Delayed seizures in bupropion overdose with concomitant ingestion of alpha-2 agonist: a case report

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CASE REPORT

ABSTRACT
Clonidine and guanfacine are common alpha-2 adrenergic receptor agonists that can cause decreased sympathetic tone. Patients who overdose on bupropion, norepinephrine, and dopamine reuptake inhibitor may present with signs or symptoms of adrenergic excess including tachycardia, tremor, and agitation or more severe effects such as cardiac dysrhythmia and seizure. These pharmacological effects appear to oppose each other. The outcomes of patients with concomitant overdoses of bupropion and alpha-2 agonists are not well described. We present the cases of two adolescent patients, a 16-year-old male, and a 17-year-old female, who overdosed on bupropion and either clonidine or guanfacine. Both patients had relatively minor symptoms until 20.5 (Case 1) and 23 (Case 2) hours when they had multiple seizures. The patient in Case 1 did not survive. Bupropion overdose may cause delayed toxicity including seizures. This fact can present a clinical dilemma to the treating physician asked to medically clear a patient for psychiatric admission. Symptoms that predict seizure are not reliable in these cases and can be further masked by concomitant alpha-2 agonist overdose. We believe that these two bupropion overdose patients had delayed seizures with minimal prodromal symptoms possibly due to the masking effect of concurrent alpha-2 agonist ingestion.

KEYWORDS
Drug overdose; adrenergic alpha-2 receptor agonists; seizures

Abbreviations
ADHD attention deficit and hyperactivity disorder;
ED emergency department;
°C degree Celsius;
CPR cardiopulmonary resuscitation;
ECG electrocardiogram;
PICU pediatric intensive care unit;
ECLS extracorporeal life support

Introduction
Clonidine and guanfacine are alpha-2 adrenergic agonists indicated for hypertension [1,2]. Extended release formulations have recently been approved for patients with attention deficit hyperactivity disorder (ADHD) [3]. They act as sympatholytics by preventing the presynaptic release of catecholamines [1,2]. In overdose, they cause sedation, bradycardia, and often hypotension [4–6]. Conversely, bupropion, an atypical antidepressant, inhibits reuptake of norepinephrine, serotonin, and dopamine in the presynaptic cleft, and can cause a sympathomimetic toxidrome [7,8]. It is structurally similar to cathinone and is known to cause seizures, hypertension, tachycardia, QRS interval prolongation, cardiac arrest, and death [8–14]. As such, the alpha-2 agonists and bupropion produce clinically opposing effects. We describe the clinical courses of two patients who ingested large amounts of bupropion whose toxicity was initially masked by either clonidine or guanfacine.

Case 1
A 16-year-old boy with a past medical history of ADHD, bipolar, and conduct disorders was presented following a suicide attempt. He reported overdosing on multiple medications including guanfacine 60 mg, hydroxyzine 1400 mg, lamotrigine 2800 mg, and extended-release bupropion 2800 mg. His medication list also included citalopram, ranitidine, and lurasidone. He was initially presented to a local hospital and was transferred to a tertiary care pediatric hospital. Upon presentation, he was uncooperative and somnolent but was easily arousable. Vital signs were normal during his entire emergency department (ED) stay with initial heart rate 67, blood pressure 123/60, and temperature 36.8 °C. His acetaminophen, salicylate, and ethanol concentrations were below the level of detection; blood count and chemistry panel were normal and venous blood gas demonstrated mild respiratory acidosis with a pH of
7.34, pCO2 50, pO2 41, and total CO2 28. A urine drug screen revealed cannabinoids. Initial electrocardiogram (ECG) demonstrated normal sinus rhythm with rate of 78/min, QTc 425 ms, QRS 84 ms, and changes suggestive of early repolarization. He received 1 L of normal saline IV and was admitted to the ward on telemetry.

No events were reported overnight. At 7 am, he was asymptomatic and ambulated to the bathroom prior to reevaluation by the inpatient team. Vital signs recorded at 8 am were blood pressure 120/67, heart rate 92, respiratory rate 28, temperature 36.5, and oxygen saturation 99% on room air. At 8:30 am (20.5 hours after ingestion), he became agitated, pulled out his IV, and had a 2 min tonic–clonic seizure. His oxygen saturation was 70% on a face mask during the seizure. Physicians were called and the patient subsequently seized twice more prior to lorazepam being administered. After seizing, he became apneic, appeared dusky, and then had cardiac arrest. Cardiopulmonary resuscitation (CPR) was initiated and a non-perfusing ventricular rhythm was observed on the monitor. The patient was intubated and return of spontaneous circulation was achieved after approximately 20 min of CPR. Repeat ECG showed sinus tachycardia with a first degree atrioventricular (AV) block, ST elevation in anterolateral leads, and non-specific intraventricular conduction delay with QRS duration of 132 ms.

He was transferred to the pediatric intensive care unit (PICU) where an echocardiogram showed poor cardiac output despite maximal vasopressor support. Pediatric surgery was consulted for emergent extracorporeal life support (ECLS) initiation. EEG was suggestive of postanoxic myoclonus. While on ECLS, he continued to be hypotensive, hypoxic, and developed a coagulopathy. His mental status never improved and his pupils remained fixed and dilated. A repeat EEG was relatively flat. He developed multi-organ system failure and care was withdrawn after a family discussion.

An autopsy was conducted which showed cerebral edema, pulmonary congestion and edema, and bilateral pleural effusions. Postmortem blood obtained the day after expiration and analyzed four days after expiration demonstrated bupropion 860 mcg/L (antemortem therapeutic target range 25–100 mcg/L), citalopram 750 mcg/L (100–1100 mcg/L), and lamotrigine 6900 mcg/L (2300–9000 mcg/L) [15]. A guanfacine concentration was not obtained. Blood obtained the day of his initial cardiac arrest was sent for bupropion testing, however, the quantity was insufficient for analysis.

**Case 2**

A 17-year-old girl ingested clonidine 2.4 mg and bupropion 1500 mg in a suicide attempt. Upon transfer to a tertiary pediatric center, she was somnolent but arousable. She had pin-point pupils and a pulse of 40 beats/min with a blood pressure of 121/88 mmHg. Salicylate, acetaminophen, and ethanol concentrations were undetectable and her comprehensive urine drug screen was positive only for clonidine and bupropion. She was not acidic and an electrocardiogram demonstrating sinus bradycardia with a heart rate of 39/min, a QRS of 86 ms, and a QTc of 379 ms. She was given 1 L of fluid IV and was admitted to the ward on telemetry.

During her hospital stay, she remained sedated with bradycardia until 23 hours after her ingestion. Suddenly, she became tachycardic with a peak heart rate of 126/min. She also developed nausea, anxiety, mydriasis, and a witnessed 3–4 min generalized tonic–clonic seizure that spontaneously resolved. She was transferred to the PICU and received lorazepam 1 mg IV for sedation and seizure prophylaxis. For the next eight hours, she was tachycardic, hypertensive, and tremulous. Thirty-one hours after ingestion, her symptoms resolved and her vital signs normalized. She was discharged to a psychiatric facility two days after her ingestion without sequelae.

**Discussion**

We believe that the alpha-2 agonists masked the sympathomimetic effects of bupropion toxicity in these two patients, falsely reassuring their physicians. Bupropion poisoning can be severe and there are numerous case reports of death and significant morbidity following overdose [9–14]. Emergency physicians are often asked to medically clear patients who overdose on medications for psychiatric admission. Patients who overdose on bupropion can develop seizures and cardiac dysrhythmias and may be difficult to evaluate and treat. However, not all patients with a bupropion overdose will develop these sequelae nor require intensive care unit admission. Exacerbating the dilemma of the emergency physician is the fact that patients may be asymptomatic and stable for many hours following a bupropion overdose before developing toxicity [16]. These two patients overdosed on large quantities of bupropion combined with alpha-2 agonists and showed no signs of bupropion intoxication for 20.5 (Case 1) and 23 hours (Case 2). The onset of bupropion toxicity in these cases was more delayed than often reported for bupropion overdoses alone. Tachycardia and tremors are suggestive of significant intoxication with bupropion but have relatively low sensitivity [16]. The two cases presented demonstrate the potential for alpha-2 agonists to mask these common symptoms of an underlying significant bupropion overdose.

Emergency physicians may experience diagnostic uncertainty when evaluating a patient following an
overdose of bupropion and an alpha-2 agonist. The patient in front of them may appear asymptomatic due to the delayed nature of bupropion intoxication or the masking effect of a concomitant alpha-2 agonist overdose. Based on a lack of signs and symptoms, they may be prematurely cleared or physicians may underestimate the degree of toxicity. Indeed, these patients may compensate many hours later, long after a disposition decision has been made. Some may argue that these patients should all be observed for 24 hours in a medical setting due to the risk of delayed seizures, even without a concurrent alpha-2 agonist ingestion [16].

However, the observation in these case reports of significantly delayed seizures may present an avenue for treatment of patients with bupropion poisoning. Although the mechanism by which bupropion causes seizures is unclear, it may be related to the primary mechanism of bupropion: inhibition of catecholamine reuptake [8]. Perhaps the reduction in central catecholamine release by alpha-2 agonists can prevent seizures and sympathomimetic toxicity in patients with bupropion ingestions. Dexmedetomidine, a central alpha-2 agonist, has been shown to increase the seizure threshold [9]. Although the mechanism by which bupropion causes seizures is unclear, it may be related to the primary mechanism of bupropion: inhibition of catecholamine reuptake [8]. Perhaps the reduction in central catecholamine release by alpha-2 agonists can prevent seizures and sympathomimetic toxicity in patients with bupropion ingestions. Dexmedetomidine, a central alpha-2 agonist, has been shown to increase the seizure threshold [9]. Perhaps the reduction in central catecholamine release by alpha-2 agonists can prevent seizures and sympathomimetic toxicity in patients with bupropion ingestions.

**Conclusion**

We present the cases of two patients who intentionally overdosed on bupropion and an alpha-2 agonist and developed delayed seizures. They initially did not demonstrate signs of bupropion toxicity possibly due to co-ingestion of the alpha-2 agonist. Alpha-2 agonists may mask the expected signs and symptoms of bupropion toxicity.

**Disclosure statement**

All authors have indicated they have no financial relationships relevant to this article to disclose.

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