71.7)
Female	142 (64.3; 57.8–70.4)	7 (53.8; 28.3–77.9)
Transgender	1 (0.5; 0–2.1)	0 (0; 0–17.3)
Race *N*, (%, 95% CI)		
Native American/American Indian	8 (3.6; 1.7–6.7)	0 (0; 0–17.3)
Asian	10 (4.5; 2.3–7.9)	0 (0; 0–17.3)
Black	22 (10; 6.5–14.4)	2 (15.4; 3.3–40.9)
Mixed/multiracial	11 (5; 2.7–8.4)	1 (7.7; 0.8–30.7)
Native Hawaiian/Pacific Islander	9 (4.1; 2–7.3)	0 (0; 0–17.3)
Other	9 (4.1; 2–7.3)	1 (7.7; 0.8–30.7)
White	152 (68.8; 62.5–74.6)	9 (69.2; 42.3–88.6)
Hispanic *N*, (%, 95% CI)	34 (15.4; 11.1–20.6)	1 (7.7; 0.8–30.7)
Chronicity *N*, (%, 95% CI)		
Acute	150 (67.9; 61.5–73.8)	9 (69.2; 42.3–88.6)
Acute-on-chronic	63 (28.5; 22.9–34.7)	4 (30.8; 11.4–57.7)
Chronic	8 (3.6; 1.7–6.7)	0 (0; 0–17.3)
Self-harm *N*, (%, 95% CI)	142 (64.3; 57.8–70.4)	10 (76.9; 50.3–93)
Abuse/misuse *N*, (%, 95% CI)		
Greater dose than prescribed	10 (4.5; 2.3–7.9)	0 (0; 0–17.3)
Someone else's medication	1 (0.5; 0–2.1)	0 (0; 0–17.3)
To get high	6 (2.7; 1.1–5.5)	0 (0; 0–17.3)
To get high using someone else's medication	1 (0.5; 0–2.1)	0 (0; 0–17.3)
To treat exacerbated pain	1 (0.5; 0–2.1)	0 (0; 0–17.3)

M median, *IQR* interquartile range, *95% CI* 95% confidence interval

Table 2 Toxidromes, symptoms, and treatments.

Characteristic *N* (%, 95%CI)	Full sample	Serotonin toxicity
Toxidrome	*N* = 221	*N* = 13
Sympathomimetic	49 (22.2; 17.1–28)	1 (7.7; 0.8–30.7)
Anticholinergic	6 (2.7; 1.1–5.5)	1 (7.7; 0.8–30.7)
Symptoms		
Seizures	104 (47.1; 40.6–53.6)	8 (61.5; 35–83.5)
Tachycardia	75 (33.9; 27.9–40.4)	6 (46.2; 22.1–71.7)
Agitation	70 (31.7; 25.8–38)	6 (46.2; 22.1–71.7)
Toxic psychosis	45 (20.4; 15.5–26)	3 (23.1; 7–49.7)
Hyperreflexia/clonus/myoclonus/tremor	42 (19; 14.3–24.6)	8 (61.5; 35–83.5)
Prolonged QTc (> 500 ms)	35 (15.8; 11.5–21.1)	3 (23.1; 7–49.7)
CNS depression	35 (15.8; 11.5–21.1)	1 (7.7; 0.8–30.7)
Hallucinations	34 (15.4; 11.1–20.6)	0 (0; 0–17.3)
Prolonged QRS (> 120 ms)	8 (3.6; 1.7–6.7)	1 (7.7; 0.8–30.7)
Numbness	4 (1.8; 0.6–4.2)	0 (0; 0–17.3)
Dystonia	3 (1.4; 0.4–3.6)	1 (7.7; 0.8–30.7)
Treatments		
Benzodiazepines	153 (69.2; 62.9–75)	11 (84.6; 59.1–96.7)
Intubation	27 (12.2; 8.4–17)	1 (7.7; 0.8–30.7)
Activated charcoal	16 (7.2; 4.4–11.2)	2 (15.4; 3.3–40.9)
Sodium bicarbonate	10 (4.5; 2.3–7.9)	1 (7.7; 0.8–30.7)
Anticonvulsants (other than benzodiazepines)	9 (4.1; 2–7.3)	2 (15.4; 3.3–40.9)
Neuromuscular blockers	8 (3.6; 1.7–6.7)	1 (7.7; 0.8–30.7)
Opioids	6 (2.7; 1.1–5.5)	1 (7.7; 0.8–30.7)
Vasopressors	6 (2.7; 1.1–5.5)	0 (0; 0–17.3)
Antipsychotics	5 (2.3; 0.9–4.9)	0 (0; 0–17.3)
Lipid rescue therapy	4 (1.8; 0.6–4.2)	0 (0; 0–17.3)
Antiarrhythmics	2 (0.9; 0.2–2.9)	1 (7.7; 0.8–30.7)
Naloxone	1 (0.5; 0–2.1)	0 (0; 0–17.3)

M median, *IQR* interquartile range, *95% CI* 95% confidence interval

unable to determine, for example, if subjects had a history of seizure disorders, the time of seizure onset, and the number of positive signs or symptoms on the Hunter Criteria. Additionally, the analysis was limited by the unrecorded medication formulation (extended release) and dose reported in the registry.

Similarly, the present study included a small sample size and a small number of ST patients. This prevented further analysis of the differences and similarities between patients that were and were not diagnosed with ST.

Since we limited our inclusion criteria to those individuals with single-agent bupropion exposures, it is possible that the rate of seizure development and the diagnosis of ST may be affected by co-exposures. Also, ST is a challenging diagnosis that relies on a careful history and physical exam. The diagnosis is clinical as there is no gold standard laboratory test for the diagnosis of serotonin toxicity. An attempt was made to apply the Hunter Criteria to the data; however, this was not possible and therefore we were unable to independently confirm diagnosis. Despite this, all patients were evaluated at bedside by a board-certified medical toxicologist with subspecialty training and experience in making this diagnosis. Lastly, this data set relies on voluntary entry by medical toxicologists and medical toxicology fellows in training. Given that less critically ill patients may have been entered at a lower rate than sicker patients, either due to lack of toxicologic consultation or personal preference of the consulting/entering physician, it is possible that the data set is incomplete and is skewed toward a more severely poisoned patient population.

Conclusion

In this study, we found an elevated prevalence of abuse or misuse of bupropion compared with prior studies. Seizures, tachycardia, and agitation were the most common clinical effects after overdose. Additionally, despite the traditional view that bupropion is not serotonergic, it appears that bupropion overdose may be associated with ST. This case series highlights the potential of bupropion as an atypical cause of ST in a significant percent of overdoses. This has substantial ramifications for the treatment of bupropion overdoses as physicians should avoid concomitant exposure to other known serotonergic agents.

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Compliance with Ethical Standards

Conflict of Interest None.

Disclaimer The view(s) expressed herein are those of the author(s) and do not reflect the official policy or position of the US Air Force Office of the Surgeon General, the Department of the Air Force, the Department of Defense, or the US Government.

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