The ToxIC NOSE (Novel Opioid and Stimulant Exposure)

Report #9 from ToxIC's Rapid Response Program for Emerging Drugs

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Bupropion Stimulant Exposures

Introduction

Bupropion, or Wellbutrin®, is a popular atypical antidepressant that is also used as an adjunct for smoking cessation and methamphetamine use disorder. Nearly 30 million prescriptions written in 2021 in the United States and it is generally well tolerated at therapeutic doses.[1] Bupropion's mechanism of action is unique among antidepressants because in addition to inhibiting the reuptake of serotonin like the typical antidepressants classified as Selective Serotonin Reuptake Inhibitors (SSRIs), it also acts as a stimulant via the reuptake blockade of norepinephrine and dopamine in a manner similar to that of cocaine and methamphetamine.[2] While this feature conveys therapeutic benefits for bupropion over standard SSRIs, it also comes with increased risk, particularly in overdose. Bupropion dose-dependently lowers seizure threshold which increases seizure risk in those with existing seizure disorder or closed head injury. In addition, seizures can occur after a small overdose, and difficulty to treat life-threatening cardiotoxicity can occur at higher doses.[2]

ToxIC Novel Opioid and Stimulant Exposures (NOSE) Reports

As a project of the Opioid Response Network (ORN), the American College of Medical Toxicology (ACMT) Toxicology Investigators Consortium (ToxIC) is using the enhanced sentinel detector field to identify and report on novel and emerging opioid and stimulant exposures reported in ToxIC every quarter over a 2-year period.

The goal of this project is to disseminate this novel information to the medical toxicology community as well as the ORN as part of a Rapid Response program.

For more information on the ToxIC Core Registry and data collection, please visit: www.toxicregistry.org

Although illicit substances such as methamphetamine are classically thought of as the mainstay of simulant use, the stimulatory effect of bupropion may make it appealing for recreational purposes. Structurally, bupropion is a synthetic cathinone. Other synthetic cathinones include illicit drugs often referred to as "bath salts" which are associated with significant morbidity.[3] Despite risks of seizure and cardiac toxicity, use of bupropion as a recreational drug has been reported.[4] Recently, the ToxIC NOSE identified a case of significant toxicity after bupropion was crushed and snorted intranasally by a young individual.

ToxIC Nose Case Description

A young woman with a history of anxiety, depression and attention deficit hyperactivity disorder (ADHD) snorted an unknown amount of bupropion XL. She was found unresponsive by emergency medical services (EMS) and was given naloxone without improvement. Upon arrival to the emergency department (ED), she had multiple seizures that were refractory to initial treatment with benzodiazepines. She was subsequently given an intravenous phenobarbital load and with resolution of her seizures. She was placed on non-invasive BiPAP for respiratory support. Her clinical course was complicated by an aspiration pneumonitis. Ultimately, she made a full recovery. She reported using bupropion via crushing the pills and snorting them multiple times a week for recreational purposes but denied any other substance use. Confirmatory comprehensive urine drug testing was only positive for her home medications, including bupropion and medications given during her hospitalization.

ToxIC Data Review

A search of ToxIC Core Registry identified 25 cases of intranasal bupropion misuse unrelated to attempts at self-harm between 2012-2022; 15 of those cases were single agent exposures. Ethanol was the most common coingestant (N=3, 30%). When reported, the dose of bupropion snorted ranged from 200-6,000 mg (median 3,750 mg; IQR 950-6000 mg). Case occurrence remained relatively stable over time (Figure 1). Average age was 39 years (range 16 to 53 years) and most cases were male (N=21, 84%). Neurologic findings were most common and occurred in 88% of cases (Table 1). Other pertinent clinical toxicity reported included sympathomimetic toxidrome (N=6, 24%), tachycardia (HR >140 sec) (N=7, 28%), metabolic acidosis (serum bicarbonate <18) (N=4, 16%), wide QRS (QRS >120 ms) (N=2, 8%), QT prolongation (QTc >500 ms) (N=1, 4%), aspiration pneumonia (N=1, 4%), respiratory depression (N=1, 4%), acute kidney injury (N=1, 4%), and rhabdomyolysis (N=1, 4%). Toxicologic treatment was administered in 76% (N=19) of cases, most commonly benzodiazepines (N=16, 64%) and IV fluid resuscitation (N=11, 44%). No patients required mechanical ventilation and no deaths were reported.

Figure 1: Intranasal Bupropion Cases Reported to the ToxIC Core Registry Over Time

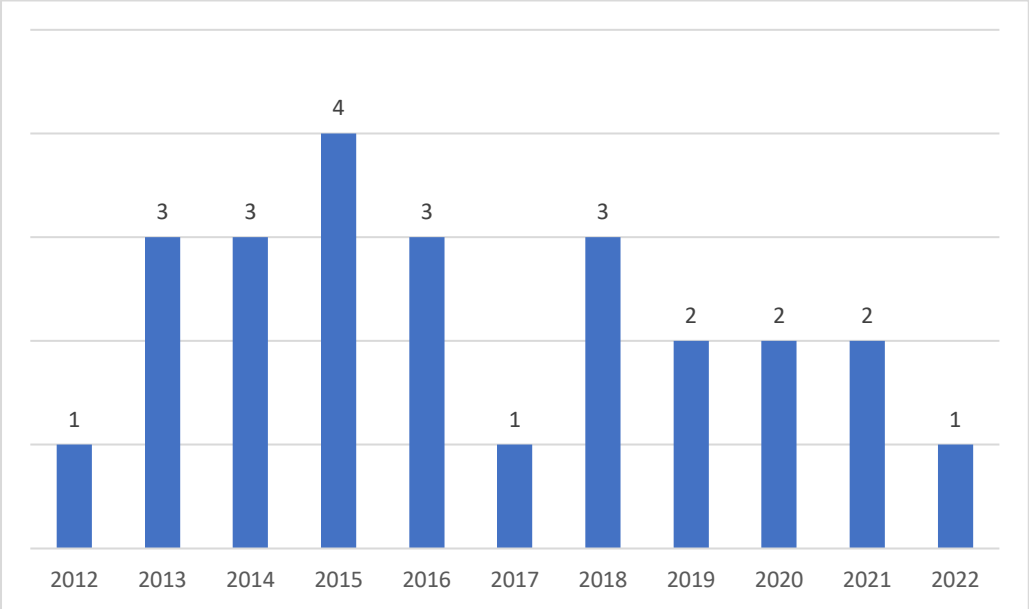

Table 1: Neurologic Signs and Symptoms: ToxIC Core Registry Bupropion Misuse

Neurologic Signs/Symptoms	**N (%)**
Agitation	8 (32)
Hyperreflexia	7 (28)
Seizures	6 (24)
Hallucinations	4 (16)
Delirium/Toxic Psychosis	3 (12)
Coma	1 (4)
Total Cases with ≥1 Neurologic finding	**22 (88)***

*Cases may have had more than one neurologic finding reported

Discussion

Bupropion was not initially thought to possess the same reinforcing effects as other misused stimulants and consequently was considered to be safe to use in patients with substance use disorders.[4] This is despite similar mechanisms of action between illicit stimulants and bupropion, including dopamine and norepinephrine reuptake inhibition at the synaptic cleft which leaves more stimulating neurotransmitters at the receptors for action.[5] Interestingly, pre-clinical animal studies demonstrated bupropion could increase motor activities usually associated with stimulant drug exposures, though to a lesser degree. [5] Other models show animals perceive similarities between the subjective experience of bupropion and other stimulant drugs such as cocaine, methamphetamine and methylphenidate. [5] Murine and non-

primate animal models likewise self-administer bupropion similarly to cocaine, further illustrating the reinforcing character of bupropion and the potential for illicit use.[5] Human clinical data presented a more mixed picture, with some studies describing similar subjective experience between other stimulant pharmaceutical agents such as methylphenidate and others showing less noticeable behavioral and emotional effects.[5]

A report of pediatric recreational use was published in 2001 and as early as 2002 a report of nasal insufflation of crushed bupropion appeared in the literature.[6,7] By 2005 it was recognized that bupropion was being misused within the correctional system as "poor man's cocaine," with insufflated crushed tablets described as a preferred mechanism of ingestion.[4,8] Insufflation bypasses first pass metabolism and may result in increased peak concentration relative to oral dosing and may be more effective at producing a euphoric "high" in the user.[5,8] Serious clinical effects, like seizures, do not appear to be related to the route of administration,[4] however tachycardia and seizures may be common after insufflation.[8,9]

Conclusion

Bupropion, a synthetic cathinone, is an effective medication used widely for depression and substance use disorders. Its unique pharmacologic properties make it both attractive for misuse and dangerous in overdose, most commonly with neurologic and cardiac toxicity. Clinicians should be aware of both the clinical presentation of bupropion overdose as well as its potential for recreational misuse.

References

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About the *Opioid Response Network (ORN)*:

ORN provides free, localized training and education for states, communities, organizations and individuals in the prevention, treatment and recovery of opioid use disorders and stimulant use. Learn more and submit a request at www.OpioidResponseNetwork.org.

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