

TOXICOLOGY TODAY



BUPRENORPHINE FOR OPIOID DEPENDENCE

by Megan Milne,
PharmD Candidate

Introduction

The Drug Addiction Treatment Act (DATA) of 2000 allows qualified physicians, primarily those who specialize in addiction medicine, to treat opioid addiction in settings outside of traditional methadone clinics. In 2002, the FDA approved the use of two formulations of buprenorphine for the treatment of opioid addiction. Suboxone® is the brand name of a combination of buprenorphine and naloxone. It comes in two strengths of sublingual tablets: buprenorphine 8 mg/naloxone 2 mg or buprenorphine 2 mg/naloxone 0.5 mg strength. Buprenorphine alone in a sublingual tablet (Subutex®) is used for the transition from opioid withdrawal to the treatment of addiction and is primarily used under the direct supervision of a physician. Buprenorphine (Buprenex®) in an injectable form is used for analgesia. Suboxone® is the only drug in its class.



<http://www.usdoj.gov/ndic/pubs10/10123/index.htm>

Other drugs used for the treatment of opioid addiction and withdrawal include methadone, clonidine, and levo-alpha-acetylmethadol (LAAM). LAAM is not available in the United States.

Physicians who are qualified under DATA and obtain the proper training are eligible to prescribe Subutex® and/or Suboxone® for up to 100 patients. Suboxone® has also gained some popularity for the treatment of pain. There are no provider training restrictions other than a DEA license to prescribe Suboxone® for the treatment of pain.

Pharmacology/ Pharmacokinetics

See Table: Pharmacokinetics of buprenorphine/naloxone

Buprenorphine is a mixed mu opioid recep-

tor partial agonist and kappa opioid receptor antagonist. Buprenorphine has poor oral bioavailability due to extensive first-pass hepatic metabolism. It has better sublingual bioavailability, which is why Suboxone® is formulated as a sublingual tablet. Buprenorphine is metabolized by the liver by CYP3A4, so the dose may need to be adjusted in patients with liver disease or patients who are concomitantly taking other drugs metabolized by CYP3A4. The manufacturer also recommends caution in patients with renal disease.

Naloxone is a mu opioid antagonist that has poor oral and sublingual bioavailability, so it has negligible effects when Suboxone® is used as directed. However, if the tablet is crushed, dissolved and injected, naloxone is well-absorbed intravenously and would precipitate opioid withdrawal, hopefully preventing IV abuse of Suboxone®.

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Agonist vs. Partial Agonist

Full opioid agonists, like methadone or heroin, bind to receptors and turn them on in a dose-dependent manner. Increasing doses of full agonists produce increasing pharmacologic activity. Partial agonists have a threshold beyond which increasing doses do not produce increasing pharmacologic activity. This ceiling effect puts a limit on the desired effects of euphoria and analgesia. The ceiling effect also limits the adverse

effects of CNS and respiratory depression. However, an opioid naive patient may reach significant CNS and respiratory depression prior to the ceiling dose. The partial agonist ceiling effect is why buprenorphine has been touted as safer than methadone, an agonist with no ceiling to respiratory depression, in the treatment of opioid addiction. Buprenorphine carries a lower risk of abuse, addiction, and side effects compared to full opioid agonists.

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	Absorption	Distribution	Metabolism	Elimination
Buprenorphine	29% sublingual bioavailability	96% protein bound	<ul style="list-style-type: none"> • CYP3A4 substrate • N-dealkylation to norbuprenorphine • Glucuronidation 	<ul style="list-style-type: none"> • $t_{1/2}$ = 37 hours • Excretion: <ul style="list-style-type: none"> • Bile 68% • Urine 27%
Naloxone	Poor sublingual bioavailability	45% protein bound	<ul style="list-style-type: none"> • Glucuronidation • N-dealkylation • Oxidation 	<ul style="list-style-type: none"> • $t_{1/2}$ = 1.1 hours • Excreted in urine

COUGH & COLD MEDICATIONS AND CHILDREN

Early in 2008 the FDA released recommendations regarding the use of over-the-counter (OTC) cough and cold medicines. The recommendation states that these products should not be used in children under 2 years of age. Later in the year another statement was released by the FDA supporting

the Consumer Health Products Associations' (CHPA) voluntary decision to modify the "do not use" age to under 4 years old. The FDA



has also expressed concern in using OTC medicines for the common cold in children between the ages of 2 and 6. Medicine labels will reflect either non-use in children under the age of 2 or non-use in children under the age of 4. This may be confusing to parents and caregivers.

TO AVOID A POTENTIAL PROBLEM, THE UTAH POISON CONTROL CENTER (UPCC) ADVISES THE FOLLOWING:

- Follow the instructions on the label.
- If your child is between the ages of 2 and 6 years, consult with your physician before giving them OTC cough and cold medicines.
- Do not use two medicines at the same time that contain the same or similar ingredients.

- Never give medicine to a child that is intended for adult use.
- Use an accurate device to measure medicine dose.
- Keep all medicines locked up and out of the reach of children.

Resources: FDA, CHPA



Checkout our website for more poison prevention information at www.utahpoisoncontrol.org

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Use in Pediatrics

Buprenorphine has been investigated in the treatment of neonatal abstinence syndrome.

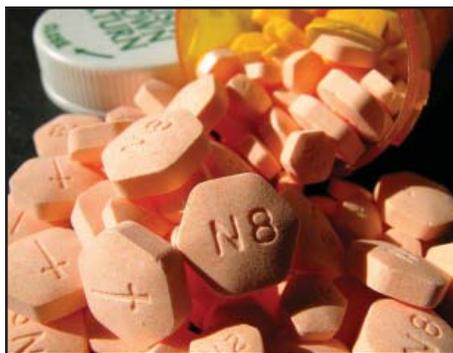
Adverse Effects

The most common adverse effects associated with sublingual buprenorphine include headache, abdominal pain, constipation, nausea, and sweating. Buprenorphine may also precipitate a withdrawal syndrome.

Poisoning & Overdose

Buprenorphine causes a typical opioid toxidrome of miosis, respiratory depression, sedation, and hypotension. If a patient crushes, dissolves, and injects a Suboxone® tablet, the ingredient naloxone will cause an immediate and uncomfortable withdrawal syndrome. US Poison Centers have seen a steady increase in the number of exposures to buprenorphine in all ages since Suboxone® came on the market. The proportion of cases involving children less than 6 years of age has increased from 19% in 2003 to 34% in 2008. Approximately

15% of exposures in children less than 6 years of age resulted in a moderate or major outcome. No fatal outcomes were reported. In comparison, less than 1% of all exposures reported to US poison centers in children less than 6 years of age result in a moderate, major or fatal outcome. Calls to the Utah Poison Control Center (UPCC) mirror what is happening on a national level. In 2008, the UPCC responded to 37 Suboxone® exposures involving in children less than 6 years of age (52% of all Suboxone® exposure calls). Thirty (81%) of these children were treated in a health care facility.



Buprenorphine photo Courtesy of NAABT

Treatment

The initial approach to a patient with a buprenorphine overdose is no different than any other opioid overdose with the exception that the patient may need higher doses of naloxone to respond. Activated charcoal is not likely to have significant benefit due to buprenorphine's limited oral bioavailability. An immunoassay is commercially available for buprenorphine but is not currently used at any Utah hospital. Buprenorphine does not cross react well with most opioid urine test panels and therefore will not screen positive. A confirmation test using gas chromatography or mass spectrometry is currently a send out to a reference laboratory out of state with a 10-day turn-around time but may be available in Utah in the future.

Naloxone is appropriate for patients who are exhibiting CNS and/or respiratory depression. Because buprenorphine's half life is much longer than the half life of naloxone, intermittent boluses or a continuous naloxone infusion may be required to fully reverse the CNS and respiratory depression. It may require higher doses of naloxone and the onset

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of antagonism may take longer than is typically seen with other opioid agonists due to buprenorphine's high binding affinity to the mu receptor. A 2-year-old boy who ingested a single Suboxone® (8mg/2mg) tablet presented to the hospital obtunded and with pinpoint pupils. He required an initial bolus of 7 mg of naloxone to fully awaken and a continuous infusion for 96 hours. (McKeown)

Summary

Buprenorphine/naloxone combination is an innovative new approach to the treatment of opioid addiction. Due to its unique pharmacology, buprenorphine is administered sublingually. This sublingual absorption has relevance to toxicology because even a taste or a lick in a child may be absorbed and produce respiratory and/or CNS depression. Suboxone overdoses and exposures in the opioid-naïve should be treated like an opiate overdose and be given high doses of naloxone and supportive care.

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INDICATIONS FOR LIVER TRANSPLANTATION IN ACETAMINOPHEN OVERDOSE

Anne Zink, MD

Emergency Medicine Resident

Acetaminophen (APAP) is the leading cause for liver transplantation in the United States, about half of which are from unintentional overdoses (1). Acute liver failure from APAP has significant mortality (around 80%), which has decreased to approximately 40% due to the use of liver transplantation (1). Currently, the King's criteria is the most commonly used method for determining which patients should be listed for transplantation and the traditional MELD's (Model of End-Stage Liver Disease) criteria are used to rank the patients in order of priority for transplantation. King's criteria for acute liver failure from acetaminophen toxicity are a blood pH < 7.30 after fluid resuscitation OR grade 3-4 encephalopathy and INR 6.5 and creatinine >3.4 mg/dl. Patients who meet these criteria have > 90% chance of dying without a transplant, although it is only about 69% specific in detecting all patients who will die without a liver transplant (2). A blood lactate of >3.0-3.5 mmol/L after fluid resuscitation is also associated with an increased risk of death without transplantation (3). New advances in transplantation are underway that may make this life saving procedure available to more patients.

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M-44 SODIUM CYANIDE

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.



TOXINS IN THE NEWS

Cocaine adulterated with **levamisole**, a veterinary antihelmintic, has been associated with fever and agranulocytosis. Levamisole was found to contaminate 30% of cocaine seized by the U.S. Drug Enforcement Agency from July to September 2008.

The labeling of OTC **cough and cold medicines** is voluntarily being changed by most manufacturers to say "do not use" for children under 4 years of age.

Oral **sodium phosphate products** (prescription and OTC) for bowel cleansing have been associated with acute phosphate nephropathy. A Boxed Warning has been added to the labeling for these products.

MEET THE UPCC STAFF

DAVID CRAIG



celebrated his first year with the UPCC in February. His work in project management allowed David to live in cities across the country gaining experience with energy conservation, finance, mechanical contracting and now the

Poison Center. A native of Pittsburgh PA, happy Steelers fan and outdoor enthusiast, David takes full advantage living along the Wasatch front. "We have an amazing back yard that offers something for everyone," David explains as he tell the story of how he met his wife Kelly hiking in Little Cottonwood Canyon. He is very proud of his wife Kelly and her 25 years with the university. His favorite call to the poison center is when the specialist comments, "Everything will be fine, we can handle this over the phone" it happens a lot and he's proud to be associated with the level of talent here.

NATIONAL POISON PREVENTION WEEK MARCH 15-21, 2009

The purpose of National Poison Prevention Week is to increase awareness to the dangers of poisonings and how to prevent poisoning. The theme of NPPW is;

"Children Act Fast...So Do Poisons".

Please join us in celebrating this important week by promoting awareness to potential poisonings and poison prevention by distributing poison prevention materials to your patients.

Contact the Utah Poison Control Center to obtain posters and other educational materials.

Call FAST to treat a poisoning!

Call FIRST to prevent a poisoning!

1-800-222-1222

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*CSPI denotes Certified Specialist in Poison Information.



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.



The University of Utah

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