

BUPROPION TOXICITY: AN OVERVIEW

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ABSTRACT

Introduction: Bupropion is an antidepressant medication which was first patented by Burroughs Wellcome in 1974 and has been FDA-approved since 1985. Before 2000, the drug was referred to as amfebutamone. Multiple formulations of bupropion is found including immediate-release (IR), sustained-release (SR), and extended-release (XL). Bupropion toxicity is commonly characterized by tachycardia, lethargy and seizures. **Objective:** This study was done to review the characteristics, clinical effects, epidemiology, treatment and management of bupropion abuse, overdose and some cases. **Conclusion:** Bupropion toxicity is commonly characterized by tachycardia, lethargy and seizures. The major safety issue with bupropion is risk of seizures which is treated with benzodiazepines, propofol, barbiturates, e.t.c. The cardiovascular effects of bupropion overdose seem to be minimal. Less than 0.5% of reported cases of bupropion overdose result in death.

KEYWORDS: Bupropion, overdose, Toxic mechanism, case studies.

INTRODUCTION OF BUPROPION

Bupropion is an antidepressant medication that is now also used in smoking cessation. Bupropion was first patented by Burroughs Wellcome (now part of GlaxoSmithKline) in 1974 and has been FDA-approved since 1985. Before 2000, the drug was referred to as amfebutamone.^[1]

The medication is FDA-approved for adult depression, seasonal affective disorder, and smoking cessation.^{[2][3][4]}

Several off-label uses, includes sexual dysfunction secondary to antidepressant use, generalized anxiety disorder, Attention-Deficit/Hyperactivity disorder (ADHD), and bipolar disorder. Multiple formulations exist, including immediate-release (IR), sustained-release (SR), and extended-release (XL).^[5]

Adverse Effect

- Increase ambulatory blood pressure (approved for weight loss therapy in the USA).^[6]
- Cardiovascular (tachycardia)^[7]
- Respiratory (rhinitis, pharyngitis)^[8]
- Central nervous system (insomnia, headache, agitation, dizziness)^[9]
- Dermatologic (diaphoresis)^[10]
- Endocrine (weight loss)^[11]
- Gastrointestinal (constipation, dry mouth, nausea)^[12]

- Musculoskeletal (tremor)^[13]
- Ophthalmologic (blurred vision)^[13]
- The most severe adverse effects are lowered seizure threshold and the potential of worsening suicidal ideation.^[14]

Bupropion abuse and overdose

Bupropion is a growing public health problem which was early suggested by the research that it did not produce any psychostimulant effects. However, clinical experience and an increasing number of case reports describe bupropion abuse, including recreational ingestion, nasal insufflation of crushed tablets and, more recently, intravenous injection.^[15]

Bupropion lowers the seizure threshold, even at therapeutic doses of 150–450 mg/d.^[16] Acute overdose typically produces seizures within a few hours after ingestion, although seizure onset may be delayed up to 24 hours in patients who ingest extended-release preparations. The median dose associated with seizures is about 4.4 g.^[17] Other reported signs of toxicity include lethargy, tremor, vomiting and agitation.^[18] Associated cardiac toxicity includes sinus tachycardia, and massive overdose can cause widening of the QRS complex, ventricular dysrhythmias and cardiovascular collapse.^[19] Death can occur. Although reported data are limited,

they suggest that less than 0.5% of reported cases of bupropion overdose result in death.^[20]

Etiology

It was reported by Pesola GR and Avasarala J that bupropion-induced seizures were the third most common cause of drug-induced seizures after cocaine ingestion and benzodiazepine withdrawal.^[21] Additionally, according to a 3-year, multicenter retrospective analysis, approximately 21% of individuals admitted with intentional bupropion IR (immediate release) overdose presented with seizures.^[22]

Rissmiller and Campo first published a case of seizures induced by bupropion ER (extended release) even though the patient was already receiving two anticonvulsants, including clonazepam, a medication efficacious in preventing bupropion-induced seizures.^{[23][24]} The authors suggest that while bupropion ER (a once-daily alternative for bupropion IR and SR [sustained release] offers a convenient once-daily dosing option, its prolonged half-life may cause seizures to have a

more protracted course, as in the case they reported.^[25] According to published reports, this long-acting formulation might prolong neurologic toxicities, including seizures occurring in overdose.^[26]

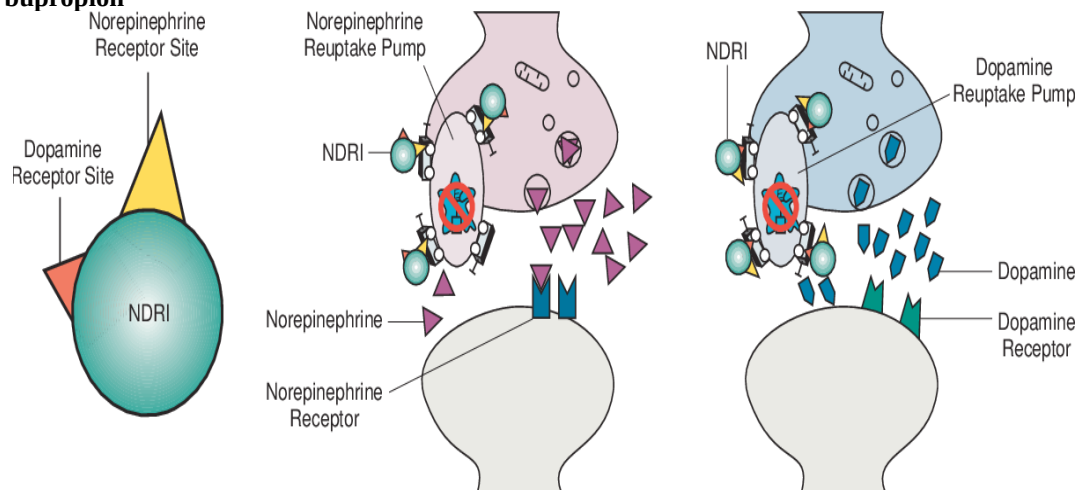
Epidemiology

Bupropion overdoses are a common source of toxicity. In 2018, nearly 15,000 overdoses involving bupropion were reported to US Poison Control Centers.^[27]

Bupropion toxicity is commonly characterized by tachycardia and seizures, which may be delayed.^[28,29] At therapeutic dosing, bupropion causes seizures in approximately 0.1% of patients.^[30, 31, 32] However, in overdose, seizures are much more common, occurring in 11–37% of patients.^[27–32] The seizures are clearly dose dependent^[33, 34, 35], and may be more common with certain preparations. Other than some suggestion that seizures occur less frequently in pediatric patients^[36, 37], and concurrent ingestion of a benzodiazepine may be somewhat protective against seizures.^[38]

Pathophysiology

MOA of bupropion^[39]



In this diagram, the norepinephrine reuptake inhibitor and the dopamine reuptake inhibitor portions of the NDRI molecule are shown inserted in the norepinephrine and the dopamine reuptake pumps, respectively, blocking them and causing an antidepressant effect.

Toxic Mechanism

Bupropion is a monocyclic antidepressant that suppresses nicotine cravings via an unknown mechanism. It increases the levels of dopamine and noradrenaline in the CNS by blocking their reuptake, also has some serotonin reuptake inhibition and moderate anticholinergic effects.^[40]

Toxicokinetics^[40]

- Good oral absorption.
- Peak levels at 2-3 hours.

- Large Volume of distribution 19.8 – 47L/kg.
- Metabolised to active metabolites which are renally excreted.

Management of bupropion poisoning

1. Decontamination

- Bupropion should undergo early decontamination.^[41]
- It has a few unique features which make it amenable to late decontamination:
 - i. Pill capsules can take >24 hours to dissolve.^[42]
 - ii. Partially dissolved pill capsules still containing active drug have been found in excrement days after overdose.^[43]
 - iii. It forms bezoars (collection of partially digested material that collects in the stomach).^[44, 45]

2. Seizures

- Benzodiazepines are first line for management of the seizing bupropion overdose.^[41]
- Propofol and barbiturates are second and third line agents.^[46, 47]
- Phenytoin, carbamazepine and valproic acid should be avoided due to evidence of harm in toxic seizures.^[47]
- Levetiracetam has no supporting evidence in the management of bupropion overdose and is currently not recommended.^[48]

3. Cardiotoxicity

- This is a rare and often fatal development in bupropion overdoses.^[41]
- The pathophysiology is unique.
- While often touted as a sodium channel blocking agent, this is based largely on an animal study from 1981 which led bupropion to be compared to TCAs.^[49]
- More recent evidence by a Canadian group however suggests that bupropion actually manifests cardiotoxicity by interfering with gap junctions (membrane proteins critical for cells to communicate with one another) causing loss of coordinated cardiomyocyte function.^[50] It prolongs the QRS interval via gap junction toxicity.^[41]
- Bupropion does not have sodium channel blocking properties.^[41]
- It is the only drug we know of with this mechanism of toxicity.^[41]

Techniques for management

1. Ultrasound

- It is recommended to perform cardiac POCUS (Point-of-Care Ultrasound) particularly in patients with primary signs of neurotoxicity, as identifying cardiotoxicity prior to fulminant cardiovascular collapse may allow time for potentially life-saving interventions.^[41]

2. Sodium Bicarbonate

- Given that sodium channel blockade does not occur in bupropion overdose, sodium bicarbonate does not have biological plausibility as a treatment mechanism.
- Additionally, there is an abundance of literature showing no beneficial outcome with this treatment in the context of bupropion poisoning.^[51–56]

3. Lipid Emulsion

Lipid emulsion theoretically functions by two mechanisms in the treatment of overdose.^[41]

- It acts as a lipid sink; functioning as intravenous decontamination and causing lipophilic drugs like bupropion to diffuse out of tissues affecting by toxicity and into the lipid-rich blood stream due to basic diffusion gradients.

- It provides the heart with free fatty acids – an additional energy source to sustain myocardial tissue.
- Evidence for lipid emulsion in the context of cardiac arrest is weak, however given absence of other options, this is a reasonable consideration.^[57, 58]

4. VA-ECMO (Venoarterial- Extracorporeal Membrane Oxygenation)

- Literature addressing ECMO for bupropion overdose is extremely limited and based on only a few case reports of successful intervention.^[41]
- Given good biological plausibility, and lack of comorbidities in most patients with bupropion overdose, ECMO should be a major consideration in the management of patients with severe bupropion overdose in refractory shock states presenting to ECMO capable centers.^[59, 60]

Case Studies

- ❖ We report the case of a patient who presented to the emergency department (ED) with a recent history of generalized tonic-clonic seizures whose etiology was initially a diagnostic mystery. After an initial visit to another ED, the patient presented to our ED later that day with a recurrence of the seizures after crushing and nasally insufflating oral bupropion tablets. We review important implications of this case to emergency medicine, including the potential for abuse of bupropion, the difference between intranasal and oral administration, the changing trends in the etiology of drug-related seizures and the importance of examining the nares in patients with unexplained seizure and delirium.^[61]
- ❖ Thirteen articles describing bupropion overdose in 116 patients were identified. Only 3 patients exhibited cardiotoxicity following acute ingestion; 2 of these patients also ingested other medications. All 3 patients experienced tachycardia and conduction delays (widened QRS complex and/or prolonged QTC interval), but none of these delays progressed to a life-threatening arrhythmia. All patients recovered, with resolution of cardiotoxicity within 2–4 days following ingestion.^[62]
- ❖ In the study conducted for the purpose of describing the incidence and outcomes of bupropion exposures reported to the Ontario Poison Centre in Canada, and to identify predictors of seizures, there were 1,065 reported bupropion overdoses. Among patients with reported outcomes, 51.9% of patients had episodes of tachycardia, (23.9% of patients had ECG changes, and 17.3% of patients experienced a seizure. The dose of bupropion ingested was significantly associated with the odds of seizure, with a 13% increased odds of seizure for every 20 mg/kg increase in bupropion dose (Odds Ratio [OR] = 1.13, 95% CI = 1.05–1.21). Co-ingestion of benzodiazepines reduced the odds of seizure by over 60% (OR = 0.32, 95% CI = 0.15–0.69).^[63]

❖ There were 975 bupropion abuse cases, which accounted for 3.3% of single substance bupropion cases reported to US poison centers. The prevalence of abuse increased by 75%, from 2000 to 2012, declining slightly in 2013. The majority of cases were 13 to 29 years old (67.4%). The most frequent clinical effects were tachycardia (57.0%), seizures (33.5%), agitation/irritable (20.2%), hallucinations/delusions (14.0%), and tremor (13.1%). Most exposures were ingestions (745) followed by insufflation (166), parenteral (17), and other/unknown (17); 30 cases involved 2 routes. Seizure frequency was not significantly different between routes ($P = 0.783$) or exposure chronicity ($P = 0.264$). Final management sites were predominantly emergency department (36.9%) and admission to critical care unit (27.3%) or noncritical care unit (20.1%). Outcomes were major (11.4%), moderate (48.2%), minor (24.5%), and no effect (15.5%). There were 4 deaths. Most bupropion abuse occurs in adolescents and young adults. Tachycardia and seizures are common indicating the potential for serious effects. Seizures occur regardless of route. Providers should be aware of risk of bupropion abuse.^[64]

CONCLUSION

Bupropion overdoses are a common source of toxicity. Bupropion toxicity is commonly characterized by tachycardia, lethargy, vomiting, agitation and seizures. The first line drug for management of the seizing bupropion overdose is benzodiazepines. Co-ingestion of benzodiazepines reduced the odds of seizure by over 60%. The cardiovascular effects of bupropion overdose seem to be minimal. Less than 0.5% of reported cases of bupropion overdose result in death.

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