Seizures induced by recreational abuse of bupropion tablets via nasal insufflation

Daniel Kim, MD,* Brian Steinhart, MD†

ABSTRACT

Bupropion is a newer generation antidepressant that is commonly used for treatment of depression and for smoking cessation. Seizures are a frequently reported adverse effect of bupropion in therapeutic oral doses; however, there are limited data about the consequences of nasal insufflation of bupropion. 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.

Keywords: bupropion, seizure, nasal insufflation, nares

INTRODUCTION

Bupropion is a newer generation antidepressant of the aminoketone class that is currently approved by the US Food and Drug Administration (FDA) and Health Canada for treatment of depression and for smoking cessation.

Bupropion-induced seizures in therapeutic oral doses have been well described in safety surveillance data and case reports. There is limited information, however, about the consequences of nasal insufflations of bupropion, known colloquially as “snorting.” To our knowledge, this is the first report in the emergency medical literature of seizures induced by nasal insufflation of bupropion.

CASE REPORT

A 38-year-old man presented to an emergency department (ED) after having a witnessed seizure at a transition home. Upon arriving in the ED, the patient had a 20-second generalized tonic–clonic seizure witnessed by the ED medical staff. The seizure spontaneously resolved, and he was given 5 mg of intravenous diazepam and loaded with 1 g of intravenous phenytoin over 1 hour.

During the seizure in the ED, the patient bit his tongue, but experienced no incontinence. There was no history of head trauma. He had had a similar episode of seizure the previous evening and described having
Potential for abuse

Bupropion hydrochloride is structurally similar to amphetamines and is a weak catecholamine reuptake inhibitor predominantly affecting serotonin, norepinephrine and dopamine. Its exact antidepressant mechanism is unknown; however, it is presumed to be related to its dopaminergic and noradrenergic effects in the brain. This case illustrates 3 important points: the potential for abuse of bupropion, the differences between intranasal versus oral administration and the importance of examining the nares, and the changing epidemiology of drug-related seizures.

Because of its structural similarities to amphetamines, the stimulant effects of bupropion have been studied. Early research demonstrated that stimulant effects in rodents manifested as increased spontaneous activity. Griffith and colleagues compared oral bupropion with oral amphetamine to determine its abuse potential and found that the physiologic effects of oral bupropion were not significantly different from placebo for producing stimulant effects. Others have compared oral bupropion with oral amphetamine and oral amitriptyline and found that oral bupropion did not produce any physiologic stimulant or sedative effects. In patients with a history of substance abuse, however, 400-mg oral doses produced mild, stimulant-like subjective changes. Our patient described a chemical euphoria similar to that attained from cocaine after the insufflation of bupropion.

Bupropion is not a controlled medication, and the FDA deems it to have a low risk for abuse if taken in recommended daily divided dosages. The increasing use of intranasal bupropion, gabapentin, quetiapine, trihexyphenidyl and tricyclic antidepressants (TCAs) has been reported in prison populations. The crushing of oral medications and subsequent insufflation has also been described with methylphenidate. Interestingly, our patient disclosed that he had learned this method of...
bupropion administration during his incarceration. Bupropion was widely ordered as a smoking deterrent for inmates after Correctional Services of Canada attempted to ban smoking in all its security facilities in 2008 (Dr. Al McBride, Medical Director, Kingston Penitentiary Regional Hospital, Kingston, Ont.: personal communication, 2009). Physicians prescribing bupropion should consider the possibility of alternative methods of administration in groups at risk for misuse of medications.

**Intranasal versus oral administration**

A MEDLINE search using the keywords “bupropion” and “insufflations” identified 3 letters to the editor that reported bupropion insufflation with 2 cases that resulted in seizures.9-11 Bupropion-induced seizures have been well described and have been reported to occur in about 0.35% to 0.44% of all patients taking oral bupropion for depression at a dose of 450 mg/d or less.12-13 This risk is considered acceptable, but seizures have been documented with single doses ranging from 575 mg to 23 000 mg.14-16 Although bupropion’s effect of lowering the seizure threshold appears to be dose-dependent, researchers have described a group of 46 patients with a mean ingestion of 2148 mg who did not have a seizure.14 It seems that some individuals are genetically more susceptible to bupropion-related seizures.

The pharmacokinetics of bupropion have only been described with oral administration. We were unable to find any data that determined the rate of nasal absorption, but various drugs are efficacious after intranasal administration, including triptans, midazolam,17 cocaine, epinephrine and fentanyl. Furthermore, the nasopharynx offers a highly vascularized surface area for systemic drug absorption, direct entry into the brain and neuronal transport along the olfactory bulb.18

For bupropion insufflation to cause seizure, significantly elevated levels of bupropion in the cerebrospinal fluid (CSF) would be required. After oral administration, bupropion is rapidly absorbed and approximately 95% of the dose undergoes extensive first-pass hepatic metabolism, primarily by cytochrome P450 2B6, before being distributed throughout the rest of the body.19 Nasal insufflation can be expected to deliver the drug to the body and CSF before circulating through the liver, thus bypassing its first-pass metabolism and resulting in higher plasma concentrations. Consequently, ED physicians should examine the nares for powder in patients with unexplained seizure and delirium.

**Drug-related seizures**

Seizures are a serious complication associated with medication or drug use. Medications and drugs are an important consideration in the differential etiology of new-onset seizure, and 6.1% of new-onset seizures20 and up to 9% of cases of status epilepticus21 are estimated to be drug-related. A retrospective analysis of data from a regional poison centre 20 years ago reported that the leading causes of drug-induced seizures at that time were TCAs, cocaine and other stimulants.22 Because of evolving prescribing patterns and changes in patterns of drugs of abuse, the epidemiology of drug-induced seizures has also changed. A retrospective study of data from a state poison centre system in 2003 found that the leading causes of drug-induced seizures were bupropion, diphenhydramine and TCAs. The overall incidence of antidepressant-induced seizures has increased despite a decreasing trend of TCA-induced seizures. This was attributed to the large contribution of bupropion-induced seizures.23 Other drugs like tramadol and venlafaxine have emerged as important causes as well.24 A retrospective study of new-onset generalized seizures presenting to an ED demonstrated that, of drug-related seizures, the most common causes were cocaine, benzodiazepine withdrawal and bupropion.20 These studies clearly demonstrate a shift in the etiology of drug-induced seizures of which ED physicians should be aware. Unfortunately there is no role for bupropion plasma levels, as levels have not correlated well with either therapeutic effect or incidence of seizures.12,24 Phenytoin is often cited as the second-line agent in the treatment of status epilepticus, but it has not been found to be commonly useful in the management of drug-induced seizures.25 Based on the timeline of seizure after bupropion insufflation in our case, phenytoin therapy should not have been given, as the seizures were likely drug-induced.

**Limitations**

There are several limitations to our conclusions about this case. The association between bupropion insufflation and our patient’s seizures does not prove causality. Furthermore, we have been forced to rely on the patient’s self-reported history and collateral history from the paramedics to confirm that bupropion insufflation took place. We did not perform a urine toxicology screen; if we had a urine toxicology screen positive for bupropion and its metabolites, our case presentation would be strengthened. There is a lack of data that determine the rate of nasal absorption of bupropion. It is possible that the insufflation was not properly performed to achieve a therapeutic effect or that the insufflation took place. Additionally, the patient’s history could not be confirmed by any third party as there was no way to contact the patient’s family. Finally, ED physicians should consider the possibility of alternative methods of administration in groups at risk for misuse of medications.
would be stronger. Based on the timeline between bupropion insufflation and seizures, as well as the exclusion of other metabolic and intracranial etiologies for seizure, we believe it is reasonable to conclude that these seizures were bupropion-induced.

CONCLUSION

Bupropion is a newer generation antidepressant that is used increasingly for treatment of depression and for smoking cessation. Although it is generally believed to have a low potential for abuse, there are data to suggest it can cause mild, stimulant-like effects, especially if administered via nasal insufflation. This can bypass the drug’s first-pass hepatic metabolism, resulting in higher plasma and CSF concentrations. Emergency physicians should be aware of this method of administration, especially among groups at risk for misuse of medications, and should examine the nares for powder residue. Finally, emergency physicians should be aware of changing trends in the etiology of drug-related seizures, especially in the sense that bupropion and other newer drugs, like tramadol and venlafaxine, have emerged as common causes of drug-induced seizures.

Acknowledgements: The authors would like to thank Dr. Margaret Thompson, medical director of the Ontario Poison Centre at the Hospital for Sick Children, for reviewing this paper and providing her valuable input and insight.

Competing interests: None declared.

REFERENCES


Correspondence to: Dr. Daniel Kim, 1912-633 Bay St, Toronto ON M5G 2G4; dkim000@gmail.com