

Bupropion Toxicity

Introduction

Bupropion (Wellbutrin®, Zyban®) is a structurally unique antidepressant (figure 1) that is also approved for the treatment of smoking cessation. Bupropion has also been used to treat attention-deficit/hyperactivity disorder (ADHD) but has not received FDA approval for this indication. It is available in immediate release, sustained release and extended release formulations.

Pharmacology/ Pharmacokinetics

The mechanism of antidepressant action is not well understood. Bupropion is thought to inhibit the reuptake of dopamine, norepinephrine and serotonin, albeit weakly. Bupropion also has selective nicotinic receptor antagonism.¹ Bupropion is extensively metabolized in the liver to both active and inactive metabolites. Metabolites are structurally similar to amphetamine. Significant pharmacokinetic differences exist between the three different formulations on the market: immediate release, sustained release and extended release (Table 1).

Table 1: Pharmacokinetic parameters of bupropion

Formulation	Immediate release	Sustained release	Extended release
Absorption	Tmax: 1.5 hours	Tmax: 2.5 hours	Tmax: 5 hours
	Tmax of metabolites: 3-4 hours	5-6 hours	7-8 hours
Distribution	Vd 19-21 L/kg Protein binding: 82% to 88%		
Metabolism	Half-life: 21 ± 9 hours Active metabolites t½: 20 to 37 hours (Metabolite activity ranges from 20 to 50 percent of bupropion potency)		
Elimination	Urine (87%); feces (10%)		

Adverse and Toxic Effects

Headache, dizziness and insomnia are the most commonly reported adverse effects with bupropion, occurring in greater than 10% of patients. The incidence of seizures with

therapeutic use of bupropion is higher than other antidepressants and is approximately 0.4% in patients taking up to 450 mg/day and 0.1% in patients taking up to 300 mg/day. The risk for seizures is associated with dose, previous history of a seizure, concomitant medications that may lower the seizure threshold and circumstances associated with an increased risk of seizures (ex. excessive alcohol use). In a retrospective review of therapeutic errors involving bupropion reported to the Toxic Exposure Surveillance System, agitation, dizziness and tremor were the most commonly reported adverse effects.²

Tachycardia, agitation and seizures were the most frequently reported clinical effects in several case series involving acute bupropion overdose reported to poison control centers.³⁻⁵ The mean time to onset of seizures was 4-5 hours with a range of 1 to 14 hours. In one case series, 40 out of 41 patients that developed seizures had a prodrome of neurologic effects including agitation, tremors and hallucinations.⁵ Multiple seizures were reported in 16-57% of patients. Hallucinations were reported in up to 21% of patients. The hallucinations were described as “bugs crawling on my skin¹.” Conduction delays, including

prolongation of the QRS and QTc, have also been reported.⁶⁻⁸ Gastrointestinal side effects were also frequently reported.

Pregnancy and Lactation Issues

Limited information is available regarding the

reproductive effects of bupropion. The FDA has classified bupropion as Category B.⁹ Bupropion and its metabolites are excreted into breast milk. The clinical significance of this is not known and breast feeding should be avoided when possible.

Monitoring

All patients who intentionally overdose on bupropion should be monitored for seizure activity and cardiac conduction disturbances. A 12-lead ECG should be obtained. Patients should be monitored for a minimum of 6 hours for immediate release preparations and up to 24 hours for sustained or extended release formulations. Bupropion is not included in routine toxicology screens. Serum bupropion concentrations are not routinely available and are unlikely to be available in time to affect patient care.

Treatment

Gastrointestinal decontamination with activated charcoal is appropriate within 1-2 hours of ingestion for immediate release formulations. Activated charcoal may be of benefit in patients presenting more than 2 hours after ingestion for sustained and extended release formulations. While more than one dose of activated charcoal may be beneficial to decrease absorption of bupropion, especially with sustained and extended release preparations, it would not be expected to enhance elimination to a significant extent due to its large volume of distribution.

Seizures should be treated with benzodiazepines. Seizures are generally limited and long-term anticonvulsant therapy is not necessary. Prophylactic treatment with a benzodiazepine is not routinely recommended. Patients who experience agitation, tremors and hallucinations should be monitored closely for the development of seizures.

Hemodialysis is not likely to enhance elimination of bupropion due to its large volume of distribution.

Summary

Bupropion is a unique antidepressant with a mechanism of action that differs from other antidepressants. Tachycardia and neurologic effects including seizures are the most commonly reported clinical effects following an overdose. While the majority of seizures occurred within 4-5 hours after ingestion, delayed seizures can occur. Please feel free to contact the UPCC for assistance in managing bupropion overdose.

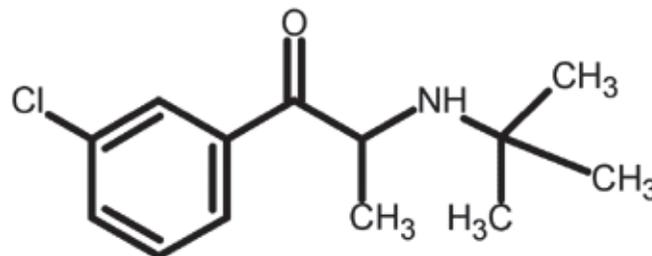
Wesley Crouch, PharmD. Student

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Figure 1: Bupropion Structure



Poison Control Update Conference 2006

The Utah Poison Control Center will host "Poison Control Update Conference 2006" on April 26th (Sandy, UT) and May 17th (Cedar City, UT).

The goal of this conference is to provide a forum for public health advocates, health professionals and other technical experts to increase awareness and information about current poisoning issues. It is partially funded by a grant from the Department of Health and Human Services, Health Resources and Services Administration.

The agenda includes the following presentations:

- Poisons Under Our Nose, An Update on Inhalants
- Antidotes; Alicorns, and Other Treasured Remedies
- Household Chemicals – There's No Place Like Home
- Herbal Remedies – Naturally Safe or Potential Poisons
- Drugs of Abuse – Uppers, Downers, and All-Arounders

If you are interested in attending, please contact Marty Malheiro at 587-0603 or marty.malheiro@hsc.utah.edu.



The University of Utah
Utah Poison Control Center

The Utah Poison Control Center expresses its sincere thanks to

MCNEIL CONSUMER & SPECIALTY PHARMACEUTICALS

for their generous contribution that allows us to produce and distribute this newsletter.

Educator's Corner

National Poison Prevention Week is March 19 – 25, 2006. “Children Act Fast, So Do Poisons” is the theme. It reminds us that young children need constant close supervision by responsible adults to keep them safe. This week highlights the dangers of unintentional poisonings, steps that can be taken to reduce risks, and what to do in case of an emergency. The Utah Poison Control Center (UPCC) receives more than 54,000 calls each year and more than 60 percent involve children less than 6 years of age. Educating each new generation of parents and other childcare providers must remain a priority to help ensure that potential poisonings are reduced. Poison prevention messages always include the importance of child-resistant packaging, storing medicines and household products in their original containers, and locking potentially dangerous items out of sight and reach of children.

The UPCC recently had 3 of our brochures professionally re-designed. *The Babysitter's Guide*, *A Guide to Plant Poisoning Prevention*, and the *Emergency Action for Poisoning* have a new look and updated information. These have a much greater visual appeal and are more effective at getting our message across. Call 1-800-222-1222 to request these brochures or you may view them on our website at www.utahpoisoncontrol.org.

M-44 Sodium Cyanide Device

The United States Department of Agriculture, Animal and Plant Health Inspection Service, Bureau of Wildlife Services would like us to remind you that the M-44 sodium cyanide device is used in Utah. The device is tubular and is placed in the ground with 1.5 inches sticking out of the ground baited with meat. This device is used in specific situations to control coyotes, redfox, gray fox and wild dogs. The purpose of the device is to protect livestock, poultry, and endangered species and to prevent the spread of disease. Although this device is primarily used on private lands, it may also be used on federal land in any county in the state. Areas where it is used are marked with signs. While human exposure to this device would be extremely unlikely, it is important to know that this device contains 91% sodium cyanide. Please report any exposure to this device to the Utah Poison Control Center at (800) 222-1222. We thank you in advance for your assistance.

Strike Out the Poisons
for Children's Safety!

CHILDREN ACT FAST...SO DO POISONS!

POISON HOTLINE: 1-800-222-1222

National Poison Prevention Week
March 19-25, 2006

POISON PREVENTION WEEK COUNCIL
PO Box 1543
Washington, DC 20013

Poster design by: Mariel Sikes (11 years old)
Submitted by: Nebraska Regional Poison Center

Calls to the UPCC are Recorded

All “emergency” calls to the UPCC are recorded. The digital recording becomes part of the patient’s medical record. Digital recordings are valuable in training new employees and are an integral part of our continuous quality improvement program.

Announcing Electronic Newsletter

We are pleased to announce that Utox Update will be transitioning to an electronic format over the next year and a paper copy will no longer be mailed after 2006. On April 15th, 2006 we will begin accepting registrations to receive Utox Update via email. Look for a link on our website at www.utahpoisoncontrol.org.

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*CSPI denotes Certified Specialist in Poison Information.

Employment Opportunities

The UPCC has one open Specialist in Poison Information-Pharmacist position available. You can find out more about this position on our website at <http://uuhsc.utah.edu/poison/employment>.

Meet the UPCC Staff



Deborah Melle had an extensive background in nursing prior to coming to the UPCC in 2004. Critical care, trauma, emergency and flight nursing occupied the major portion of her career. She was also the Project Coordinator for the Metropolitan Medical Response System, a medical WMD response plan, for Salt Lake City. She is the proud momma of two grown sons, Mikell, a biology major at the University of Utah and Christopher, a US Marine. She hails from Philadelphia, PA, but moved to the mountains 26 years ago. Deb's free time is spent in those mountains skiing, snowshoeing, and hiking, along with an annual stint in Margaritaville.

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