Bupropion Overdose and Management

By Taylor Rhien, PharmD, and Kyle Murray, PharmD

Bupropion has been associated with seizures even at therapeutic doses and was removed from the market shortly after it was initially approved in 1986. Data showed that seizure risk was dose-dependent and highest in patients with eating disorders, previous head trauma, or epilepsy. Bupropion was reintroduced to the market 3 years later with label adjustments that included a lower maximum daily dose and contraindications for use in epilepsy, eating disorders, or head trauma. While these measures improved the safety at therapeutic doses, seizures continue to be a serious effect in overdoses.

As with other antidepressants, bupropion is commonly involved in poisonings. In 2014, antidepressants were the fifth most common substance class involved in human poison exposures reported to US poison control centers. Bupropion, specifically, was involved in 11,222 reported exposures, and moderate or major outcomes were reported in 1,453 exposures and death in 4 cases where bupropion was the only substance.

Pharmacology and Pharmacokinetics

Bupropion inhibits the reuptake of norepinephrine and dopamine, and unlike many other antidepressants, it has little effect on serotonin reuptake. Bupropion shares structural similarities to stimulant drugs, including cathinone and amphetamine derivatives.

Bupropion is available orally as a hydrochloride or hydrobromide salt, in combination with naltrexone, and in immediate and modified release formulations (Table 1).

Bupropion concentrations peak in less than 2 hours for immediate release preparations, but take as long as 5 hours with the modified-release formulations. Its half-life is 21 hours. Bupropion has 3 active metabolites with half-lives ranging from 20-37 hours. The primary metabolite, hydroxybupropion, is formed in the liver through CYP2B6 and has a peak plasma concentration 7 times the peak of the parent drug.

Adverse and Toxic Effects

Adverse effects, including dry mouth, abdominal pain, nausea, anorexia, myalgia, insomnia, dizziness, agitation, anxiety, tremor, pharyngitis, palpitation, sweating, rash, tinnitus, and urinary frequency, occur in greater than 5% of patients taking bupropion therapeutically. Manufacturer information reports seizures occur in approximately 0.1% of patients who take 300 mg SR and 0.4% who take 300 mg-450 mg IR. In a review of 7,348 immediate- (cont. on pg. 4)

Table 1: US Available Bupropion Products

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Active ingredient</th>
<th>Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aplenzin®</td>
<td>Bupropion hydrobromide</td>
<td>XL</td>
</tr>
<tr>
<td>Contrave®</td>
<td>Bupropion hydrochloride / naltrexone</td>
<td>SR</td>
</tr>
<tr>
<td>Forfivo XL®</td>
<td>Bupropion hydrochloride</td>
<td>XL</td>
</tr>
<tr>
<td>Wellbutrin®</td>
<td>Bupropion hydrochloride</td>
<td>IR*, SR*, XL*</td>
</tr>
<tr>
<td>Zyban®</td>
<td>Bupropion hydrochloride</td>
<td>SR*</td>
</tr>
</tbody>
</table>

IR = immediate release, SR = 12-hour sustained release, XL = 24-hour extended release; * = generic products available

IN THIS ISSUE

Bupropion Overdose and Management
Outreach Education: Holiday Poison Hazards
Toxins in the News: Kratom
Poison Pearls: Drug-Induced Seizures

Meet the UPCC Staff:
- Christian Clark
- Jina Kim
- Andy Tominaga
Holiday Poison Hazards

By Sherrie Pace, MS, MCHES

Along with winter holidays comes the potential for unique poison exposures. There are situational poison hazards that arise when family and friends gather together, and when out-of-town visitors arrive with dangers lurking in their travel bags. There are also hazards that stem from traditions such as holiday plants, ornaments, and meals. Awareness of poison risks and prevention strategies is the first step to poison safety during the holiday season.

Food and Drink

- Food poisoning due to improper food handling can cause illness. Avoid cross-contamination by washing hands, surfaces, and utensils often, and by separating raw meat from other foods. Cook food to appropriate temperatures, and thaw meat and poultry in the refrigerator. Do not leave perishable food at room temperature longer than 2 hours.
- Alcoholic beverages within the reach of children are a hazard. Clean up all glasses and cups after parties, and keep alcohol out of reach of children.

Decorations

- Tree ornaments such as glass bulbs, tinsel, and bubble lights can be harmful in the hands of children. Ornaments can pose a choking hazard for young children. Cuts in the skin may occur when handling broken glass bulbs. Tinsel poses not only a choking hazard, but it may cause blockage in the intestine. Bubble lights are typically filled with alcohol or other solvent that can cause eye and skin irritation and nausea. Do not allow children to handle these items.
- Fireplace flame color enhancers that create brightly colored flames may be caustic or contain heavy metals such as lead and arsenic, and can be harmful if swallowed. Keep this product up and away from children.
- Lamp oils that are colored and/or scented may be used in holiday celebrations. Lamp oils are very dangerous if swallowed. Lamp oils and other like products can easily get into the lungs and cause chemical pneumonia. The colorful and scented oils are attractive to children and are sometimes mistaken for something safe to drink. To avoid poison exposure, store lamp oil in its original container and up and out of reach before, during, and after use.
- Plants are frequently used in holiday decor. Holly berries are considered toxic, and ingestion of a handful may cause severe vomiting and diarrhea. American mistletoe (Phoradendron serotinum) may cause stomach upset if eaten but is considered less toxic than the European mistletoe (Viscum album). Contrary to common belief, the poinsettia (Euphorbia pulcherrima) is not toxic. To be safe, keep all plants up and out of reach of children and pets.

Toy/Gift Hazards

- Button batteries can be found in toys, games, and greeting cards. They can cause serious and life-threatening injury if swallowed. Do not let children play with toys or cards that contain button batteries.
- Rare earth magnets are strong tiny magnets that are sold as toys and can be very harmful if swallowed. Keep magnets in a locked cabinet up and away from small children. Count all pieces after each use to ensure none are missing.

Medications

- Medications are poison hazards year-round, but disruptions in routine and extra holiday guests often increase risk for a poison event when medications are left in pockets, suitcases, and purses. Provide a safe place for visitors to store medicine up and out of reach of children. If taking children to other homes, be aware of medications within reach, and ask that they be secured up and away during the visit.

References: NCPC, CDC

Kratom

By B. Zane Horowitz, MD

A plant from Thailand, long banned as a drug of abuse in that country, recently caught the attention of the Drug Enforcement Agency. The DEA issued “notice of intent” to place Kratom on Schedule I, the most restrictive designation for drugs, beginning on October 30, 2016. However, a grass roots outcry challenged that, and in an unprecedented reversal the DEA backed down, opening a comment period to the public before deciding. So what is Kratom, and does it have a role in therapy, as its proponents claim?

Kratom is a derivative from the leaves of the plant Mitragyna speciosa, a tropical evergreen tree in the coffee family. Two psychoactive substances from this plant have been identified: mitragynine and 7-hydroxymitragynine. Traditionally, when kratom was used in Thailand and Malaysia, farmers would pick and chew the leaves as they worked. At these small doses, usually less than 5 grams, there was a stimulant effect, not unlike caffeine. However, at doses above 5 grams, kratom acts more like an opioid, demonstrated to bind to mu receptors. Recognizing the drug’s abuse potential, Thailand banned the drug in 1943, and Malaysia followed in 1952.

Within the last decade, a form of kratom, desiccated leaves sold as loose powder or encapsulated in gel caps, started showing up among adventure travelers, college campuses, and underground websites such as EROWID. The more potent ingredient, 7-hydroxymitragynine, with a potency from 13 to 46 times that of morphine, started to show up in products for sale. Deaths, all with polypharmacy of other drugs, started to appear in the medical literature, and calls to (cont. on pg. 3)
**POISON PEARLS**

**TREATMENT OF DRUG-INDUCED SEIZURES**

By Kaitlyn Brown, PharmD, Clinical Toxicology Fellow

Drug toxicity is estimated to cause 6.1% of new-onset seizures. Antidepressants, stimulants, anticholinergics, and antiepileptics are the most common drug classes associated with seizure (Table 1). While the majority of drug-induced seizures are self-limited, an estimated 3.6-10% of patients develop status epilepticus. Proper management and good supportive care is necessary to prevent complications from seizure, such as hyperthermia, hypoxic injury, aspiration, and death. Drug-induced seizures are diffuse and pathologically different than idiopathic seizure. Thus, treatment of drug-induced seizure and status epilepticus differs from guideline management of idiopathic status epilepticus.

Benzodiazepines are recommended as first-line therapy for drug-induced seizures; however, no studies have compared efficacy of individual benzodiazepines. Intravenous (IV) lorazepam, IV diazepam, or intramuscular midazolam are considered equally efficacious for initial management of seizure. If isoniazid toxicity is suspected, intravenous pyridoxine in combination with a benzodiazepine is recommended as first-line therapy.

Propofol or barbiturates are recommended as second-line therapy for drug-induced seizures refractory to benzodiazepines. Unlike treatment of idiopathic status epilepticus, phenytoin/fosphenytoin is not recommended for drug-induced seizures. Phenytoin blocks sodium channels and inhibits electrical propagation from a seizure focus. Since drug-induced seizures lack a focus of abnormal neurons, phenytoin is ineffective. Additionally, IV phenytoin is associated with cardiac arrhythmia and hypotension. Many drugs associated with seizure also cause conduction disturbances, and administration of phenytoin may increase the risk of cardiotoxicity.

Levetiracetam has been considered for use in treatment of drug-induced seizure. Levetiracetam’s mechanism of action differs from other anticonvulsants since it inhibits proteins that are required for exocytosis of excitatory neurotransmitters from presynaptic neurons. A recently published abstract reported a 71% rate of seizure control in patients with drug-induced status epilepticus after administration of levetiracetam. Its unique mechanism of action, availability as an IV preparation, and lack of cardiotoxicity with therapeutic use make levetiracetam a reasonable candidate when first- and second-line therapies fail. However, more studies are needed to confirm its role for treating drug-induced seizures.

Current standard of care for drug-induced seizure involves benzodiazepines for first-line therapy, barbiturates or propofol for second-line therapy, and good supportive care. Phenytoin has no role in the management of drug-induced seizure, and further studies are needed to define the role of levetiracetam.

---

**Table 1. Common Drugs Associated with Drug-Induced Seizure**

<table>
<thead>
<tr>
<th>Anticholinergics</th>
<th>Antiepileptics</th>
<th>Antidepressants</th>
<th>Stimulants</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenhydramine</td>
<td>Lamotrigine</td>
<td>Tricyclics</td>
<td>Cocaine</td>
<td>Tramadol</td>
</tr>
<tr>
<td>Doxylamine</td>
<td>Carbamazepine</td>
<td>Bupropion</td>
<td>Amphetamines</td>
<td>Ionizad</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Venlafaxine</td>
<td>MDMA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Citalopram</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**POISON TIPS**

1. Do not use phenytoin or fosphenytoin to treat drug-induced seizures.

---

**References**


---

**Poison Help 1 (800) 222-1222**

---

**TOXICOLOGY TODAY**

---

**Kratom**

poison centers nationwide about patients on kratom with clinical signs of obnubilation skyrocketed in the last 24 months. As a result, many, but not all, states banned it as a drug of abuse, and the DEA finally stepped in to create a nationwide halt to its use and classify kratom along with drugs with no known medical indication, such as heroin and LSD.

However, some protested, claiming that kratom was valuable to detoxify from opioid addiction—both heroin and prescription medications. Unfortunately, the only evidence that it works as a detoxification modality from opioids is the testimonials and surveys of user’s experiences. Nonetheless, the DEA has taken a step back to allow for public commentary, and a decision on its schedule classification is expected as this newsletter goes to press. If it is a drug useful for detoxification, then like all medications, it should have studies done to show its efficacy, side effects, doses, and contraindications, as required of any medication used to diagnose or cure disease.

---

**Reference**

Bupropion release and sustained-release bupropion exposures reported to US poison centers between 1998 and 1999, clinical effects were documented in 2,247 (30.6%). The most common effects were tachycardia (30.0%), drowsiness/lethargy (22.6%), seizures (18.6%), agitation/irritability (14.8%), vomiting (14.1%), and tremor (11.8%). Single seizures occurred in 265 patients, multiple seizures in 133 patients, and status epilepticus in 19 patients. Five deaths were reported.

Most patients who have a seizure experience a prodrome that includes tachycardia, agitation, tremor, and/or hallucinations. In a review of 385 intentional bupropion exposures reported to Texas poison control centers from 1998-1999 by Shepherd, 40 out of 41 patients (97.6%) experienced agitation, hallucinations, or tremor prior to their first seizure. In a 3-year study at 5 different poison control centers conducted by Starr, patients who seized after ingesting bupropion were more likely to experience agitation (29.7% vs. 12.5%, p < 0.05), tremor (40.5% vs. 17.5%, p < 0.005), and tachycardia (91.8% vs. 51.2%, p < 0.0005) when compared to patients who did not seize. The onset of seizures can vary widely in bupropion overdose and is likely dependent on drug formulation. In exposures reported to Texas poison control centers, onset time to initial seizure ranged from 1 hour to 14 hours post-ingestion (mean, 4.3 ± 3.2 hours). Sustained-release preparations accounted for 71% of these exposures. Looking at ingestions of the XL formulation only, Starr found that onset time to initial seizure ranged from 0.5 to 24 hours post-ingestion (mean, 7.3 ± 5.4 hours). Initial seizure occurred within 8 hours in 68% of patients, between 8 and 24 hours in 24% of patients, and with unknown timing in 8% of patients. Nearly half (49%) of the patients who seized experienced a second seizure with average onset of 9.8 hours (range 1.5-19 hours) post-ingestion.

Severe cardiac toxicity is rare following bupropion overdoses. However, conduction disturbances (QRS prolongation, QTc prolongation), dysrhythmias, hypotension, and cardiovascular collapse have been described.

Management
Decontamination may be appropriate in patients presenting soon after large bupropion overdoses. Activated charcoal may be considered within 1 hour of ingestion in patients who are not actively seizing or post-ictal who are able to protect their airway. Whole bowel irrigation may be considered in patients who ingest very large quantities of modified release preparations. Bupropion exposures require extended observations due to the risk of delayed onset seizures. Modified-release preparations are commonly preferred for their dosing convenience, and symptom onset does not correlate well with the pharmacokinetics of the parent drug but may be due to its active metabolites. This is especially true for the risk of developing delayed-onset seizures after a relatively asymptomatic period of 8 hours or more in overdose situations. The Utah Poison Control Center recommends monitoring patients at least 8 hours post-ingestion for immediate release bupropion and 24 hours post-ingestion for sustained and extended release bupropion and all self-harm attempts. If patients become symptomatic, observe until symptoms are resolved. There is no specific antidote for bupropion, and management is supportive. Benzodiazepines are the drug of choice to treat bupropion seizures and should be strongly considered for patients with agitation, tachycardia, hallucinations, or tremor in order to prevent progression to seizures. Carbamazepine and propofol may be considered for refractory seizures. Since drug-induced seizures are diffuse and have no identifiable seizure focus, phenytoin is less likely to terminate these seizures when compared to other sedative-hypnotic anticonvulsants. A baseline ECG and frequent vital sign monitoring should be performed on all patients who ingest bupropion. For all self-harm ingestions, patients should be placed on continuous cardiac monitoring, paying close attention to the QRS and QTc intervals. In the case of severe cardiac toxicity, intravenous lipid emulsion therapy may be considered, and consultation with a medical toxicologist is recommended.

Summary
Bupropion is a unique antidepressant with an increased risk for seizures in supratherapeutic doses. Onset of seizures can be delayed 16-24 hours, necessitating prolonged observation times following ingestion of modified-release formulations. The Utah Poison Control Center is available at 1-800-222-1222 for toxicology consultation, 24 hours a day, 7 days a week, 365 days per year.

References

HOW THE UPCP PROVIDES VALUE TO UTAH HEALTH CARE FACILITIES

- Helps decrease crowding in the emergency departments
- Minimizes unnecessary EMS ambulance transport
- Frees critical emergency medical staff for true emergencies
- Provides cost-effective treatment recommendations for hospitalized patients

www.utahpoisoncontrol.org
WHAT WOULD UTAHNS DO IF THE UPCC WAS NOT AVAILABLE?

30% would visit the emergency department, estimated cost $18.3 million annually

22% would call 911, estimated cost $22.7 million annually

27% would call a physician, estimated cost $10.5 million annually*

*Cost savings when ED visits are averted. Studies show physicians refer poisoned patients to ED.

MEET THE UPCC STAFF

Christian Clark, PharmD, was raised in Utah. He began working at Poison Control in June 2015. Christian received his PharmD from the University of Utah. While in pharmacy school, he completed a rotation at Poison Control and discovered his love of toxicology. His toxicology interests include ethylene glycol and dietary supplements. When Christian is not at work, he is planning his next trip, listening to podcasts about movies, or playing with his precocious two-year-old son.

Jina Kim, BA, started working at the Utah Poison Control Center in December 2014. She grew up in Studio City, California, and received her BA degree in psychology at the University of California, Riverside. She worked in mental health services before she decided to pursue her career in pharmacy. Jina is a P3 pharmacy student at the University of Utah College of Pharmacy. In her free time, she enjoys reading a nice book with a cup of coffee, watching Friends, and traveling. Jina’s toxicology interests include antidotes in overdose cases and antidepressants.

Andy Tominaga, BS, has been working at UPCC since the summer of 2015. Andy received his undergraduate degree in biology at the University of Utah in 2014. He is in his third year of pharmacy school at the University of Utah. Andy enjoys being a part of the UPCC team, because it’s a great service to the community and a unique field in medicine. In his free time, Andy tries to stay as active as possible. Andy loves to play basketball and hike, but recently he is all about the Pokémon GO fad.

WHAT WOULD UTAHNS DO IF THE UPCC WAS NOT AVAILABLE?

Christina Clark, PharmD, was raised in Utah. He began working at Poison Control in June 2015. Christian received his PharmD from the University of Utah. While in pharmacy school, he completed a rotation at Poison Control and discovered his love of toxicology. His toxicology interests include ethylene glycol and dietary supplements. When Christian is not at work, he is planning his next trip, listening to podcasts about movies, or playing with his precocious two-year-old son.

Jina Kim, BA, started working at the Utah Poison Control Center in December 2014. She grew up in Studio City, California, and received her BA degree in psychology at the University of California, Riverside. She worked in mental health services before she decided to pursue her career in pharmacy. Jina is a P3 pharmacy student at the University of Utah College of Pharmacy. In her free time, she enjoys reading a nice book with a cup of coffee, watching Friends, and traveling. Jina’s toxicology interests include antidotes in overdose cases and antidepressants.

Andy Tominaga, BS, has been working at UPCC since the summer of 2015. Andy received his undergraduate degree in biology at the University of Utah in 2014. He is in his third year of pharmacy school at the University of Utah. Andy enjoys being a part of the UPCC team, because it’s a great service to the community and a unique field in medicine. In his free time, Andy tries to stay as active as possible. Andy loves to play basketball and hike, but recently he is all about the Pokémon GO fad.

**Certified Specialist in Poison Information
** Diplomate of the American Board of Applied Toxicology

Thank You

The Utah Poison Control Center expresses its sincere thanks to the health care professionals, public health officials, and toxicology colleagues that work together to treat and prevent poisonings.

Contact Us:

poison@hsc.utah.edu
Utah Poison Control Center
30 South 2000 East, Suite 4540
Salt Lake City, Utah 84112

*Certified Specialist in Poison Information
** Diplomate of the American Board of Applied Toxicology

TOXICOLOGY TODAY

Executive Director/Editor
Barbara Insley Crouch, PharmD, MSPH, FAACT, DABAT

Interim Medical Director/Editor
B. Zane Horowitz, MD, FACMT

Assistant Director
Heather Bennett, MPA

Clinical Toxicology Fellow
Kaitlyn Brown, PharmD

Training & Communication Coordinator/Publisher
Kelly Teemant, BS, CHES

Health Educator
Sherrie Pace, MS, MCHES

Education Assistants
Sophie Cole
Celine Vu

Administrative Assistant
Brenda Clausing

Data Analyst
Stephanie Keller, BA

Specialists in Poison Information
Kathleen T. Anderson, PharmD, CSPI
Michael Andrus, PharmD, CSPI
Christian Clark, PharmD
Candice Colby, PharmD
Bradley D. Dahl, PharmD, CSPI
Michael L. Donnelly, RN, BSN, CSPI
Paul Hinckley, PharmD
Amberly R. Johnson, PharmD, DABAT
Brittani Petersen, PharmD
Taylor Rhien, PharmD
Cathie Smith, RN, BSN, CSPI
John Stromness, BS Pharm, RPh, CSPI

Poison Information Providers
Peter Chad Adamovich, BS
Abi Banigbola, BS
Brianna Cajacob, BA
Angela Cheung, BS
Benjamin T. Davies, BS
Jina K. Kim, BA
Rachael E. Morley, BS
Simon Rodriguez, BS
Andrew Tominaga, BS

Contact Us:

poison@hsc.utah.edu
Utah Poison Control Center
30 South 2000 East, Suite 4540
Salt Lake City, Utah 84112

*Certified Specialist in Poison Information
** Diplomate of the American Board of Applied Toxicology

Thank You

The Utah Poison Control Center expresses its sincere thanks to the health care professionals, public health officials, and toxicology colleagues that work together to treat and prevent poisonings.

Utah Poison Control Center
30 South 2000 East, Suite 4540
Salt Lake City, Utah 84112

*Certified Specialist in Poison Information
** Diplomate of the American Board of Applied Toxicology

Thank You

The Utah Poison Control Center expresses its sincere thanks to the health care professionals, public health officials, and toxicology colleagues that work together to treat and prevent poisonings.

Utah Poison Control Center
30 South 2000 East, Suite 4540
Salt Lake City, Utah 84112

*Certified Specialist in Poison Information
** Diplomate of the American Board of Applied Toxicology

Thank You

The Utah Poison Control Center expresses its sincere thanks to the health care professionals, public health officials, and toxicology colleagues that work together to treat and prevent poisonings.

Utah Poison Control Center
30 South 2000 East, Suite 4540
Salt Lake City, Utah 84112

*Certified Specialist in Poison Information
** Diplomate of the American Board of Applied Toxicology

Thank You

The Utah Poison Control Center expresses its sincere thanks to the health care professionals, public health officials, and toxicology colleagues that work together to treat and prevent poisonings.

Utah Poison Control Center
30 South 2000 East, Suite 4540
Salt Lake City, Utah 84112

*Certified Specialist in Poison Information
** Diplomate of the American Board of Applied Toxicology

Thank You

The Utah Poison Control Center expresses its sincere thanks to the health care professionals, public health officials, and toxicology colleagues that work together to treat and prevent poisonings.

Utah Poison Control Center
30 South 2000 East, Suite 4540
Salt Lake City, Utah 84112

*Certified Specialist in Poison Information
** Diplomate of the American Board of Applied Toxicology

Thank You

The Utah Poison Control Center expresses its sincere thanks to the health care professionals, public health officials, and toxicology colleagues that work together to treat and prevent poisonings.

Utah Poison Control Center
30 South 2000 East, Suite 4540
Salt Lake City, Utah 84112

*Certified Specialist in Poison Information
** Diplomate of the American Board of Applied Toxicology

Thank You

The Utah Poison Control Center expresses its sincere thanks to the health care professionals, public health officials, and toxicology colleagues that work together to treat and prevent poisonings.

Utah Poison Control Center
30 South 2000 East, Suite 4540
Salt Lake City, Utah 84112

*Certified Specialist in Poison Information
** Diplomate of the American Board of Applied Toxicology

Thank You

The Utah Poison Control Center expresses its sincere thanks to the health care professionals, public health officials, and toxicology colleagues that work together to treat and prevent poisonings.