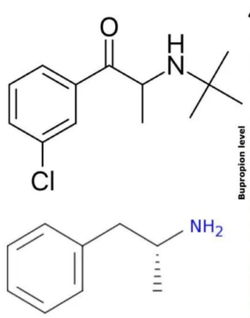
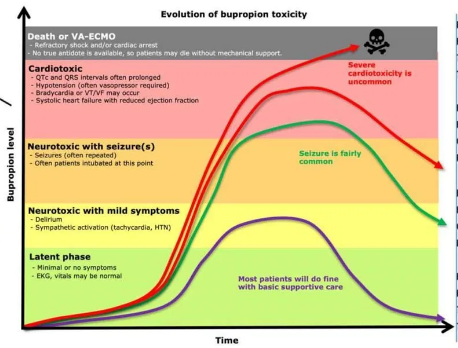
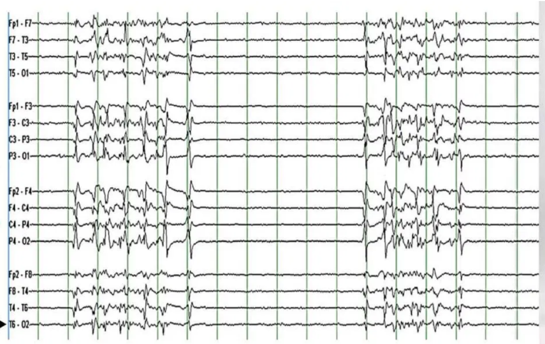
Search the site ...

Bupropion intoxication

November 14, 2019 by **Josh Farkas**







CONTENTS

overview

(back to contents) (#top)

Bupropion is increasingly used for several indications (depression, tobacco cessation, and ADHD). Unfortunately, it is also a uniquely dangerous and increasingly common source of intoxication (especially the extended-release formulations). For example, it's the number one cause of intoxication-induced seizures in some contexts (18072153 (https://www.ncbi.nlm.nih.gov/pubmed/18072153)). There are several reasons for this:

- Bupropion is far more dangerous than other commonly used antidepressants (especially selective serotonin-release inhibitors). In particular, bupropion's ability to cause cardiogenic shock is somewhat unique.

- Tricyclic antidepressants have largely fallen out of favor for treatment of depression, but bupropion remains commonly used. This makes bupropion one of the most dangerous anti-depressants in widespread circulation (28944696 (https://www.ncbi.nlm.nih.gov/pubmed/28944696)).
- The extended-release formulation of bupropion may cause *delayed* emergence of symptoms (a delayed "toxin bomb"). Subsequently, ongoing drug absorption can be relentless.

---

pharmacodynamics

(back to contents) (#top)

---

inhibition of dopamine & norepinephrine re-uptake

- This is the therapeutic mechanism of action of bupropion.
- Structurally and pharmacodynamically, bupropion works similarly to *amphetamines* (no wonder this makes depressed folks feel better, without causing weight gain or sexual dysfunction).

cardiotoxicity

- The most notable effect is via inhibition of gap junctions.
  - Gap junctions are connections between adjacent cardiomyocytes involved in cell-cell signaling. Bupropion can inhibit them, impairing cardiac function (e.g. prolongation of QRS interval and systolic heart failure).
  - There is no way to counteract this. For example, sodium bicarbonate *won't* help (because sodium bicarbonate works on the sodium channels).
- Another effect is blockade of cardiac potassium channels (24131328 (https://www.ncbi.nlm.nih.gov/pubmed/2413128)).
  - This may cause an increased QTc interval.
  - However, bupropion overdose doesn't seem to cause Torsades de pointes clinically (Giroski 2012 (https://www.jem-journal.com/article/S0736-4679(12)01277-2/abstract)).

some anti-cholinergic activity

- May help explain a few minor clinical features (e.g. mydriasis, facial flushing)(27648505 (https://www.ncbi.nlm.nih.gov/pubmed/27648505)).

---

pharmacokinetics

(back to contents) (#top)

Bupropion (especially the XR formulation) is a pharmacokinetic slug. It takes a long time to be absorbed, and even longer to be excreted.

absorption

- With therapeutic dosing (24131328 (https://www.ncbi.nlm.nih.gov/pubmed/24131328)):
  - With immediate release formulations, serum levels may peak after ~1.5 hours.
  - With extended release formulations, serum levels may peak after ~5 hours.
- A *toxic* dose of bupropion may take far *longer* to reach peak levels (due to ongoing absorption). The slow absorption of bupropion XR may be a rationale for using whole bowel irrigation in severe cases (more on this below).

metabolism & elimination

- Bupropion is largely metabolized by CYP2B6 in the liver.
- Metabolism occurs very slowly, with a half-life of about a day (for the extended-release formulation). In overdose, this could occur even more slowly.
- Hydroxybupropion is a potentially toxic metabolite (24131328).

---

diagnostics & doses

(back to contents) (#top)

(1) diagnosis of bupropion intoxication

- Diagnosis is most often based on exposure history. Patients often attempt suicide with whatever medications they have on hand.

- Urine toxicology results may reveal a "positive" amphetamine level, which is a false-positive due to chemical similarities with amphetamines (21191682 (https://www.ncbi.nlm.nih.gov/pubmed/21191682)).
- QRS and QTc intervals are increased in patients with cardiotoxicity, but this is usually *not* evident upon admission.

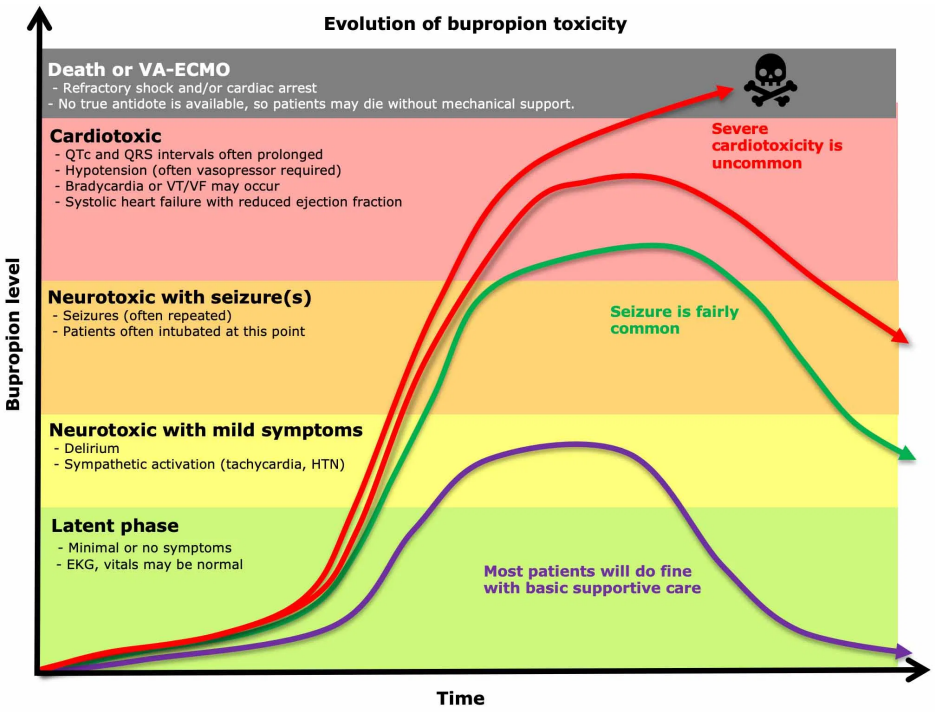
(2) estimating severity based on amount ingested

- This is a very, very poorly defined area (because reported amounts are often incorrect and patients' pharmacokinetics and pharmacodynamics vary).
- The therapeutic dose range is 150-450 mg daily.
  - There is a relatively narrow therapeutic window (with seizures possible even at therapeutic dosing). Thus, seizure is possible even with a relatively small overdose.
- The lowest dose which has been associated with seizure is 575 mg (19857406 (https://www.ncbi.nlm.nih.gov/pubmed/19857406)). With overdoses over **~~3 grams**, seizures become increasingly likely (Rusnyak 2018 (https://emcrit.org/toxhound/illbutrin/) , 19857406 (https://www.ncbi.nlm.nih.gov/pubmed/19857406)).
- With overdose over **~~10 grams**, cardiac toxicity may become more likely (27648505 (https://www.ncbi.nlm.nih.gov/pubmed/27648505) , 22561480 (https://www.ncbi.nlm.nih.gov/pubmed/22561480) , 17924251 (https://www.ncbi.nlm.nih.gov/pubmed/17924251) , 14623854 (https://www.ncbi.nlm.nih.gov/pubmed/14623854)).

---

clinical evolution

(back to contents) (#top)



Stereotypical evolution of bupropion intoxication. This won't apply to every patient (for example, some patients may progress *directly* to seizures without developing mild neurologic symptoms).

-The Internet Book of Critical Care, by @PulmCrit

(#1) latent phase

- Patients who just ingested an extended-release formulation of bupropion may have minimal symptoms initially.
- There is a risk that these patients could be inappropriately discharged home or to a low-acuity unit (e.g. psychiatry ward).
- Duration of the latent phase depends on the drug formulation:
  - Immediate-release formulations: usually under ~6 hours
  - Sustained-release formulations: may last up to ~24 hours!

(#2) neurotoxic phase

- (2a) **mild symptoms**

- *Delirium* may be a prominent symptom here (often agitated delirium, but hypoactive delirium can also occur).
- This may be accompanied with sympathomimetic features (e.g. tachycardia, hypertension, pupillary dilation, tremor).
- Myoclonic jerks may occur (28246063 (https://www.ncbi.nlm.nih.gov/pubmed/28246063)).

- (2b) **seizure**
  - Often the first dramatic symptom to emerge is seizure. Patients with mild neurologic symptoms are more likely to seize, but seizures can occur without other preceding symptoms (19857406 (https://www.ncbi.nlm.nih.gov/pubmed/19857406)).
  - Seizure onset may occur between 30 minutes to 24 hours after ingestion of Bupropion XR, with 25% occurring >8 hours after ingestion (28246063 (https://www.ncbi.nlm.nih.gov/pubmed/28246063)).
  - Isolated seizures can occur, but about half of patients will have multiple seizures (28246063 (https://www.ncbi.nlm.nih.gov/pubmed/28246063)).
  - Status epilepticus is not uncommon. Patients often will need to be intubated at this point.

(#3) cardiotoxic phase

- If drug levels continue to rise, the next life-threatening symptom to emerge is often cardiotoxicity.
- Clinical features may include:
  - Prolongation of QRS and QTc intervals.
  - Hypotension requiring vasopressors.
  - Cardiogenic shock with reduced ejection fraction (may cause refractory shock requiring VA ECMO).
  - Malignant ventricular arrhythmias.
- Fortunately, this is fairly rare. Refractory shock or malignant arrhythmias occur in <5% of patients (19857406 (https://www.ncbi.nlm.nih.gov/pubmed/19857406)).

other clinical features which may occur

- Brain death mimic (29290899 (https://www.ncbi.nlm.nih.gov/pubmed/29290899)).
  - High levels of bupropion may completely shut down the brain (including an iso-electric video EEG and lack of brainstem reflexes). Clinically these patients will appear as if they're brain dead (e.g. with fixed and dilated pupils).
  - These patients are usually NOT actually dead (in fact, they often have excellent neurologic outcomes). Horrifically bad neurologic examination should NOT dissuade clinicians from providing maximally aggressive supportive care.
  - Don't pronounce these patients brain dead, or you may end up in the news (http://www.thepoisonreview.com/2013/07/08/hospital-fined-after-overdose-patient-awakes-just-before-surgeons-harvest-her-organs/) . In order to diagnose brain death in the context of bupropion intoxication, advanced neuroimaging studies are mandatory (e.g. cerebral flow scan (https://emcrit.org/pulmcrit/brain-death-flow-scan/)).
- Non-epileptic myoclonus
  - Ongoing myoclonic jerking is described both prior to seizure, and also after intubation for status epilepticus.
  - This may *not* necessarily reflect seizure activity (and, as such, might *not* require anti-epileptic therapy)(29067833 (https://www.ncbi.nlm.nih.gov/pubmed/29067833)).
  - When doubt exists regarding whether this reflects ongoing seizure activity, video EEG will sort it out.

---

activated charcoal

(back to contents) (#top)

---

basic principles

- Bupropion is lipophilic, so it should bind to activated charcoal.
- For a large bupropion ingestion, the amount of charcoal needed to bind all of the bupropion may be excessive. Thus, the ability of charcoal to bind bupropion may be out-stripped (Greller 2018 (https://emcrit.org/toxhound/the-purge/)).

when to consider charcoal

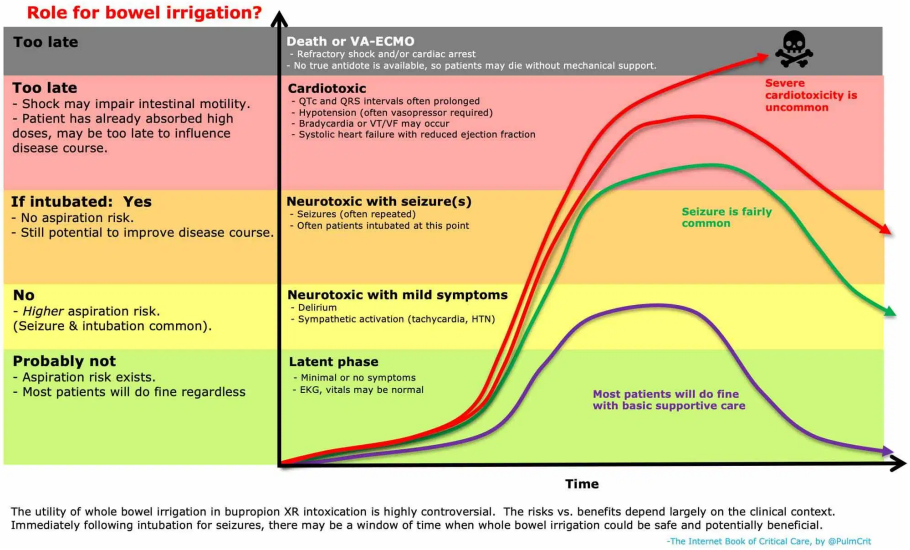
- (1) For patients who present very early and are protecting their airways.
- (2) For patients who are intubated for another reason (usually seizures).

---

whole bowel irrigation

basics

- Whole bowel irrigation may be a rational approach to large intoxications of *sustained-release* bupropion.
- The main goals of whole bowel irrigation are roughly two-fold:
  - (1) Avoid death due to cardiogenic shock. Massive bupropion ingestion can be refractory to all conventional therapies (there is no effective antidote).
  - (2) Minimize time on mechanical ventilation. Patients with large overdoses of bupropion XR can require prolonged support on mechanical ventilation due to coma or seizures. Minimizing the absorbed dose and avoiding persistent drug absorption could accelerate weaning off ventilation.
- This is a controversial topic about which no solid evidence exists. For more, see an excellent discussion of bowel irrigation by Howard Greller here (https://emcrit.org/toxhound/the-purge/) .
- Like everything in toxicology, clinical context is key. Whole bowel irrigation may have a role, but only in a very specific situation…

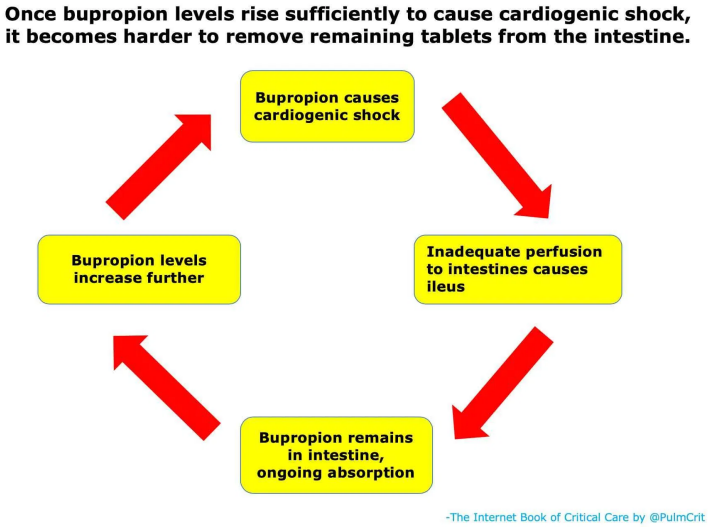


The utility of whole bowel irrigation in bupropion XR intoxication is highly controversial. The risks vs. benefits depend largely on the clinical context. Immediately following intubation for seizures, there may be a window of time when whole bowel irrigation could be safe and potentially beneficial.

-The Internet Book of Critical Care, by @PulmCrit

niche treatment for the patient who was just intubated for seizures/coma

- Whole bowel irrigation should be considered for patients who are intubated following bupropion XR intoxication. Whole bowel irrigation makes the most sense in this context, for many reasons:
  - (1) These patients have severe intoxication, so they may benefit more from aggressive therapy (compared to *most* patients with bupropion intoxication, who will generally do OK with conservative measures).
  - (2) The airway has already been protected (to be clear, patients should *not* be intubated for the purpose of bowel irrigation).
  - (3) Obtaining gastric access is easy (most patients will have an orogastric tube placed anyway).
  - (4) If you wait too long to perform bowel irrigation, cardiogenic shock and ileus may occur, rendering this intervention impossible (figure below)(28246063 (https://www.ncbi.nlm.nih.gov/pubmed/28246063)). Thus, the post-intubation period may represent a window of time when whole bowel irrigation can be done safely.
- Some notes on the nuts & bolts:
  - This may be conceptualized as an *accelerated preparation for a colonoscopy*.
  - Following intubation, infuse an isotonic solution of polyethylene glycol ("GoLytely") via an orogastric tube, beginning at a rate of 1.5-2 liters/hour. If emesis occurs, reduce the rate by 50%.
  - Continue until effluent is clear (just as you would for a colonoscopy prep). If the patient received a dose of charcoal, passage of charcoal per rectum may also be a sign of adequate evacuation.



treatment of neurotoxicity

(back to contents) (#top)

agitation/delirium

- Front-line therapy here is benzodiazepines (which could potentially reduce the risk of seizure).

seizure

- Front-line therapy is benzodiazepines.
- For recurrent seizures or status epilepticus, consider intubation and propofol infusion.
- Levetiracetam is often used to prevent seizure recurrence (although no good evidence exists regarding this).
- It might be ideal to avoid the following therapies:
  - (1) Definitely avoid phenytoin (may promote bradycardia, hypotension; generally not a favored agent for seizures due to intoxication).
  - (2) Phenobarbital might not be an ideal option due to its potential hypotensive effects (if patients progress into a cardiotoxic phase, phenobarbital cannot be withdrawn).

brain-death mimic

- Continue aggressive supportive care (these patients will generally make a full recovery).
- Wait for bupropion to metabolize (which may take days).
- Video EEG monitoring to surveil for seizure might be considered.

treatment of cardiotoxicity

(back to contents) (#top)

catecholamine vasopressors

- These are often required.
- There is no evidence regarding the optimal agent.
- Norepinephrine is often a good choice, but this may also depend on the individual patient's hemodynamics.

Intralipid

- Evidentiary support
  - (a) In an animal model involving Yorkshire pigs, the combination of intralipid plus epinephrine was more successful in treatment of bupropion-induced cardiac arrest than was epinephrine alone (27136657 (https://www.ncbi.nlm.nih.gov/pubmed/27136657)).
  - (b) In humans, intralipid is supported by a handful of case reports. One case study did demonstrate increased blood bupropion levels following administration of intralipid, supporting the concept that intralipid functions as a "sink" to remove bupropion from the myocardium (17766009 (https://www.ncbi.nlm.nih.gov/pubmed/17766009) , 21726409 (https://www.ncbi.nlm.nih.gov/pubmed/21726409)).

- Role?
  - Overall, current opinion seems to be moving away from the use of intralipid (28644682 (https://www.ncbi.nlm.nih.gov/pubmed/28644682)). However, intralipid may remain a treatment of last resort in centers lacking ECMO (for cardiogenic shock refractory to other interventions).
  - There is some concern in the literature that intralipid could cause occlusion of the oxygenator membrane if ECMO is subsequently pursued. However, it seems that this phenomenon may occur only at rather high doses of intralipid. Thus, low/moderate doses of intralipid could still be used to stabilize a patient as a bridge to ECMO.
- Nuts & bolts
  - Newer guidelines recommend a revised dosing scheme with a reduced maintenance infusion, which could optimize the risk/benefit balance. These recommend the following dosing scheme for 20% lipid emulsion (e.g. intralipid):
  - (1) Start with a bolus of 1.5 ml/kg over ~2-3 minutes (e.g. ~100 ml). Repeat bolus may be considered if no response to the first bolus.
  - (2) Give an additional 0.75 ml/kg over three minutes (e.g. ~50 ml).
  - (3) Start a maintenance infusion rate of 0.025 ml/kg/min (e.g. ~2 ml/min).
  - (4) If there is an initial response to the bolus followed by re-emergence of instability during the maintenance infusion, consider re-bolusing and/or increasing the infusion rate. There is no known maximal dose, but it may be best to limit the dose to 10 ml/kg total.
  - More information: Full text PDF of the ACMT 2016 Lipid Emulsion Position Statement (https://emcrit.org/wp-content/uploads/2019/11/ILE-Guidance-New-Dosing-Infusion-2016-J-Med-Toxicol.pdf) .

VA ECMO

- This is an excellent option for patients with bupropion-induced *cardiogenic* shock refractory to other treatments (e.g. with profoundly reduced ejection fraction).
- It is supported by case-report level evidence only (26856351 (https://www.ncbi.nlm.nih.gov/pubmed/26856351)).
- The potential mechanism of action of ECMO
  - Primary mechanism: Native organ function should improve once drug has been metabolized, so the goal here is to keep the patient alive until the drug can be cleared ("bridge to metabolism").
  - Secondary mechanism: Possible that bupropion may adsorb onto the circuit to a certain extent (which could be therapeutically advantageous?).

podcast

(back to contents) (#top)

(https://i1.wp.com/emcrit.org/wp-content/uploads/2016/11/apps.40518.14127333176902609.7be7b901-15fe-4c27-863c-7c0dbfc26c5c.5c278f58-912b-4af9-88f8-a65fff2da477.jpg)

Follow us on iTunes (https://itunes.apple.com/ca/podcast/the-internet-book-of-critical-care-podcast/id1435679111)

The Podcast Episode

00:00 00:00 /(javascript:void(0);)

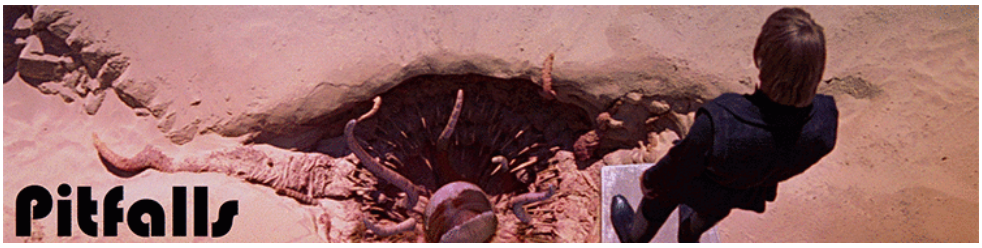
Want to Download the Episode?

Right Click Here and Choose Save-As (http://traffic.libsyn.com/ibccpodcast/IBCC_EP_64_-_Bupropion_Toxicity.mp3)

questions & discussion

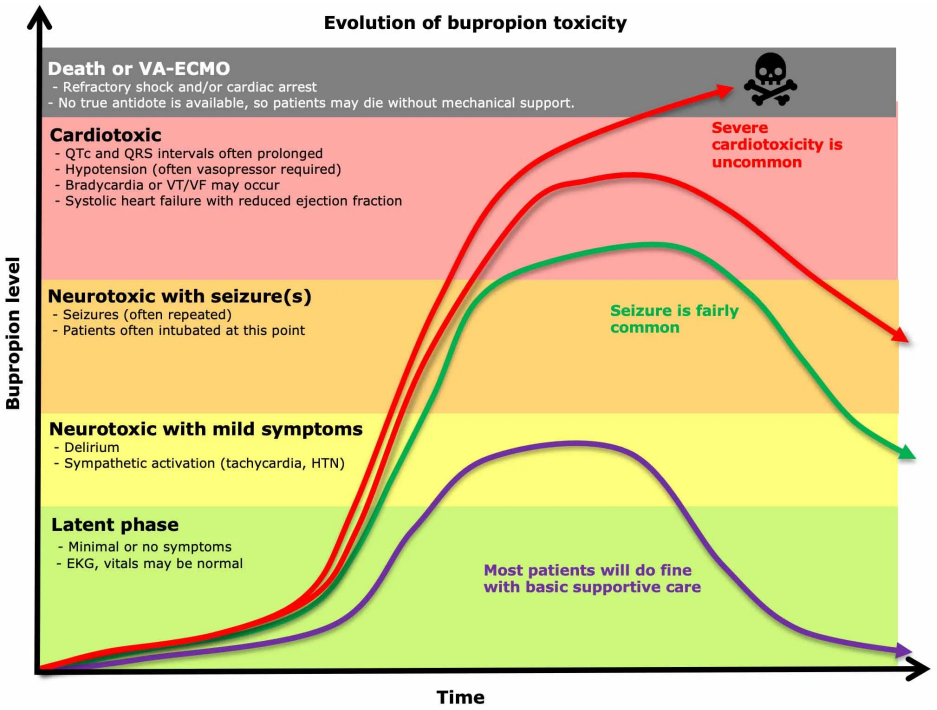
(back to contents) (#top)

To keep this page small and fast, questions & discussion about this post can be found on another page ***here*** (https://emcrit.org/pulmcrit/bupropion/) .



(https://i0.wp.com/emcrit.org/wp-content/uploads/2016/11/pitfalls2.gif)

- Lack of awareness that bupropion intoxication can be life-threatening (and far more severe, for example, than selective serotonin reuptake inhibitors).
- Failure to understand the latent phase of bupropion intoxication, leading to inappropriately early discharge.
- Failure to consider whole bowel lavage for an intubated patient with massive bupropion XR intoxication (especially at a non-ECMO center, where this intoxication can outrun all available therapies).
- Incorrect diagnosis of brain death in a patient with bupropion intoxication, leading to inappropriate withdrawal of life-sustaining therapy.



Stereotypical evolution of bupropion intoxication. This won't apply to every patient (for example, some patients may progress *directly* to seizures without developing mild neurologic symptoms).

-The Internet Book of Critical Care, by @PulmCrit

Going further:

- Series on bupropion by Tox & Hound:
  - Illbutrin (https://emcrit.org/toxhound/illbutrin/) (Dan Rusyniak)
  - The Purge (https://emcrit.org/toxhound/the-purge/) (Howard Greller)
  - ECMO for toxicology indications (https://emcrit.org/toxhound/drug-circuit/) (Jeanna Marraffa)
- Severe bupropion overdose and ECMO (http://www.thepoisonreview.com/2016/02/12/severe-bupropion-overdose-and-ecmo-two-great-saves/): two great saves (Leon Gussow, The Poison Review)

The Internet Book of Critical Care is an online textbook written by Josh Farkas (@PulmCrit), an associate professor of Pulmonary and Critical Care Medicine at the University of Vermont.