

# Patient Safety Tip of the Week

February 12, 2019

## 2 ER Drug Studies: Reassurances & Reservations

In the past month we came across two drug studies done in emergency departments that gave us both reassurance and reservations.

The first was a study of a clinical decision rule about how long you need to observe patients following opiate overdoses ([Clemency 2019](#)). The researchers did a validation study of St. Paul's Early Discharge Rule, developed in 2000 at St. Paul's Hospital in Vancouver, BC but apparently not yet validated elsewhere. The rule was derived to determine which patients could be safely discharged from the emergency department after a 1-hour observation period following naloxone administration for opiate overdose ([Christenson 2000](#)). The rule suggested that, one hour after the administration of naloxone for presumed opioid overdose, patients can be safely discharged from the ED if they meet all six criteria:

- Can mobilize as usual
- Have a normal O2 saturation (>95%)
- Have a normal respiratory rate (>10 and <20 breaths/min)
- Have a normal temperature (>35.0 and <37.5°C)
- Have a normal heart rate (>50 and <100 beats/min)
- Have a GCS score of 15

In the current study by Clemency and colleagues, a total of 538 patients received at least one administration of prehospital naloxone, were transported to the study hospital, and had a 1-hour evaluation performed by a provider. Adverse events (AE's) occurred in 15.4% of patients. The rule exhibited a sensitivity of 84.1%, a specificity of 62.1%, and a negative predictive value of 95.6%. Only one patient with a normal 1-hour evaluation subsequently received additional naloxone following a presumed heroin overdose.

There were no deaths. The most frequent adverse events were:

- Supplemental O2 for hypoxia 11.3%
- Repeat naloxone for hypoventilation 3.0%
- Assisted ventilation 2.6%

Both provider judgement and the clinical prediction rule were predictive of adverse outcomes. Among the 10 cases in which both provider judgment and the rule failed to

predict an AE, two patients received a repeat dose of naloxone after the 1-hour evaluation and one patient was treated with artificial ventilation (bilevel positive airway pressure).

The authors attribute the expanded availability of intranasal naloxone as one of the key differences between the derivation study and the current study (85.4% of patients in the current study received IN naloxone). Also, 64.3% of patients in this study had actual ED lengths of stays greater than 4 hours, compared to 28.8% of patients whom had hospital stays of greater than 4 hours in the derivation study.

The one patient who received naloxone following a heroin overdose and had a normal 1-hour evaluation was given another dose of naloxone 5 hours 30 minutes after her first dose in the field. In that case, the repeat naloxone administration occurred beyond the 4-hour window they typically observe such patients.

This validation study did not include information on the route or type of opioid involved in the exposure when determining the performance characteristics of the rule.

Our reservations about the study have to do with long-acting and extended-release forms of opioids that have become so widely available. The problem arises when the half life of the administered naloxone is exceeded by the half life of the opioid taken or when there is delayed absorption of the opioid that allows “re-emergence” of opioid toxicity when blood levels rise after the naloxone effect has disappeared. We’ve done several columns on these drugs (see full list below). In our May 10, 2016 Patient Safety Tip of the Week “[Medical Problems in Behavioral Health](#)” we mentioned we’ve seen patients who have taken such drugs and been alert in the ED with low levels of drug in their urine screen yet become obtunded due to opioid intoxication the following day due to the delayed absorption of these drugs.

And, as one of the cases in the Clemency study demonstrated, pulse oximetry does not provide a good prediction of impending respiratory depression.

The Clemency study is reassuring that the majority of opioid overdose patients may be safely discharged after an hour if they meet the St. Paul's Early Discharge Rule criteria. However, we'd be very reluctant to discharge such patients that early if there is any doubt about the type of opioid (and route of administration) that led to the overdose.

The second study we came across compared 4 different pharmacologic agents (and 5 regimens) for treatment of acute agitation in the emergency department ([Klein 2018](#)). Medications were administered according to an a priori protocol in which the initial medication given was predetermined in the following 3-week blocks: haloperidol 5 mg, ziprasidone 20 mg, olanzapine 10 mg, midazolam 5 mg, and haloperidol 10 mg (all doses administered intramuscularly).

A total of 737 patients were included in the study. The proportion of patients adequately sedated at 15 minutes (assessed by the Altered Mental Status Scale) was greater for patients treated with midazolam than with haloperidol, olanzapine, and ziprasidone.

Olanzapine also resulted in a greater proportion of patients adequately sedated at 15 minutes compared with haloperidol and ziprasidone.

Adverse events were uncommon: cardiac arrest (0), extrapyramidal adverse effects (2; 0.3%), hypotension (5; 0.5%), hypoxemia (10; 1%), and intubation (4; 0.5%), and occurred at similar rates in each group. Many patients required more than one dose or more than one medication and this occurred more often when midazolam used.

The results sound like a resounding endorsement of use of IM midazolam for acutely agitated patients. But we have a few reservations. The median age of the patients was 40, and the underlying etiology was thought to be acute alcohol intoxication in 88%.

We are surprised at the relative infrequency of serious adverse events. We suspect that we'd see more AE's in older patients or those with multiple comorbidities.

So we'd probably say the real conclusion of this study is that IM midazolam is safe and effective for management of relatively young males with acute alcohol intoxication. The generalizability to other populations is certainly suspect. And we would emphasize that even in the currently studied population, the potential for respiratory depression due to the combined effects of alcohol and midazolam merits close monitoring.

A second question is whether adequate sedation at 15 minutes is the most appropriate outcome measure. That certainly might help you get bloodwork done and perhaps some other interventions. But probably more important would be parameters like time to disposition or time to discharge.

So you have 2 studies that statistically provide some reassurance on strategies for managing certain patients in the ED setting but leave enough questions that make it difficult to generalize about their use at this time.

### **Our prior articles pertaining to long-acting and/or extended release preparations of opioids:**

- April 2010                    “[RCA: Epidural Solution Infused Intravenously](#)”
- July 13, 2010               “[Postoperative Opioid-Induced Respiratory Depression](#)”
- January 18, 2011           “[More on Medication Errors in Long Term Care](#)”
- April 12, 2011             “[Medication Issues in the Ambulatory Setting](#)”
- June 28, 2011             “[Long-Acting and Extended-Release Opioid Dangers](#)”
- September 13, 2011       “[Do You Use Fentanyl Transdermal Patches Safely?](#)”
- November 8, 2011       “[WHO's Multi-Professional Patient Safety Curriculum Guide](#)”
- May 2012                    “[Another Fentanyl Patch Warning from FDA](#)”
- July 24, 2012             “[FDA and Extended-Release/Long-Acting Opioids](#)”
- September 2012           “[Joint Commission Sentinel Event Alert on Opioids](#)”
- March 2013                 “[Try Googling Fentanyl Accidents](#)”

- September 2013 “[ISMP Outreach on Fentanyl Patch Safety](#)”
- October 2013 “[Opioid Safety Actions and Resources](#)”
- February 24, 2015 “[More Risks with Long-Acting Opioids](#)”
- February 2017 “[FDA Approves Even More Long-Acting Opioids](#)”

## References:

Clemency BM, Eggleston W, Shaw EW, et al. Hospital Observation Upon Reversal (HOUR) With Naloxone: A Prospective Clinical Prediction Rule Validation Study. Academic Emergency Medicine 2019; 26(1): 7-15  
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Christenson J, Etherington J, Grafstein E, et al. Early discharge of patients with presumed opioid overdose: development of a clinical prediction rule. Acad Emerg Med 2000; 7(10): 1110-1118  
<https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1553-2712.2000.tb01260.x>

Klein LR; Driver BE; Miner JR; Martel ML et al. Intramuscular Midazolam, Olanzapine, Ziprasidone, or Haloperidol for Treating Acute Agitation in the Emergency Department. Ann Emerg Med 2018; 72(4): 374-385  
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