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# Sustained-Release Bupropion Overdose: A Case Report

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### Authors' contributions

*This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.*

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Case Report

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## ABSTRACT

Bupropion is an atypical antidepressant with a unique aminoketone structure similar to amphetamines. A narrow therapeutic margin is evident from observational studies that show seizure activity with doses of 400-600 mg or higher.

A 38-year old woman took an overdose of 6 grams of bupropion with 110 grams of alcohol. She presented to the Emergency Department with agitation, visual hallucinations and myoclonus of the upper limbs; eyes spontaneously open with isochoric and light reactive pupils with horizontal nystagmus; afebrile, normotensive (121/63 mm Hg) and tachycardic (120 beats/minute). The electrocardiogram revealed a sinus tachycardia with prolonged QT interval (QT/QTc: 0.46/ 0.537) and a QRS complex length in the upper limit of normal. Arterial blood gases revealed metabolic acidosis (pH = 7.16) with increased anion-gap (value=18). She developed mal epilepticus needing thiopental induced coma and Intensive Care Unit (ICU) admission. She suffered prolonged symptoms including seizures before fully recovering.

The narrow therapeutic range and the increasing use in the treatment of smoking cessation boosted the number of intentional and unintentional poisoning by this drug. Previous reports of

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bupropion overdose almost all involve the immediate release formulation. There are some reports of overdose with sustained-release formulation, but there is limited information on its spectrum of toxicity.

*Keywords: Sustain-release bupropion; intentional overdose; adverse effects; prognosis.*

## 1. INTRODUCTION

Intentional drug overdose usually with multiple substances and alcohol is a reality in critically ill intoxicated patients, many of which needing admission to critical care environment. In recent years, scientific development promoted the emergence of many potential drugs with overlapping manifestations, requiring high demands on recognition, monitoring and treatment [1,2].

Bupropion is an atypical antidepressant with a unique aminoketone structure similar to amphetamines. It is thought that its mechanism of action comprises selective inhibitory effects on transporter and neuronal reuptake particularly on dopamine and serotonin but also norepinephrine and a moderated anticholinergic effect [3,4,5,6]. This agent was approved in 1986 as an antidepressant at a dose of 400 to 600 mg per day and promptly removed from the market for higher incidence of seizures, particularly in patients with bulimia, epilepsy or history of head trauma. It was reintroduced to the market in 1989 in a lower dose range (maximum of 450 mg per day) and with contraindications in high risk populations [3,4,5,6,7]. Since 1997, bupropion was particularly important as adjunctive therapy in smoking cessation at a dose of 150 mg per day and in higher doses in cocaine addiction, not as a substitute but by increasing the concentration of dopamine in the nucleus accumbens, traditionally linked to the sense of well-being and pleasure [5,6].

The narrow therapeutic range and the increasing use in the treatment of smoking cessation boosted the number of intentional and unintentional poisoning by this drug. Previous reports of bupropion overdose almost all involve the immediate release formulation, available in the United States but not everywhere else (including Western Europe). There are reports of the sustained-release formulation in overdose, but there is limited information on its spectrum of toxicity.

The authors present a case of intentional overdose by sustained-release bupropion, with

review of the literature regarding clinical effects and standards of therapeutic orientation.

## 2. CASE REPORT

A 38 year old woman with previous history of depression including two previous suicide attempts (at 21 and 28 years old) was admitted to the Emergency Department 2 hours after a voluntary intake of 6 grams of bupropion (20 pills of 300 milligrams of sustained release) and 110 grams of alcohol. Medical and psychiatric history was notable only for depression. There was no history of epilepsy or eating disorders. She was taking no other medications and bupropion was prescribed by family doctor, two weeks ago, at 300 mg day. On examination she presented with agitation, visual hallucinations and myoclonus of the upper limbs; the eyes were spontaneously open with isochoric and light reactive pupils and with spontaneous horizontal nystagmus; afebrile, normotensive (121/63 mm Hg) and tachycardia (120 beats/minute) with unremarkable cardiopulmonary auscultation. Arterial blood gases revealed metabolic acidosis (pH = 7.16) with increased anion-gap (value = 18). The electrocardiogram showed a sinus tachycardia with prolonged QT interval (QT/QTc: 0.46/ 0.537) and a QRS complex length in the upper limit of normal. She underwent medical treatment with gastric lavage without recovery of pills, followed by administration of activated charcoal. Four hours after presentation she suffered three generalized tonic-clonic seizures, resistant to the administration of diazepam and phenytoin evolving to mal epilepticus prompting ICU admission and thiopental induced coma. The blood alcohol level was 110 grams by enzymatic assay with alcohol dehydrogenase. Drug screening in urine (tricyclic antidepressants, benzodiazepines, opioids and amphetamines) was negative by fluorescence immunoassay.

The patient had a benign course under anticonvulsant drugs, without paroxysmal activity on electroencephalogram and with electrocardiography normalization after 24h.

She had aspiration pneumonia, treated with amoxicillin and clavulanic acid 2.2 g 8/8hours, as secondary complication.

Clinical stability allowed downstage to the high dependency unit three days after and further guidance to the Psychiatry ward.

### 3. DISCUSSION

Our article has focused on intentional bupropion ingestion with alcohol resulting in seizures. Fortunately, the majority of these patients had self-limited seizures and recovered without any permanent damage like how our patient. Seizures were more common when patients had co-ingested stimulants or alcohol, which may result in a further lower threshold. Although seizures often occur early, late presentation is also possible, particularly if other neurological symptoms are preceding, like tremors and hallucinations, as occurred in this case.

Bupropion is an atypical antidepressant with a unique aminoketone structure similar to amphetamines, particularly important as adjunctive therapy in smoking cessation and cocaine addiction [3-7]. A narrow therapeutic margin is evident from observational studies that show seizure activity with doses of 400-600 mg or higher [6,8].

Metabolized by multiple pathways without any preference it leads to the production of 3 active metabolites that prolonged the adverse effects - hydroxybupropion (~ 4 hours), treohydrobupropion (~ 6 hours), erythrohydrobupropion (~ 8 hours). The first one is to be considered the main determinant for the adverse effects of the drug [4,5,8,9].

The half-life is estimated to be 21 hours and may be extended by the simultaneous use of other substances, with particular emphasis on alcohol (as in the case here described) and monoamine oxidase inhibitors, or in the presence of a large amount of active metabolites, themselves with a longer half-life (8.9). The removal by hemofiltration or hemodialysis is ineffective and

the lack of an antidote requires support of dysfunctions until the effective elimination of the drug [3] (Table 1).

The toxicity of bupropion is expressed by a wide spectrum of clinical manifestations including gastrointestinal, neurological and cardiovascular symptoms [10-12] (Table 2).

Adverse effects usually occur within 4 hours of taking the dose, but seizure activity may be delayed for several hours [13,14].

Gastrointestinal symptoms are present in about one third of patients namely nausea and vomiting, described as the earliest and usually self-limiting. Neurological manifestations stand out by their frequency and exuberance. Tremors (24%), drowsiness (16%), agitation (32%), delirium and hallucinations (21%) are the first signs of intoxication, as in our patient. Seizures occur in 15-37% of patients, and generally are late manifestations and dose-dependent [6,10,11,13,14]. Delayed onset of seizure activity occurred up to 14 hours (mean, 4.3 hours) with overdoses on sustained-release bupropion [7]. Typically with multiple episodes of short duration and self-terminating and rarely generalized with toxic levels less than 3 grams of bupropion. However, nearly 5% of patients who had a seizure developed status epilepticus [15]. The sustained-release formulations and the association with alcohol (> 25grams) are enhancers and promote recurrence of seizures for up to 72 hours, although seizures occur with both therapeutic formulations of bupropion overdose [9,16]. Our patient took 6 grams of bupropion of sustained-release and 110 grams of alcohol and four hours after presentation, she suffered three generalized tonic-clonic seizures evolving to mal epilepticus. Likewise she experienced prolonged symptoms including evolution into mal epilepticus, needing ICU admission for three days before fully recovering.

**Table 1. Pharmacokinetics of the various pharmacological forms of bupropion [10,12]**

Bupropion formulation	Immediate release 100 mg tid	Sustained-release 150 mg bid	Extended-release 150 mg, 300 mg qd
Absorption	1,5 hours	2,5 hours	5 hours
Metabolites	3-4 hours	5-6 hours	7-8 hours
Distribution	Volume distribution: 19-21 L/Kg Protein binding: 77-88%		
Half-life of bupropion	21 ± 9 hours		
Half-life of active metabolites	20 – 37 ± 10 hours		
Elimination	Renal, intestinal		

**Table 2. Clinical manifestations of bupropion toxicity [3-5,10-12,14]**

<b>System</b>	<b>Manifestations</b>
Gastrointestinal	Nausea, vomiting, diarrhea, abdominal pain
Neurological	Tremors, agitation, visual hallucinations, seizures, insomnia, paresthesias, light headedness, headache, confusion, coma
Cardiovascular	Tachycardia, hypertension, QT and QRS prolongation, systolic dysfunction , electromechanical dissociation , cardiogenic shock
Others	Xerostomia , metabolic acidosis

More recently, cases of cardiotoxicity have been reported with sinus tachycardia (83%), hypertension (56%), prolonged QT interval and abnormal interventricular conduction with high potential malignant arrhythmias [10,11]. These changes can cause systolic dysfunction and even cardiogenic shock with high risk of death. Despite tachycardia and prolonged QT interval, systolic dysfunction did not happen in this case. The pathophysiology of cardiac dysfunction remains unknown, although it is believed that the adjunctive therapy for the intoxication may have an influential role. With the exception of sinus tachycardia, other cardiac manifestations are uncommon with less than 1.5 g doses. Malignant arrhythmias and sudden death are only seen on massive poisoning. Death from cardiac causes rarely occurs with less than 10g poisoning [3,5]. The risk of toxicity and death may be increased with involvement of certain co-ingestants, especially alcohol [14,15]. The treatment of this poisoning is the support of dysfunctions until the effective elimination of the drug. Gastric lavage and oral administration of activated charcoal should be accomplished in the first hour after intake of the drug. Oral administration of additional doses of activated charcoal or intestinal irrigation is not recommended, except in cases of poisoning with sustained release formulations, with high potential delayed toxicity, which wasn't performed in the case [3-5].

Seizures are often self-terminating but therapeutic intervention may be required, mainly in the case of sustained release bupropion intoxication or in association with alcohol. Anticongestants calcium channel blockers (carbamazepine, phenytoin) should not be used by favoring cardiotoxicity. In these situations benzodiazepines are the preferred approach, even in high dose and in refractory cases are recommended barbiturates drugs, as it was in the present case. The use of benzodiazepines is also effective in visual hallucinations, which should not be dealt with antipsychotic drugs that

lower seizure threshold [3,4,5]. The electrocardiographic changes usually solve with supportive treatment, rarely requiring antiarrhythmic drugs.

Dosage adjustment and restriction on prescription of bupropion improved the safety profile of this drug use. Nevertheless the increasing use of new formulations in the treatment of smoking cessation and the common association with other toxic agents, namely alcohol, enhanced dramatically the number of voluntary and involuntary intoxication. The most important adverse effects are reflected in the central nervous system with changes in the mental status and seizures and in the cardiac system with arrhythmias and QT prolongation. This entity usually has a benign course, except in cases of massive poisoning (> 10g) and in cases related to sustained-release formulations where adverse effects are delayed and may persist up to 72h, being the neurological system the most worrisome. In most series the risk of death is low but there is no data mortality rate. The lack of an antidote and the impossibility of effective elimination by hemofiltration or hemodialysis require an aggressive and prolonged monitoring of neurologic and cardiovascular systems up to at least 12 hours. The treatment is support of dysfunction, mainly neurological and cardiovascular which might require ICU admission as in the current case.

#### 4. CONCLUSION

Bupropion, like other antidepressant agents, lowers seizure threshold. Further attention should be placed towards the lifetime presence of suicidal attempts or ideation, personal or familial history of medication abuse and substance use disorder, including alcohol. This seems particularly true for drugs like bupropion SR, which albeit generally safe within standard ranges of doses, may pose serious and life-threatening conditions in case of intoxication.

Specifically, psych education and an accurate monitoring for bipolar hints even in course of DSM-IV defined “unipolar” major depressive episodes seems mandatory for this high-risk population, as already directed by the recent guidelines released by the FDA about the prescription of antidepressants in depressed patients.

Our report is limited by lack of generalizability and high chance of confounding factors, namely the concomitant assumption of alcohol, but demonstrates the importance of recognizing the potential for deliberate self-poisoning and draws attention to physicians for carefully monitor patients taking any form of bupropion.

## CONSENT

All authors declare that written informed consent was obtained from the patient for publication of this case report.

## ETHICAL APPROVAL

Not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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