Critical Review Form
Prognosis

Watson WA, Steele MT, Muelleman RL, Rush MD. Opioid toxicity recurrence after an initial response to naloxone. J Toxicol Clin Toxicol. 1998;36(1-2):11-7.

Objectives: **"to determine the frequency of opioid toxicity recurrence after a response to naloxone in sequential adult ED patients with toxicity caused by various opioids." (p. 12)**

Methods: **This retrospective case control study was conducted at Truman Medical Center in Kansas City, MO using cases presenting between August 1, 1987 and October 31, 1995. Cases involving both opioid toxicity and naloxone administration were included. Records were reviewed and data abstracted by trained reviewers using a pretested data collection form according to previous recommendations for retrospective chart reviews (Gilbert 1996).**

A nine member Delphi Panel consisting of toxicologists and emergency physicians reviewed the case information and determined if there was a response to naloxone, and whether such response was followed by a recurrence of opioid toxicity. Panel members categorized response and recurrence as definite, probable, or indeterminate. For an outcome to be definite, at least 8 members had to agree to this. For an outcome to be probable, no more than one member could define the outcome as indeterminate. Cases determined by the panel to be definite or probable were defined as either having a response to naloxone or as having a recurrence of toxicity.

The primary outcome was the recurrence of opioid toxicity following a response to naloxone. Those who had a recurrence were compared to those without recurrence based on duration of action of the opioid involved, the presence of other CNS depressants, patient demographics, the reason for opioid exposure, and the route of exposure. Opioids were categorized as either long-acting (methadone, sustained-release morphine, propoxyphene) or short-acting (heroin, codeine, oxycodone, hydrocodone, hydromorphone, meperidine, morphine, pentazocine).

There were 221 cases of opioid toxicity identified, of which 90 were treated with naloxone. Six cases were excluded to lack of evidence of opioid toxicity, leaving 84 cases for review. The mean age was 33 years and 42% were female. The reason for overdose was suicide in 48%, substance abuse in 32%, chronic pain management in 11%, and unknown in 9%. Respiratory depression was documented in 27% of cases and 21% were endotracheally intubated. Oral ingestion was documented in 68 cases (81%) and IV use was documented in 13 cases (15%). A single dose of naloxone was given in 66% of cases, and given IV in all but 2 cases.

Guide		Comments
I.	**Are the results valid?**	
A.	**Was the sample of patients representative?** *In other words, how were subjects selected and did they pass through some sort of "filtering" system which could bias your results based on a non-representative sample. Also, were objective criteria used to diagnose the patients with the disorder?*	Yes. All patients presenting to the ED with suspected opioid toxicity requiring administration of naloxone were included. The study does not include any potential patients that were treated with naloxone by EMS (unless such patients received subsequent doses of naloxone in the ED), and does not include patients released by EMS prior to transport.
B.	**Were the patients sufficiently homogeneous with respect to prognostic risk?** *In other words, did all patients share a similar risk from during the study period or was one group expected to begin with a higher morbidity or mortality risk?*	No. Patients were included regardless of the formulation, dose, timing, or route of opioid administration, all of which could potentially impact the likelihood of toxicity recurrence. Additionally, naloxone dose was not standardized, and the dosages were not provided.
C.	**Was follow-up sufficiently complete?** *In other words, were the investigators able to follow-up on subjects as planned or were a significant number lost to follow-up?*	Yes. The outcome was recurrence of toxicity during the ED stay, and the authors were able to collect follow-up data for all eligible patient.
D.	**Were objective and unbiased outcome criteria used?** Investigators should clearly specify and define their target outcomes before the study and whenever possible they should base their criteria on objective measures.	No. The primary outcome was recurrence of opioid toxicity, as determined by a Delphi Panel. Objective criteria were not used to determine if such an outcome had occurred, and as a result the outcome was defined as definite, probable, or indeterminate.
II.	**What are the results?**	
A.	**How likely are the outcome? In other words, how many patients had the outcome of interest?**	• 42 cases had either a definite or probable response to naloxone (50%, 95% CI 35-65%), and 22 cases were classified as indeterminate. No response was documented in 17 cases and 9 cases had no documentation. • Recurrence of opioid toxicity was identified as either definite or probable in 13 of these 42 cases (31%, 95% CI 17-45%). Two of these cases had a

		decrease in respiratory rate or depth recorded; six patients required an additional dose of naloxone, two of these requiring a continuous infusion. 18 cases were reported as no recurrence and 11 cases as indeterminate. • Patients with a recurrence of toxicity were similar to those without a recurrence with respect to age, sex, reason for opioid exposure, the presence of respiratory depression or coma, or the presence of a concurrent intoxicant. The rate of hospitalization was higher in those with a recurrence of toxicity (54% vs. 21%) though this did not achieve statistical significance (p = 0.08). • Recurrence of toxicity was more common following use of long-acting opioids compared to short-acting opioids (58% vs. 20%, p = 0.04). • There was no increased risk of recurrence of toxicity following IV exposure compared to oral exposure (15% vs. 32%, p = 0.42). • Opioid toxicity recurred over a range from 3 to 120 minutes after the initial dose of naloxone.
B.	**How precise are the estimates of likelihood?** *In other words, what are the confidence intervals for the given outcome likelihoods?*	See above.
III.	**How can I apply the results to patient care?**	
A.	**Were the study patients and their management similar to those in my practice?**	No. This study was conducted in the late 1980s and early 1990s, and the routes and types of opioid ingestions involved differ from those seen in our practice. Nearly 50% of cases were due to suicide attempt, and 81% involved oral ingestion. Anecdotally, the majority of cases in our practice involve IV, SQ, or intranasal use of heroin in accidental overdose, and the duration of effect would likely differ. Additionally, respiratory depression was documented in only 27% of cases, suggesting there may have been no true indication for naloxone administration in the majority of cases.
B.	**Was the follow-up sufficiently long?**	Uncertain. This was a retrospective chart review based on the ED documentation. The duration of ED observation was not standardized, and some opioid recurrence may have occurred after patients left the ED.
C.	**Can I use the results in the management of patients in my practice?**	No. Differences in patient population, lack of standardized naloxone dosing and duration of observation, the subjective nature of the outcomes, and the questionable clinical significance of the outcome

		make it difficult use these results in our practice.

Limitations:

1. **The dosage of the initial dose of naloxone was not standardized, and the dose actually used was not provided.**

2. **The primary outcome was subjective, and not necessarily a reflection on morbidity or mortality if such patients did not receive subsequent doses of naloxone (patient-important outcomes).**

3. **There were several key factors in included patient population that likely make them very different from patients seen in our practice with opioid overdose: i.e. nearly half of cases due to suicide attempt, 81% with oral ingestion (external validity).**

4. **Respiratory depression was documented in only 27% of cases, suggesting there may have been no true indication for naloxone administration in the majority of cases.**

Bottom Line:

In this small study of ED patients with opioid overdose requiring naloxone, recurrence of toxicity occurred in 31% of cases (95% CI 17-45%). Differences in route and formulation of opioid ingestion between the included patients and those observed in our population limit our ability to apply the results in our practice. Additionally, the use of subjective outcome criteria, and the lack of a clear clinical significance of the reported outcomes, makes it difficult to interpret these results.