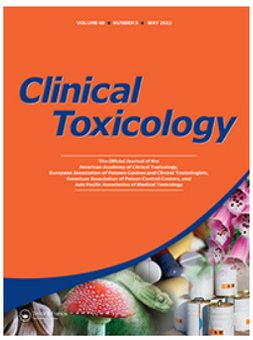

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POISON CENTRE RESEARCH

Adverse effects associated with bupropion therapeutic errors in adults reported to four United States Poison Centers

Michael C. Beuhler[a], Henry A. Spiller[b], Dalia Alwasiyah[a], Robert Bassett[c], Jeanette Trella[c], Martin Huecker[d] and Ashley N. Webb[e]

[a]North Carolina Poison Control, Atrium Health, Charlotte, NC, USA; [b]Central Ohio Poison Center, Columbus, OH, USA; [c]Children's Hospital of Philadelphia, Philadelphia, PA, USA; [d]Department of Emergency Medicine, University of Louisville, Louisville, KY, USA; [e]Kentucky Poison Control Center, Louisville, KY, USA

ABSTRACT

Context: Bupropion is a frequently used medication. Excessive doses may cause altered mental status, seizures, and dysrhythmias. There is a need for accurate estimate of seizure risk with therapeutic errors and determination if minor symptoms are harbingers of more severe effects.

Methods: A retrospective review of adult, acute, unintentional therapeutic error, single substance bupropion ingestions with known outcome reported to four poison centers from January 1, 2004 to December 31, 2016. Data included age, gender, single error dose, total bupropion dose over 18 h, prior history of seizure, management site, observation time, occurrence of an out-of-hospital adverse event, "jittery"/anxious/agitated, tachycardia/palpitations, seizures, and dysrhythmias. We recorded the total bupropion dose over 18 h if known; otherwise, we used the single error dose. We compared means for parametric data. We used Fisher's exact test and Mann–Whitney for nonparametric data.

Results: We identified 754 potential cases, of which 637 met inclusion criteria after case review. Median age was 42 years, and 76.1% were female. Cases were predominantly managed at home (56.2%). Outcomes were no effect (50.1%), minor (45.5%) and moderate (4.4%). The reported dose with no effect/minor outcome was 694 (±297) mg, and for moderate outcome was 1250 (±815) mg ($p < 0.0001$). Seizures occurred in four patients with median onset time of 7 h [range 2–21.5 h]. The median reported dose in patients who seized was 900 mg [range 600–3000 mg]. Of patients who developed a seizure and/or an out-of-hospital adverse event, 83% were "jittery"/anxious/agitated whereas "jittery"/anxious/agitated was present in 27% of cases that did not ($p = 0.008$). Tachycardia/palpitations was reported in 12% of cases; more serious dysrhythmias were not reported.

Conclusions: Outcomes from single unintentional ingestions of bupropion in adults are overall mild and appear to be dose related. Home management may be an option with doses up to 900 mg in an appropriate patient population.

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Seizures; overdose; medication errors; bupropion; triage

Introduction

Bupropion, an N-alkylated cathinone was discovered in 1969 and it has been used to treat a myriad of disorders, including depression, attention deficit hyperactivity disorder, obesity, and smoking [1]. It is available as an immediate and extended-release preparations (XL and SR). Rarely, with therapeutic doses, it can cause seizures and with excessive doses, altered mental status and dysrhythmias [2,3].

It was initially used in doses of up to 600 mg, but due to an unacceptably high incidence of seizures (≈2%), it was withdrawn and re-released with a maximum daily dose of 450 mg [2,4]. The point when the risk of seizures increases with a single therapeutic accident is not clear. Poison control centers (PCCs) are often consulted on triage decisions by the public when bupropion dosing accidents (unintentional therapeutic error ingestions) occur, and due to the risk of seizures, PCCs will commonly refer patients to the emergency department for monitoring. Although previous work has suggested the risk of seizures or dysthymias is low with these exposures, no study has looked at this specific group to determine the exact risk of the various adverse effects to be used during the triage process which often involves shared decision making with the patient and the poison center staff [5]. Additionally, while some symptoms often precede more severe ones (such as seizures) in larger overdose, it is not clear if there will be a reliable prodrome with smaller, unintentional ingestions. We sought to determine the incidence of seizures and other significant adverse events in acute adult unintentional bupropion ingestions, assess if minor symptoms are harbingers of more concerning clinical effects, and determine if there were any patterns behind the reason for the ingestion.

Materials and methods

This was a retrospective review of adult (age 18+ years), unintentional, therapeutic error, single substance bupropion

CONTACT Michael C. Beuhler michael.beuhler@ncpoisoncontrol.org North Carolina Poison Control, Atrium Health, 4400 Golf Acres Drive, Suite B2, Charlotte, USA

ingestions with known outcomes reported to four PCCs from 1/1/2004-12/31/2016. This represented a concurrent time where all four centers had consecutive full years of data to contribute. Bupropion cases were identified using all United States, Canada and Mexico product codes for bupropion, bupropion HCl and bupropion HBr as well as the generic code for bupropion. Cases where the error dose was taken more than four hours after the initial amount, when substances other than bupropion were also taken in error, and cases with incorrect reason, acuity (i.e., chronic exposures without an acute component) or route were excluded. The four-hour period was chosen to select cases that are typical of single unintentional exposures which include cases where a dose is taken by mistake usually within an hour or two of the earlier dose.

Data included age, gender, single error dose, total bupropion dose over the previous 18 h, type of bupropion preparation (immediate or extended release), reason for error (intended to take ibuprofen/aspirin, forgot and took 2nd dose, dosing/formulation change or other), past medical history (seizures, cardiac arrhythmias, autism/debilitating neuro condition, CNS lesions/head trauma or hepatic cirrhosis), management site, activated charcoal administration, observation time, medical outcome, and an out-of-hospital adverse event which was defined as an unexpected, concerning or harmful event prior to any health care facility (HCF) presentation. Medical outcomes were the standard AAPCC case outcomes [6]; minor (some symptoms but minimally bothersome and resolve rapidly), moderate (more pronounced and prolonged symptoms and usually some form of treatment would be indicated), and major (life threatening symptoms or residual disability/disfigurement resulted). Signs and symptoms examined were the combination "jittery"/anxious/agitated (defined as no altered mental status, mild agitation, and no restraints or sedation required), hallucinations/AMS, tachycardia (which included reports of "palpitations"), seizures, and arrhythmias. Time to develop seizure(s) was also examined.

We used the bupropion dose over the 18 h preceding the call (if known). Because bupropion doses are commonly twice daily (BID), we sought to include doses taken approximately 12 h earlier and to exclude doses taken approximately 24 h in our dose of interest. When this was unknown, we used the single dose taken in error. Cases where neither dose was known were excluded from all analysis requiring dose. Unknown dose cases were included in the demographics, management site, signs/symptoms, preparation type, specific reason for exposure, and observation time analysis.

All case documentation records were reviewed by two researchers who reached agreement on all discrete fields. Cases with out-of-hospital adverse events and seizures were reviewed by three authors who reached agreement on all fields. Case documentation (the free text clinical case notes) took precedence over coded fields, including adjusting medical outcome when appropriate. For time analysis, if an event happened between two follow up calls without documentation supporting a specific time, the midpoint of the time between calls was used. All time elements were the average of two reviewer's assessments.

We compared means for parametric data. We used Fisher's exact test and Mann–Whitney for non-parametric data. All data were collected and analyzed using Excel 2017 (Microsoft Corp., Redmond, WA, USA) with the Real Statistics Resource Pack software (Charles Zaiontz). The study was deemed by all individual site's IRB to be not human research and exempt from oversight.

Results

There were 754 identified cases and 637 cases were included. There were 117 cases excluded; 24 for chronic exposure, 34 for not followed to known outcome, 28 for an error dose taken more than 4 h after an initial dose, 13 for the wrong exposure reason, and 18 for the wrong substance. Median age was 42 years and 76.1% were female. Table 1 presents the management sites with the majority managed out of a HCF (56.2%). Specific reason for the exposure is presented in Table 2; the ibuprofen/aspirin errors often happened when handfuls of medication were taken without looking. The percentages of signs/symptoms listed in Table 3 are for all included cases.

The vast majority ($n = 602$, 95%) of cases were of an extended-release preparation, only 19 cases (3%) were of an unknown preparation and 16 (3%) were immediate release. The dose was unknown in five cases with the single dose (as opposed to the 18-hour dose) used in 59 (9.3%) of cases. The average reported dose for the outcome of no effect or minor was 694 (±287) mg (median 600 mg, IQR 600–900), and for moderate outcome it was 1250 (±815) mg (median 900 mg IQR 900–1200) ($p < 0.0001$, Mann–Whitney). Figure 1 shows the number of patients for each 100 mg dose interval.

Table 1. Case management site.

Location	Number of cases (%)
Non-health care facility	358 (56.2%)
ED treatment and discharge	180 (28.3)
Admit non-critical care	77 (12.1%)
Admit critical care	18 (2.8%)
Private caregiver	4 (0.6%)

Table 2. Specific reason for exposure.

Reason	Number of cases (%)
Forgot and took 2nd dose	174 (27.3%)
Intended to take ibuprofen or aspirin	91 (14.3%)
Formulation change	53 (8.3%)
Other scenario	319 (50.1%)

Table 3. Reported signs and symptoms.

Signs and symptoms	Number of cases	Percent of total cases ($n = 637$)
Jittery/Anxious/Agitated	178	28%
Hallucinations/AMS	11	2%
Tachycardia/Palpitations	76	12%
Seizures	4	0.6%
Conduction delays	3	0.5%
Dysrhythmias	0	0

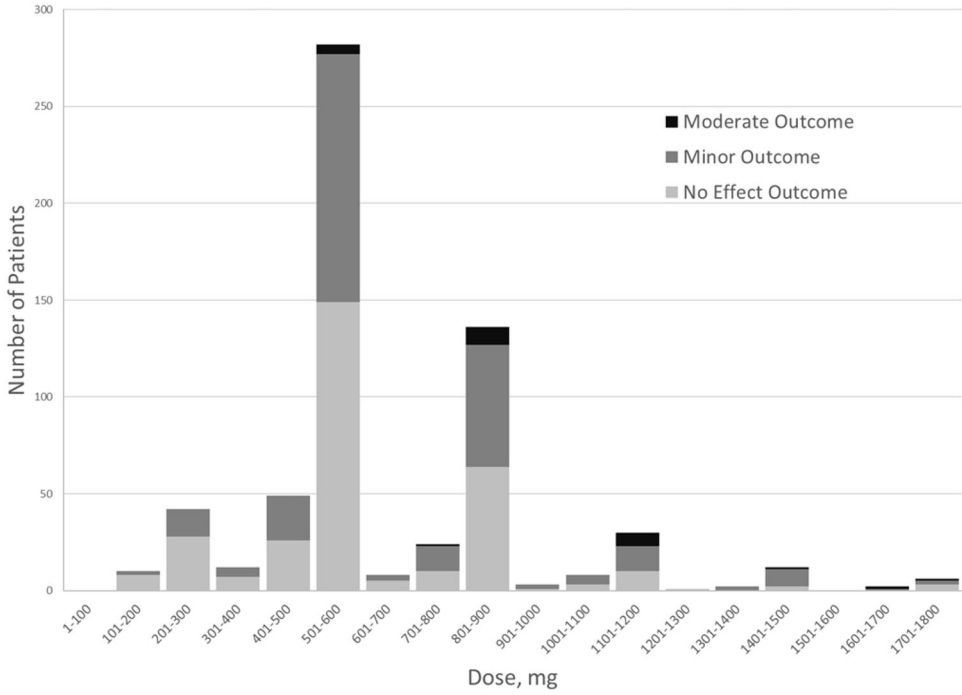

Figure 1. Number of patients with known doses. Does not include the patients with dose greater than 1800 mg ($n = 5$). All doses are the 18-hour total dose when it was known, single dose when it was not.

Table 4. Patients experiencing an out-of-hospital event or seizure.

Patient number	Bupropion dose, 18 h	Bupropion dose, Single	Age/Sex	Time until seizure, hours	"Jittery"/ Anxious/Agitated	Out of hospital event
1	600 mg	450 mg	54F	21.5	No	Seizure
2	Unknown	600 mg	18F	10.75	Yes	N/A
3	Unknown	900 mg	43F	N/A	Yes	Hallucinations
4	1200 mg	1200 mg	24M	2*	Yes	N/A
5	Unknown	1200 mg	37F	N/A	Yes	Near syncope
6	3000 mg	3000 mg	24M	3.25	Yes	N/A

*Patient #4 had two seizures treated with 2 mg of lorazepam without clinical sequela and was managed in non-critical care unit.

Seizures occurred in four patients with median onset time of 7 h [range 2 to 21.5 h]; one patient had 2 seizures. All reported ingestion with seizures were of an extended-release preparation. Out-of-hospital adverse events were reported in 3 patients; one had a seizure. All reported ingestion with the out of hospital adverse events were of an extended-release preparation. See Table 4 for additional details regarding these six patients. None of the six had any past medical history believed contributory to the seizures or out-of-hospital event and only one (#2) received activated charcoal. No patients with an unknown dose had a seizure or an out-of-hospital adverse event.

Patients were jittery/anxious/agitated in 5 (83%) of cases that developed a seizure and/or out-of-hospital event and 173 (27%) of cases that did not, this difference was significant ($p = 0.008$) with jittery/anxious/agitated having a negative predictive value of 99.8% and a positive predictive value of 2.8% for seizures or out-of-hospital adverse event.

The frequency of having an out-of-hospital adverse event and/or a seizure with dose of 600–900 mg was 0.67% [$n = 3$ of 447, 95% confidence interval 0.14–1.9%]. The frequency of having an out-of-hospital adverse event and/or a seizure with dose of greater than 900 mg was 4.3% [$n = 3$ of 69, 95% confidence interval 0.9–12.2%].

Median observation time was 9.5 h (interquartile range 5.0–19.5). Outcomes were no effect (50.1%), minor (45.5%) and moderate (4.4%). There were no major outcomes or deaths. Only 12.6% of patients received activated charcoal. There was no difference in the frequency of seizures or out-of-hospital adverse event in patients who received activated charcoal and those that didn't ($p = 0.55$). Tachycardia/palpitations was reported in 12% of cases. The average dose in patients with tachycardia/palpitations was 981 mg (range 300–4350mg); its presence was not associated with seizures or out-of-hospital event ($p = 0.09$). No patient had any dysrhythmias other than sinus tachycardia.

Discussion

Bupropion acts by inhibiting dopamine and norepinephrine reuptake as well as inhibitory action at some nicotinic receptors and 5-hydroxytryptamine ($5HT_{3A}$) receptors [1]. Bupropion is metabolized in the liver, mainly by CYP2B6. It has three active metabolites: hydroxybupropion, threohydrobupropion, and erythrohydrobupropion and all reach higher plasma concentrations than the parent compound. This is especially relevant for hydroxybupropion, which is believed

to be about half as potent as bupropion but reaches a steady state seven times the peak concentration of bupropion [1]. Bupropion is formulated as immediate release, sustained release and extended-release formulations with peak plasma concentrations reached after 1.5, 3, and 5 h of administration respectively [7].

At therapeutic doses, bupropion is associated with multiple adverse effects with the most serious one being seizures [2,3]. The incidence of seizures with bupropion treatment is around 0.4% for doses of 300–450 mg, and about 4% for doses greater than the maximum recommended 450 mg per day; the risk is higher with immediate release preparations when compared to extended/sustained release preparations at similar doses [2,3,8]. For years, this seizure incidence data from chronic dosing has been part of guidance used to refer in adults with unintentional exposures for monitoring. However, one cannot compare the risk of adverse effect from chronic dosing to the situation when a patient takes a single additional dose of medication.

To date, this study is one of the largest studies of patients with therapeutic errors of bupropion. It confirms that the population at risk of seizures are patients who take doses of 600 mg or more as well as provides an accurate estimate of the incidence of both seizures and out-of-hospital adverse events at escalating doses. In one poison center study the overall risk of seizures for a patient with any extra dose of bupropion was 0.8%, however, this study did not report the doses in patients who had seizures [5]. In another study of unintentional double doses of medication, seizures occurred exclusively in patients who ingested doses $\geq$600 mg of bupropion [9]. Both studies used the single dose ingested rather than the 18 h dose [5,9]. One should use caution with any attempt to extend these findings to other types of bupropion ingestions such as intentional ingestions even with dose ranges similar to what were reported here.

Using medical outcome as a primary outcome for poison center studies has limitations when the medical outcome is driven by a clinical effect that is subjective or difficult to be exacting with, especially without a medical exam. In the case review process, we found that some patients described as "jittery" or "shaky" were occasionally miscoded as having the clinical effect of tremors. When tremors are coded in a case it will be automatically up coded to (at least) a moderate outcome. Using the symptom combination of "jittery"/anxious/agitated captured the mild acute toxic effects of bupropion which is not the same as true tremors and was easier to identify in the case record when the various synonyms for that type of symptom were used. This data suggests that patients who are not "jittery"/anxious/agitated have a very low incidence of significant adverse effects as only 1 patient out of 459 that did not report having this symptom combination had a seizure or out-of-hospital adverse event, but this symptom had a very low positive predictive value.

Knowing the risk and the severity of potential adverse events is critical for making an informed medical decision. Seizures and arrythmias are the greatest concern with bupropion toxicity but neither this nor any other studies suggested any significant risk for an arrhythmia following a therapeutic bupropion error. In this study, the four patients that had a seizure all had moderate clinical outcomes with only one patient having two seizures who did not require admission to an ICU. Correia et al. [9] found four patients with single seizures among 56 patients with double doses of bupropion. Three were discharged from the ED and one was admitted for observation. Shepherd studied 476 patients who inadvertently took extra doses of bupropion [5]. Three patients had single seizures and one patient had status epilepticus. The patient with status epilepticus was a 43 year old female who unintentionally ingested six tablets of 150 mg bupropion (personal communication G. Shepherd, August 1, 2021). However, as only the coded fields were used in the study (i.e., not the case documentation) there is no information about past medical history, other regular medications, reason for taking six times their usual dose, hospital course, or the exact reason for coding status epilepticus and so the ramifications of this one patient is unclear. Approximately 1/6th of the initially included cases in the current study were excluded after assessment of the free text case documentation. Considering just those with dose greater than 450 mg but less than 1800 mg, none of the patients in this study had a major outcome which suggests with 99% confidence (one tailed) of such an event happening is less than 0.9%.

The annual risk of first unprovoked seizure in the general population is $\approx$0.08% but increases to a risk of $0.1-1\%$ for patients treated with an antidepressant; this increased risk is highly dependent on the medication, dose and the population studied [10]. When compared to other antidepressant treatments, bupropion treatment is associated with a higher risk of seizures, but it is dose related. When a patient's daily dose is less than 450 mg per day, the risk of seizures seems to be comparable to other antidepressants [3,10]. It is interesting that the incidence of adverse effect found in this study with a dose equal to double the daily maximum dose (900 mg) was just 0.67%, which is little different than the incidence of seizures with therapeutic dosing.

Referral to the ED for extended monitoring is expensive and time consuming, especially those who are not insured or under insured. If there are no severe out-of-hospital events caused by the exposure, then monitoring in a HCF may not be necessary. Even if there is a "significant" probability of a concerning but not life-threatening event, having an informed discussion with a patient can mitigate both medical and legal risk based on their behavior choices and expectations. Patients seem to have a higher risk tolerance than physicians when it comes to discharging them [11,12] and having a less than 1% chance of developing a seizure (i.e., a trivial increase from the baseline risk) might be a risk that an individual and caregivers are willing to accept, depending on multiple other factors such as comorbidities, home support resources, time of day, concomitant use of other medications which could lower seizure threshold, potential drug interactions, and the distance to health care, especially when the increase in the risk of seizure from expected population baseline is so small.

The out-of-hospital adverse event outcome was intended to provide an estimation of patients with clinical effects

(beyond seizures) that potentially required medical treatment that occurred outside a HCF. There are significant limits to this outcome with probably the most important one being its asymmetrical nature. If an out-of-hospital adverse event was manifested by a patient outside a health care facility, then that outcome would be present, whereas if a patient manifested the same symptoms in a health care facility, then the outcome would not be present. In contrast, a mildly confused patient might be managed at home by a calm companion without any pharmacologic intervention (and therefore not an out-of-hospital adverse event), while in a health care facility they might receive some sedation. Therefore, it is impossible to extrapolate this outcome for clinical effects occurring in a HCF and it should be viewed as a low estimation of these potential adverse events.

Further limitations in this study are those inherent to retrospective poison center studies such as the possibility of incomplete history, a convenience sample of patients who contacted the center and lack of in-person medical evaluation in most patients. Even for patients evaluated in a HCF, they may only capture the initial vital signs and not document any late changes. Additionally, the median observation time was 9.5 h; while most seizures from bupropion are reported during this time frame some are not, and 25% of cases were followed for 5 h or less. Thus, there was the possibility of missing later events in some patients. However, unlike poison center studies of pediatric ingestions where the history is often unobtainable, and studies on intentional overdoses where the history may not be trustworthy, this study was conducted on adults who initiated contact with the poison center and willingly provided a history. This study is also limited in that other medications were not assessed specifically that could contribute (beyond general medical conditions) and the patient's weight was not considered with the ingested dose.

Conclusions

Unintentional adult ingestions of bupropion generally have little or no effect. Effects are dose related. Seizures are rare. Doses above 900 mg are more likely to cause either seizures or out of hospital adverse events. Patients with therapeutic errors of up to 900 mg and asymptomatic patients may be able to remain at home.

Disclosure statement

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