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Serotonin toxicity from isolated bupropion overdoses

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1. Introduction

Bupropion is an aminoketone antidepressant that structurally is a synthetic cathinone. As such, it causes tachycardia, tremor, hallucinations, seizures, and agitation in overdose [1–3]. The primary mechanism of action is inhibition of norepinephrine and dopamine reuptake [1]. Human studies have shown no direct serotonergic activity by bupropion, but case reports of serotonin toxicity from bupropion overdose exist in the literature [4,5]. A recent retrospective analysis of cases using data from a national database identified a 5.9% rate of serotonin toxicity, higher than previously reported [3].

2. Methods

This is a retrospective analysis of patients who overdosed on bupropion from 2015–2017 managed by a primary toxicology admission service at a tertiary care center. The study was approved by the IRB committee at our university. Patients who had overdosed on other serotonergic medications as identified by history were excluded. Urine gas chromatography/mass spectrometry (GC/MS) drug screen was utilized when performed, but testing was qualitative and therefore history took precedence in determining toxic exposures. However, if any non-prescribed serotonergic medications were identified or no bupropion was present, patients were excluded. Patient data recorded included: tachycardia (heart rate [HR] > 100 bpm) within 24 h of admission; peak HR in the emergency department; hyperthermia (>100.4 F); documented altered sensorium, agitation, or diaphoresis; and physical exam findings of hyperreflexia, clonus, and/or tremor. If no clonus or hyperreflexia were documented, they were assumed to be absent. The circumstances of the overdose (recreational use, suicide attempt, or accidental ingestion), length of stay (LOS), and reported dose ingested were also recorded. Two reviewers (KK and AS) analyzed the patient records and recorded data onto a shared standardized data sheet. Serotonin toxicity was diagnosed retrospectively using the Hunter Serotonin Toxicity Criteria.

3. Results

Over a three-year period, 96 patients were managed by our Medical Toxicology service with a reported bupropion overdose. Eighteen patients were identified as having an overdose on bupropion with no serotonergic co-ingestions. Baseline characteristics are recorded in Table 1. Five patients had GC/MS testing confirming bupropion ingestion. Patients had bupropion toxicity from either a suicide attempt (n = 7), recreational use (n = 8), or accidental ingestion (n = 3). Tachycardia was present in all patients (peak HR: 122 bpm [95% CI: 115–129]). Toxic encephalopathy was the most common sign identified. Incidence of other signs are recorded in Table 2. Records of physical exam findings from the initial
presentation of two patients were not available as they were transferred from outside facilities. They were still included in the data, but findings for clonus and hyperreflexia were recorded as absent. Inducible clonus was present in six patients, one of whom did not meet criteria for serotonin toxicity given a lack of hyperthermia, agitation, diaphoresis, or hypertonia.

Serotonin toxicity was diagnosed in 6 patients (33%) by Hunter Criteria. Patient characteristics are included in Table 3. The treating physician documented serotonin toxicity in three of these patients. Criteria that led to a diagnosis of serotonin toxicity included agitation/diaphoresis and inducible clonus (N = 3), and hyperreflexia and tremor (N = 3) with one of these patients additionally having hyperthermia and inducible clonus. Clonus was sustained in three patients with the remainder having 2–4 beats of clonus on exam. Patients tended to improve within 24 h of admission.

No deaths were identified in this cohort. Patients categorized as having serotonin toxicity overdosed on higher reported doses of bupropion and had a longer LOS (mean: 2.6 d [95% CI: 1.6–3.6] vs. 1.3 d [1.0–1.6]) [Table 2]. Incidence of serotonergic toxicity was higher in those who overdosed on bupropion in suicide attempts (3/7) compared to recreational use (2/8) or accidental ingestions (1/3). Seizures were common in those patients using bupropion recreationally (5/8), but none of the patients with seizures from recreational use were diagnosed with serotonin toxicity. Only one of the patients diagnosed with serotonin toxicity had a seizure, which had occurred prior to presentation.

All patients diagnosed with serotonin toxicity were treated with benzodiazepines. No patients received cyproheptadine or anti-psychotics. Two were admitted to the intensive care unit. None were intubated and none developed later seizures. One patient developed rhabdomyolysis [CPK 6880 IU/L] and hyperthermia despite initial treatment with low-dose lorazepam [Table 3]. Additional benzodiazepines were used to control symptoms and the patient was admitted to the ICU, but toxicity improved within twenty-four hours of admission.

4. Discussion

Our findings suggest that serotonin toxicity from isolated bupropion overdoses likely occurs, albeit in a mild form, more often than we are aware. Serotonin toxicity was determined retrospectively by applying Hunter Criteria rather than with the use of billing codes or provider documentation. The Hunter Serotonin Toxicity Criteria, published in 2003, has a higher sensitivity and specificity than the previously used Sternbach’s Criteria [6]. Prior studies have incorporated data from national databases, which can be prone to error due to incomplete data entry by providers or from inaccurate information being conveyed from the treating facility [2,3]. While the methods used in this study may increase the incidence of serotonin toxicity identified, we feel that the use of validated criteria may lead to a more accurate representation of toxicity than with the use of billing codes or provider documentation. Moreover, these patients had clonus, tremor, and/or hyperreflexia documented on multiple examinations by a medical toxicologist adding to our confidence in the findings. If results were based on documented serotonin toxicity, we would have still identified an incidence of serotonin toxicity of 17% (3/18).

Though bupropion is thought to act solely on dopamine and norepinephrine reuptake, it has been shown to enhance serotonergic activity in animal studies possibly from alpha-2 adrenoreceptor and 5HT1a auto-receptor desensitization [1,7,8]. Despite controversy over whether or not bupropion causes serotonin toxicity, prior case reports have documented the development of serotonin toxicity from isolated bupropion overdose and from bupropion use in combination with selective serotonin receptor inhibitors [4,5]. A recent review of the ToxIC registry affirmed these findings, showing a 5.9% rate of serotonin toxicity after single-agent bupropion overdoses [3].

While the increased incidence of serotonergic toxicity may not change the treatments needed for an overdose, it is still of clinical significance as it is important for the assessment of these patients. Development or progression of signs of serotonin toxicity may serve as an objective marker of bupropion toxicity and should prompt aggressive treatment to prevent the onset of severe effects such as seizures. Under-treatment of the initial symptoms can lead to worsening toxicity. One patient in our study developed hyperthermia and rhabdomyolysis despite treatment with serial administration of low-dose lorazepam (1 mg × 3) in the emergency department.

Benzodiazepines served as the sole treatment of toxicity in all of the patients identified with serotonin toxicity, which is indicative of the treatment preferences of providers in our group, but also appropriate with bupropion toxicity, which may initially appear with mixed features and carries a risk of seizures. Benzodiazepines were the first choice in treatment in these cases as they help manage the sympathomimetic
and epileptogenic effects of bupropion toxicity. None of the patients developed complications from treatment.

In this study, seven patients (39%) had a seizure, a common complication after bupropion overdose with an increased risk at doses >600 mg [9]. Seizures appeared to be more likely from recreational use and occurred at a higher rate in this population than prior studies [10]. Nonetheless, serotonin toxicity did not develop in this cohort (recreational overdose complicated by an initial seizure). It is possible that intravenous injection or insufflation of bupropion led to higher peak levels thus causing generalized seizures through catecholamine release rather than from serotonergic toxicity.

There are various limitations to this study. Firstly, it is a retrospective review with a small sample size. This may have reduced the accuracy of the findings as the results depended on the thoroughness of the physical exam documentation at the time of assessment. Limited data was available for two patients due to their transfer from an outside facility reducing our ability to detect the presence of initial or short-lived serotonin toxicity. They were still included in the data set, but clonus and hyperreflexia were recorded as absent in these patients. An additional limitation was that we did not analyze whether patients’ use of daily serotonergic medications influenced the risk of developing serotonin toxicity. The use of GC/MS was not widespread and even when employed was qualitative and therefore did not rule out an overdose on patients’ daily medications.

5. Conclusion

In our 2-year retrospective analysis, 33% of patients with isolated bupropion overdoses developed serotonin toxicity. The incidence of serotonin toxicity, though mild, is higher than previously reported. Clinicians should monitor for signs of serotonergic toxicity when evaluating a patient after a bupropion overdose as this could portend the development of worsening toxicity and seizures.

Disclosure statement

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

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References


Table 3. Patients with serotonin toxicity: characteristics, treatments, complications.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Dose (mg)</th>
<th>Clonus</th>
<th>Agitation/Diaphoresis</th>
<th>Tremor</th>
<th>Seizure</th>
<th>Complications</th>
<th>LOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>38 F</td>
<td>3000</td>
<td>Sustained</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>None</td>
<td>3.1 d</td>
</tr>
<tr>
<td>22 F</td>
<td>1500</td>
<td>None</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>None</td>
<td>1.7 d</td>
</tr>
<tr>
<td>47 M</td>
<td>6000</td>
<td>Sustained</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>None</td>
<td>2.3 d</td>
</tr>
<tr>
<td>21 F</td>
<td>4500</td>
<td>3–4 beats</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>None</td>
<td>1.7 d</td>
</tr>
<tr>
<td>23 F</td>
<td>900</td>
<td>2 beats</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>None</td>
<td>1.5 d</td>
</tr>
<tr>
<td>20 F</td>
<td>1500</td>
<td>Sustained, ocular</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Rhabdomyolysis</td>
<td>5.2 d</td>
</tr>
</tbody>
</table>

All patients were treated with benzodiazepines. LOS: Length of stay.