

## Session Title: Critical Pharmacotherapy Updates for Prehospital Providers

### 1. Treat and Release after Naloxone

A full review of this topic was covered in [a previous ALiEM post](#).

A 2016 prehospital study, published in *Prehospital Emergency Care*, assessed the risk of administration of naloxone with subsequent refusal of care ([Levine et al, Prehosp Emerg Care 2016](#)). The authors conducted a retrospective review of all patient encounters by the Los Angeles Fire Department during July 1, 2011-December 31, 2013. The Coroner's records were reviewed to determine if a patient with the same or similar name had died within 24 hours, 30 days, or 6 months of the initial EMS encounter. Of the 205 subjects identified, one (0.49%) died within 24 hours of the initial EMS encounter. The cause of death was coronary artery disease and heroin use. Two additional subjects died within 30 days, but the cause of death was either unknown or unrelated in both cases.

#### Application to ED Clinical Practice

1. If a patient presents to the ED after receiving prehospital naloxone for opioid toxicity, it is worth observing them for at least an hour (longer dependent on the situation). Be sure that after the naloxone has worn off, s/he doesn't have recurrent opioid toxicity. Only one of the studies evaluated ED patients and found a higher rate of recurrent toxicity compared to the prehospital studies. The primary outcome in the prehospital studies was death. We can monitor more closely in the ED and can provide resources including substance abuse referrals and take-home naloxone.
2. The most common opioid in the earlier studies was heroin. A one-time naloxone dose is generally sufficient to reverse heroin with a limited threat of recurrent toxicity. However, the opioid epidemic has changed, such that [heroin is only part of the current problem](#). Prescription medications, fentanyl, and other opioids can be longer acting than naloxone's 45-60 minute duration of effect. Adulterants also play a role, as highlighted by the [recent CDC report](#) on increased deaths related to fentanyl. The Levine study aimed to reevaluate the earlier data in light of the current times, but only captured patients up through the end of 2013. Although they found a low rate of death in 205 patients, recurrent toxicity may have been missed by their inclusion criteria.

#### Bottom Line

- We should not overturn the practice of ED observation for 4-6 hours. The data simply suggests that if a patient refuses transport at the scene or wants to sign out against medical advice after receiving naloxone, s/he has a low risk of death.
- Keep in mind that the available data predate 2014, when fentanyl, carfentanyl, etc. were not yet a big part of the scene. Therefore, all of the studies most likely included predominately heroin and oral opioids and do not account for the new, more dangerous adulterants.

### 2. Ketamine for Prehospital Agitation

Ketamine is gaining traction as a prehospital option for managing severe agitation or excited delirium syndrome. Previous reports have mostly been case series, but a new prospective study adds some important information that may help delineate ketamine's role in this setting ([Cole et al, Clin Toxicol 2016](#)). An accompanying commentary was published in the same issue ([Hayes, Clin Toxicol 2016](#)).

### What They Did

Open-label before-and-after prospective comparison of haloperidol (10 mg IM) versus ketamine (5 mg/kg IM) for the treatment of acute undifferentiated agitation.

### What They Found

- Ketamine demonstrated a statistically and clinically significant difference in median time to sedation compared to haloperidol, 5 min vs. 17 min ( $p < 0.0001$ , 95% CI: 9-15)
- Complications: ketamine, 49%; haloperidol, 5%
  - Ketamine complications: hypersalivation (38%), emergence reaction (10%), vomiting (9%), and laryngospasm (5%)
- Intubation rate: ketamine, 39%; haloperidol, 4%

### Application to Clinical Practice

- Ketamine works for prehospital agitation (and more rapidly)
- Ketamine has a higher complication and intubation rate
- Though this study did not find a dose relationship between ketamine and intubations, future studies should evaluate further and potentially use lower ketamine doses
- At MGH, we start with 2-3 mg/kg IM (max 200 mg) and repeat if necessary after 5 min. Most patients have not required a second dose and none have been intubated. This allows time to place an IV line and initiate additional treatment.

### 3. Syringe labeling

- We frequently draw up medications for administration, but most IV meds are clear liquids. How can we tell the difference between a BP med and a neuromuscular blocker? What if a syringe has a dose written on it, but someone gives half and puts the syringe back down? How will the next person know how much is actually in there?
- The two critical pieces of information that must be on every syringe are: drug name and concentration ([Kothari D, et al. Br J Anaesth 2013;110\(6\):1056-8.](#))
- Further reading: <https://www.aliem.com/2015/art-of-syringe-labeling-in-the-ed/>

### 4. Tricyclic Antidepressant Poisoning (during a sodium bicarbonate shortage)

- The American Society of Health-System Pharmacists (ASHP) has a great resource center for drug shortages: <http://www.ashp.org/shortages>
- If sodium bicarbonate is not available, it may actually be the sodium that is the most important factor in reversing ECG findings from TCA poisoning, as opposed to pH manipulation. Consider administering hypertonic saline if needed ([Ann Emerg Med 2003](#), [Ann Emerg Med 1998](#))

- One amp/syringe (50 mL) of 8.4% sodium bicarbonate contains the same amount of sodium as 97 mL of 3% sodium chloride or 38 mL of 7.5% sodium chloride.
- A central line is recommended if giving > 3% hypertonic saline.

## 5. Calcium Channel Blocker Overdose Poisoning Guidelines

New expert consensus expert recommendations for the management of calcium channel blocker poisoning in adults were published in 2016 ([St-Onge M, et al. Crit Care Med 2016](#)).

- Interventions with the strongest evidence are high-dose insulin and extracorporeal life support.
- Interventions with less evidence, but still possibly beneficial, include calcium, dopamine, norepinephrine, 4-aminopyridine (where available), and lipid emulsion therapy.
- Glucagon is no longer recommended for CCB overdose.

### Treatments for Toxin-Induced Shock

1. Initial assessment and treatment of toxin-induced shock (particularly beta blockers and calcium channel blockers) should include charcoal (if indicated), atropine (if bradycardia), calcium, and crystalloid fluids. Goals: preserve organ perfusion and increase survival.
2. Glucagon for beta blocker overdoses at a dose of 3-5 mg IV/IO. Beware of vomiting.
  - a. Available in 1 mg vials (powder). Each vial must be reconstituted with sterile water. This takes a few minutes to prepare.
3. Calcium – give it, optimal dose unclear. Start with at least 1 gm CaCl<sub>2</sub> or 2 gm calcium gluconate.
  - a. Does calcium gluconate act slower than calcium chloride because it needs hepatic activation? No!
    - i. Serum ionized calcium levels were measured in 15 hypocalcemic patients during the anhepatic stage of liver transplantation. Half received CaCl 10 mg/kg, the other half received calcium gluconate 30 mg/kg. Serum concentrations of ionized calcium were determined before and up to 10 min after calcium therapy. Equally rapid increases in calcium concentration after administration of CaCl and gluconate were observed, suggesting that calcium gluconate does not require hepatic metabolism for the release of calcium and is as effective as CaCl in treating ionic hypocalcemia in the absence of hepatic function. ([Martin TJ, et al. Anesthesiology 1990;73:62-5](#))
    - ii. Same result in another study of children and dogs ([Cote CJ, et al. Anesthesiology 1987;66:465-70](#))
    - iii. Same result in a third study of ferrets and in vitro human blood ([Heining MP, et al. Anaesthesia 1984;39:1079-82](#))
4. Vasopressors should be instituted early on. Though no one vasopressor is preferred, epinephrine or norepinephrine both seem to be a good starting choice considering the  $\beta$  1 and  $\alpha$  1 agonist properties of each.
  - a. One inpatient toxicology service reported good success with high-dose vasopressors for CCB toxicity over a 25-year period ([Levine M, et al. Ann Emerg Med 2013;62\(3\):252-8](#)).
  - b. Vasopressors should generally be used in conjunction with high-dose insulin therapy.

- c. Human cases suggest that even though vasopressors are not often effective, they don't seem to be harmful (unlike in the animal data) ([Skoog CA, et al. Clin Toxicol 2017](#))
5. Insulin ([Jang, et al. Emerg Med Clin N Am 2014](#), [Engebretsen, et al. Clin Toxicol 2011](#))
  - a. High-dose boluses and infusions of insulin can be safe in the treatment of refractory calcium channel blocker/beta-blocker overdose.
  - b. In the nonstressed state, the heart primarily utilizes free fatty acids for its energy needs, but the stressed myocardium switches to carbohydrates. Insulin seems to provide positive inotropic effects because of metabolic support during hypodynamic shock.
  - c. Calcium channel blocker overdose patients typically present with hyperglycemia. This may be one way to differentiate CCB overdose from beta blocker (may present with hypoglycemia or normoglycemia).
  - d. The recommended dose for regular insulin is 1 unit/kg IV bolus. Yes 1 unit/kg! An infusion of 0.5 to 1 unit/kg/hour should follow.
    - i. Monitor potassium (generally need to supplement)
    - ii. Monitor glucose (need to supplement)
6. IV Lipid Emulsion
  - a. Seems to work like a shuttle to accelerate redistribution from targets to reservoir organs ([Fettiplace, et al. J Control Release 2015](#), [Fettiplace, et al. Reg Anesth Pain Med 2018](#))
  - b. Consider lipid emulsion for CCB, BB, TCA, local anesthetics, bupropion, chloroquine and other lipid soluble, cardiotoxic agents ([French, et al. Clin Toxicol 2011](#)).
  - c. Evidence-based recommendations ([Gosselin, et al. Clin Toxicol 2016](#)).
  - d. 'Best' dose for oral poisonings: 20% lipid emulsion - 1.5 mL/kg bolus, 0.25 mL/kg/min X 3 min, 0.025 mL/kg/min up to 6.5 hrs ([Fettiplace, et al. Ann Emerg Med 2015](#))
  - e. Possible adverse effects include acute lung injury, pancreatitis, allergic reaction, fat emboli, and DVT ([Hayes BD, et al. Clin Toxicol 2016](#)).
  - f. Also beware of laboratory interference ([Grunbaum, et al. Clin Toxicol 2012](#)) and incompatibility with other resuscitation medications ([Cocchio C, et al. SOJ Pharm PharmSci 2014;1\(1\):3](#)). Labs should be drawn before lipid is given, if possible, and it should be administered in its own line.

## 6. Opioid Alternatives in the Prehospital and ED Settings

### Tramadol

Tramadol has a reputation for being a safe, non-opioid alternative to opioids. Nothing could be further from the truth. It is an opioid after all, and it comes with significant adverse effects ([Young 2013](#)).

- [Tramadol: When to Avoid It](#) from Academic Life in EM
- [Three Reasons Not to Prescribe Tramadol](#) from EM PharmD
- [Hypoglycemia: Another Adverse Effect Associated with Tramadol](#) from Poison Review

Tramadol is an opioid, a synthetic one that is now schedule IV according to the DEA.

### Problems with Tramadol

- It may not work very well ([Sachs 2005](#))
  - Osteoarthritis-related pain: modestly effective in placebo-controlled trials ([Cepeda 2006](#))
  - Neuropathic pain: efficacy comparable to gabapentin, TCAs, & carbamazepine ([Hollingshead 2006](#))
  - Emergency Department
    - Musculoskeletal: Inferior to hydrocodone/APAP ([Turturro 1998](#))
    - Ankle sprain: tramadol/APAP equivalent to hydrocodone/APAP ([Hewitt 2007](#))
- Seizure risk
  - Previous studies have been unable to confirm an increased seizure risk with therapeutic doses of tramadol ([Seizure Risk Associated with Tramadol Use](#) from EM PharmD blog). However, a newer study refutes that premise reporting up to 22% of first-seizure patients had recent tramadol use ([Asadi 2015](#))
- Serotonin syndrome risk ([Sansone 2009](#))
- Hypoglycemic risk ([Fournier 2015](#))
- Erratic metabolism ([Leppert 2011](#))
- Abuse/dependence/withdrawal risk ([Senay 2003](#))

### **Ketorolac (NSAID) Dose Ceiling**

For acute pain, parenteral ketorolac is generally administered as 30 mg IV or 60 mg IM. Dr. Chris Bond ([@socbmobem](#)) has written about the ‘[ceiling effect](#)’ of NSAIDs. The question is: are we using too much ketorolac without getting additional pain benefit? A recent randomized, double-blind trial addresses this question. ([Motov 2017](#))

What they did: 240 patients with acute pain were randomized to receive 10 mg, 15 mg, or 30 mg of IV ketorolac as a single-dose.

What they found: No difference in reduction of pain scores between the groups

1. 10 mg – 7.7 to 5.2 vs. 15 mg – 7.5 to 5.1 vs. 30 mg – 7.8 to 4.8

### Implications for Clinical Practice

- Doses of 10 mg or 15 mg are just as effective as 30 mg (or 60 mg) and should be used preferentially over higher doses ([Reuben 1998](#), [Staquet 1989](#), [Minotti 1998](#), [Brown 1990](#))
- Higher doses can cause more adverse effects, especially if more than one dose is administered ([Quan 1994](#), [Corelli 1993](#), [Gallagher 1995](#), [Dordoni 1994](#))

### **Ketamine**

Early RCT’s did not find an overall advantage of sub-dissociative ketamine for acute pain relief in the ED ([Sin 2015](#)). A 2015 prospective, randomized, double-blind trial compared subdissociative ketamine to morphine for acute pain in the ED and found no difference in pain scores at 30 minutes. ([Motov 2015](#))

### Application to clinical practice

1. In an effort to reduce opioid use in the ED, low-dose ketamine may be a reasonable alternative to opioids for acute analgesia.
2. State/institution nursing regulations govern who can administer IV ketamine.
3. What to prescribe on discharge? Lead author Dr. Motov recommends a "pain syndrome targeted" approach with "patient-specific opioid and non-opioid analgesics."

A follow up study asked the question of how best to administer the 0.3 mg/kg IV ketamine dose while minimizing the risk of adverse effects ([Motov 2017](#)). They found that administering it in 100 mL over 15 minutes reduces side effects without compromising its pain control ability. A second study utilized this same approach with positive results ([Sin 2017](#)).

### *Final Thoughts on Ketamine*

1. While most of the studies have been performed in the ED, there is no clinical reason it could not be used in other areas.
2. After receiving ketamine, patients still may need patient-specific opioid and/or non-opioid analgesics for short-term outpatient management.
3. Even short courses of opioid therapy are associated with dependence, with 6% of patients still filling opioid prescriptions a year after their initial prescription (3% at 2 years). ([Shah 2017](#))
4. The American Academy of Emergency Medicine (AAEM) has a [Clinical Practice Statement](#) on the role for IV Sub-Dissociative-Dose Ketamine in the ED
5. Intranasal ketamine may also be an option in pediatric and select adult patient populations ([Shimonovich 2016](#), [Farnia 2017](#), [Rech 2017](#), [Graudins 2015](#)) or potentially for prehospital use.

### **Lidocaine**

- Both topical and IV lidocaine have been studied for a wide variety of pain ([Golzari 2014](#))
- Lidocaine seems to interrupt neuronal transmission, but exact mechanism of how it provides systemic analgesia remains largely unknown ([Eipe 2016](#)). It also has anti-hyperalgesic, and anti-inflammatory properties.
- Early clinical evidence came from its use in chronic neuropathic pain
- More recently, lidocaine has been studied for renal colic, headache, post-surgery, post-herpetic neuralgia, and others
- IV dose is 1-2 mg/kg as an initial bolus followed by a continuous infusion of 0.5–3 mg/kg/hr
- Safe and effective in older adults ([Daykin 2017](#))
- IV and IN lidocaine has not been successful in all studies, respectively ([Tanen 2014](#), [Avcu 2017](#))
- For renal colic specifically, IV lidocaine seems to be more effective than morphine, although no studies have compared it to NSAIDs, the standard of care ([Best Evidence Topics' analysis](#), [Firouzian 2016](#), [Soleimanpour 2012](#))
- Lidocaine patches are a great option for many patients ([Castro 2017](#)). 5% patches are prescription-only and quite expensive, but 4% patches are available OTC and are much cheaper