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CME Information: Hospital Observation Upon Reversal (HOUR) With Naloxone: A Prospective Clinical Prediction Rule Validation Study

CME Editor: Corey Heitz, MD

Authors: Brian M. Clemency, DO, William Eggleston, PharmD, Evan W. Shaw, Michael Cheung, Nicholas S. Pokoj, Michael A. Manka, MD, Donald J. Giordano, Laura Serafin, Han Yu, MA, Heather A. Lindstrom, PhD, and David Hostler, PhD

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Educational Objectives
After reading the article, participants should be able to discuss the utility of a prediction rule for safe discharge of patients after receiving prehospital naloxone reversal of opioid overdose.

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Hospital Observation Upon Reversal (HOUR) With Naloxone: A Prospective Clinical Prediction Rule Validation Study

Brian M. Clemency, DO, William Eggleston, PharmD, Evan W. Shaw, Michael Cheung, Nicholas S. Pokoj, Michael A. Manka, MD, Donald J. Giordano, Laura Serafin, Han Yu, MA, Heather A. Lindstrom, PhD, and David Hostler, PhD

ABSTRACT

Objective: St. Paul’s Early Discharge 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. The rule suggested that patients could be safely discharged if they could mobilize as usual and had a normal oxygen saturation, respiratory rate, temperature, heart rate, and Glasgow Coma Scale score. Validation of the St. Paul’s Early Discharge Rule is necessary to ensure that these criteria are appropriate to apply to patients presenting after an unintentional presumed opioid overdose in the context of emerging synthetic opioids and expanded naloxone access.

Methods: In this prospective, observational validation study, emergency medicine providers assessed patients 1 hour after administration of prehospital naloxone. Unlike in the derivation study the threshold for normal oxygen saturation was set at 95% and patients were not immediately discharged after a normal 1-hour evaluation. Patients were judged to have a normal 1-hour evaluation if all six criteria of the rule were met. Patients were judged to have an adverse event (AE) if they had one or more of the preestablished AEs.

Results: 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. AEs occurred in 82 (15.4%) patients. The rule exhibited a sensitivity of 84.1% (95% confidence interval [CI] = 76.2%–92.1%), a specificity of 62.1% (95% CI = 57.6%–66.5%), and a negative predictive value of 95.6% (95% CI = 93.3%–97.9%). Only one patient with a normal 1-hour evaluation subsequently received additional naloxone following a presumed heroin overdose.

Conclusion: This rule may be used to risk stratify patients for early discharge following naloxone administration for suspected opioid overdose.

Opioid-related emergency department (ED) visits continue to increase, with the number nearly doubling from 2005 to 2014.1 Although opioid use disorder and its associated harms are not a new phenomenon, appropriate patient disposition after naloxone reversal of a presumed opioid overdose remains...
unclear. Some providers have advocated for a 4- to 6-hour observation period, but a recent systematic review concluded that 1 hour of observation is sufficient for patients who are able to ambulate as usual, have normal vital signs, and have a Glasgow Coma Scale (GCS) score of 15. This recommendation was based on the St. Paul’s Early Discharge Rule. This clinical prediction rule was derived from a single clinical site but was never externally validated.

The landscape of opioid use disorder has changed dramatically since 2000, when that derivation study was originally published. Since that time, there has been a rise in opioid-related overdose deaths, partly due to increasing heroin use. From 2014 to 2015, there was a 20.6% increase in heroin-involved deaths in the United States. The emergence of fentanyl and other synthetic opioid analogs has also played a significant role, resulting in a 72.2% increase in deaths involving synthetic opioids (other than methadone) over the same time period. Finally, while naloxone administration was limited to hospitals and paramedics at the time of the derivation study, access to naloxone has drastically expanded over the past decade. Today, naloxone is also carried and administered intranasally by emergency medical technicians, firefighters, police officers, and the lay public. These factors have complicated the disposition of patients presenting to EDs after a presumed opioid overdose. Validation of the St. Paul’s Early Discharge Rule is necessary to ensure that these criteria are appropriate to apply to patients presenting after an unintentional presumed opioid overdose in the context of emerging synthetic opioids, expanded naloxone access, and the emergence of intranasal naloxone administration. Our objective was to validate a modified version of St. Paul’s Early Discharge Rule.

METHODS

Study Design
This was a prospective observational study to determine if clinical judgment and/or a six-component clinical prediction rule applied 1 hour after prehospital naloxone administration for suspected opioid overdose could predict which patients would not have an adverse event (AE) in the first 24 hours. This study was approved by the University at Buffalo Institutional Review Board.

Study Setting
The study took place at a single urban academic tertiary care center with an annual ED census of approximately 65,000 visits. The hospital has specialized services for trauma, psychiatric, and substance abuse care. The city is covered by a single large commercial ambulance provider with advanced life support and basic life support (BLS) units. The outlying areas are covered by multiple agencies with a variety of staffing patterns. Advanced life support ambulance crews can administer naloxone via the intravenous (IV), intraosseous, intramuscular (IM), or intranasal (IN) route. BLS providers, firefighters, and police officers can provide naloxone via the IN route. Laypersons trained through a community naloxone program can administer naloxone via the IM or IN route.

Patient Enrollment
Adult patients (≥18 years of age) who arrived at the ED via ambulance after being treated with naloxone by emergency medical services (EMS), firefighters, police, or laypersons were enrolled in the study as a convenience sample. Patients were excluded if they were prisoners or under arrest, did not receive a 1-hour evaluation, had an incomplete but otherwise normal 1-hour evaluation, received in hospital naloxone prior to the 1-hour evaluation, their study data could not be linked to their hospital records, or they requested to be withdrawn from the study. On arrival, hospital triage staff identified potential study patients, and research associates in the ED helped facilitate enrollment and data collection.

Patient Care
All study patients received usual care at the discretion of the treating emergency medicine provider, regardless of their enrollment in the study or their risk stratification based on the prediction rule. At the time of the study, the typical duration of observation following naloxone administration in the study ED was 4 hours. All patients were free to leave the ED against medical advice at any time during the study if they had capacity to do so. Patients were able to be discharged earlier than 4 hours based on their providers’ clinical judgment.

One-hour Evaluation
A 1-hour evaluation by the emergency medicine provider (attending physician, resident, or advanced practice
provider) was planned 1 hour after the first dose of out of hospital naloxone. At that time, providers were asked to evaluate if the patient had the ability to mobilize as usual, a normal oxygen saturation, a normal respiratory rate, a normal temperature, a normal heart rate, and a normal GCS. Providers were asked to provide a binary “yes” or “no” for each component, with “yes” representing a normal examination finding. The normal criteria for each component of the rule were the same as those used in the derivation study, except that the threshold for normal oxygen saturation was increased from >92% to >95%. The revised prediction rule used for this study is shown in Table 1. If all six criteria were noted to be normal, the patient was deemed low risk for AEs based on the prediction rule, and the prediction rule was considered negative. Independent of the results of the prediction rule, providers were also asked if the patient appeared safe for discharge at that time based on their clinical judgment.

AEs

After the patient was discharged, the hospital record was reviewed for the presence of AEs. Three reviewers (MC, NP, ES) abstracted data from the hospital records. All reviewers were medical students trained by the primary investigator in study procedures. The reviewers were blinded to the results of the recorded 1-hour evaluation while reviewing the hospital records for AEs. The reviewers used a list of a priori clear AEs and unclear AEs based on those used in the original derivation study (Table 2). An AE was considered to be present if it was noted in any one of the following during the first 24 hours: the nursing note, the providers’ notes, or the orders.

All clearly defined AEs were treated as AEs without further adjudication. If the patient was found to have one or more unclear AEs, but no clearly defined AEs, one of two board-certified emergency medicine physicians (BC, MM) reviewed the hospital record. The emergency medicine physicians were blinded to the results of the recorded 1-hour evaluation while reviewing the records for AEs. Based on predetermined criteria, the physicians determined if the unclear AE met the criteria for an AE.

| Table 2
<table>
<thead>
<tr>
<th>AE Criteria</th>
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<tbody>
<tr>
<td><strong>Clearly defined AEs</strong></td>
</tr>
<tr>
<td>Death</td>
</tr>
<tr>
<td>Repeat naloxone for respiratory rate ( \leq 10 ) breaths/min or oxygen saturation ( \leq 92% )</td>
</tr>
<tr>
<td>Delivery of supplemental oxygen for a saturation ( \leq 92% )</td>
</tr>
<tr>
<td>Assisted ventilation (including BiPAP)</td>
</tr>
<tr>
<td>Administration of IV inotropic agents</td>
</tr>
<tr>
<td>Administration of antiarrythmic medications for sustained tachycardia ( &gt; 130 ) beats/min</td>
</tr>
<tr>
<td>Cardioversion</td>
</tr>
<tr>
<td>Administration of mannitol</td>
</tr>
<tr>
<td>Dialysis</td>
</tr>
<tr>
<td>Administration of bicarbonate for ( \text{HCO}_3^- &lt; 5 ) mmol/L in ABG or ( \text{CO}_2 &lt; 5 ) mmol/L in VBG</td>
</tr>
<tr>
<td><strong>Criteria for Adjudicating Unclear AEs</strong></td>
</tr>
<tr>
<td>Unclear AE</td>
</tr>
<tr>
<td>Additional naloxone without recorded respiratory rate or oxygen saturation</td>
</tr>
<tr>
<td>Oxygen administration without recorded oxygen saturation</td>
</tr>
<tr>
<td>IV antibiotics</td>
</tr>
<tr>
<td>Fluid bolus ( \geq 1 ) L</td>
</tr>
<tr>
<td>Any unscheduled surgery</td>
</tr>
<tr>
<td>Antiarrythmic medications without a recorded heart rate of ( &gt; 130 ) beats/min</td>
</tr>
<tr>
<td>Activated charcoal</td>
</tr>
</tbody>
</table>

**Note:** From “Early discharge of patients with presumed opioid overdose: development of a clinical prediction rule,” by Christenson J, et al., 2000, Academic Emergency Medicine, 7, p. 1116. Copyright 2000 by John Wiley and Sons. Adapted with permission. Adapted with modifications made to the lower limit of acceptable \( \text{O}_2\) saturation.

GCS = Glasgow Coma Scale; HOUR = hospital observation upon reversal.
Finally, local county medical examiner records were queried for patient death within 48 hours. All deaths within 48 hours were considered AEs.

**Sample Size Calculations**

The sample size calculations for this study mirrored those from the derivation study. The sample size calculations were performed with a goal of obtaining a lower-bound 95% confidence interval (CI) of 97% and with the assumption that there would be one prediction failure. This would require 160 patients with AEs. The expected AE rate among all patients was 30%, making the required sample size 540 patients.

**Data Analysis**

Statistics regarding patient age, sex, total naloxone dose, time to 1-hour evaluation, route of naloxone administration, and ED length of stay were obtained and compared to that of the derivation study. A chi-square test was used to calculate the sensitivity, specificity, positive predictive value, and negative predictive value for the prediction rule, clinical judgment, the prediction rule in combination with clinical judgment, and each of the six components of the prediction rule.

Additional information was provided for cases in which the rule and/or the provider’s clinical judgment failed to predict an AE. This statistical approach was designed to facilitate comparison between data from the derivation study and this study.

**Data Validation**

To ensure agreement among the reviewers, each of the three reviewers independently reviewed a sample of 50 charts to assess for agreement regarding the presence or absence of clearly defined and unclear AEs. A Cohen’s kappa coefficient was calculated to assess for inter-rater agreement.

To ensure agreement among the board-certified emergency physician adjudicators, each of the two adjudicators independently reviewed a sample of 50 charts that had been identified by the reviewers as having a potentially AE to assess for agreement regarding the presence or absence of an AE. A Cohen’s kappa coefficient was calculated to assess for inter-rater agreement.

To assess for systematic bias among the cases excluded for absence of a 1-hour evaluation, a sample of 50 excluded cases were reviewed for the presence of an AE from the hospital records. The prevalence of AEs was compared to the prevalence of AEs among patients included in the study.

**RESULTS**

A convenience sample of patients was enrolled from May 2016 to September 2017. A total of 690 patients were screened for inclusion on arrival; 538 (78.0%) patients met the inclusion/exclusion criteria and were included in the analysis (Figure 1). A description of patient characteristics and a comparison to patients from the deviation study are shown in Table 3. AEs occurred in 82 (15.4%) patients (Table 4). No patients died within 48 hours.

**Prediction Rule**

The rule and each of its individual components were predictive of AEs. Among the components of the rule, not having the ability to mobilize as usual had the greatest sensitivity (58.0%), and not having a normal temperature had the greatest specificity (99.1%) to predict AEs (Table 5). The rule exhibited a sensitivity of 84.1% (95% CI = 76.2%–92.1%), a specificity of 62.1% (95% CI = 57.6%–66.5%), and a negative predictive value of 95.6% (95% CI = 93.3%–97.9%). The rule failed to predict AEs in 13 (2.4%) of 538 cases.

**Provider Judgments**

Provider judgment was predictive of adverse outcomes. Provider judgment exhibited a sensitivity of 85.4% (95% CI = 77.7%–93.0%), a specificity of 60.9% (95% CI = 56.3%–65.4%), and a negative predictive value of 95.8% (95% CI = 93.4%–98.1%). Provider judgment that the patient was safe for discharge failed to predict AEs in 12 (2.3%) of 529 cases.
Provider Judgment Plus Prediction Rule

The combination of provider judgment plus the rule (considered normal if both were normal, considered abnormal if either or both were abnormal) exhibited a sensitivity of 87.8% (95% CI = 80.7%–94.9%), a specificity of 53.0% (95% CI = 48.4%–57.7%), and a negative predictive value of 96.0% (95% CI = 93.5%–98.4%). When provider judgment and the rule were used together, they failed to predict AEs in 10 (1.9%) out of 529 patients.

Prediction Failures

The cases in which the clinical prediction rule, provider judgment, or both failed to predict an AE are shown in Table 6. 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). These cases may have led to morbidity or mortality if left untreated. Of the remaining seven cases, six received low-flow supplemental oxygen via nasal cannula and one received IV fluid for hypotension. These final seven cases met the predefined AE criteria, but the AEs were unlikely to have caused morbidity or mortality if left untreated.

Data Validation

Three medical student reviewers reviewed a sample of 50 charts to assess for agreement on study outcomes. Among the 50 charts reviewed, they agreed on the presence or absence of at least one clearly defined AE in 50 charts (κ = 1.000). They agreed on the presence or absence of at least one potential AE in 49 charts (κ = 0.987).

Two attending physicians reviewed a sample of 50 charts that had been identified as having a potentially AE to assess for agreement. They agreed on the presence or absence of at least one true AE in 47 cases (κ = 0.789).

Three medical student reviewers reviewed a sample of 50 charts that were excluded because no 1-hour evaluation had been performed. Among the charts there were three true AEs in the hospital. The rate of AEs was 6%, demonstrating a lower prevalence of AEs among excluded patients.

DISCUSSION

Christenson et al.⁴ derived the original prediction rule prospectively from 31 potential predictive variables. That study was performed in Vancouver, Canada, in the late 1990s. The study sample had an AE rate of 16% and a negative predictive value of 99%.

In this data set, there was only one patient with a normal 1-hour evaluation per the clinical prediction rule that subsequently received additional naloxone.
following a presumed heroin overdose. Despite their differences in study design and study population, similar AE rates were found in the derivation study and this study. No patients in either study died following a normal 1-hour evaluation.

In this validation study, the prediction rule demonstrated somewhat lower sensitivity and negative predictive value, but somewhat higher specificity and positive predictive value compared to the derivation study. There are multiple reasons for this both inherent to the prediction rule creation process in general and specific to the study context. The derivation study assessed 31 potential variables and included six (19.3%) in the final rule in an effort to maximize sensitivity. It is not uncommon for prediction rules to have less favorable results when validated with a

<table>
<thead>
<tr>
<th>Overdose</th>
<th>Predefined AEs</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 PO acetaminophen/hydrocodone and PO carisoprodol</td>
<td>Repeat naloxone</td>
<td>Multiple repeat doses of naloxone and naloxone infusion</td>
</tr>
<tr>
<td>2 PO clonazepam</td>
<td>Supplemental oxygen</td>
<td>Nasal cannula oxygen for desaturations</td>
</tr>
<tr>
<td>3 PO oxymorphone and PO benzodiazepines</td>
<td>Supplemental oxygen</td>
<td>Nasal cannula oxygen for desaturations</td>
</tr>
</tbody>
</table>

The cause of the overdose is based on the treating provider’s clinical documentation. The term “heroin” was used in the describe what patients believed was heroin and may have contained synthetic opioids or other drugs. BIPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; IVF = intravenous fluid; PO = oral.
different patient population, but this step is critical to establish the generalizability of the rule.\textsuperscript{10} The derivation study also excluded five patients with adverse outcomes due to “intervening incidents.”\textsuperscript{4} It is unclear how many of these excluded patients from the derivation study had normal 1-hour evaluations using the rule. No such exclusions were incorporated in the design of the validation study.

Many patients received more than one prehospital naloxone administration. This finding is consistent with the increase in the frequency of multidose naloxone administrations that was described by Faul et al.\textsuperscript{11} Robertson et al.\textsuperscript{12} demonstrated that patients receiving IN naloxone were more likely to receive repeat doses than those receiving parenteral naloxone, likely due to its delayed onset of action. It is unclear what effect the increased onset time from IN administration,\textsuperscript{12,13} administration by nonparamedics, and the presence of synthetic opioids in the drug supply had on the total dose of naloxone received by patients in this study.

The expanded availability of IN naloxone is one of the key differences between the derivation study and our study. A majority (85.4\%) of our patients received IN naloxone at a mean dose of 3.1 mg. The route of naloxone administration is an important aspect to consider when considering an appropriate observation period. Pharmacokinetic studies in healthy volunteers demonstrate that higher dose IN administrations may produce a higher maximum serum concentration than IM administration and a larger area under the curve than the lower-dose IM and IV administration typically utilized.\textsuperscript{14,15}

Adverse outcomes were determined based on an a priori list adapted from the derivation study’s design. There were multiple cases that met the criteria for AEs following normal evaluations that were unlikely to have been clinically significant in this observational study. The majority of patients whom had predefined AEs following normal 1-hour evaluations required supplemental oxygen administered as low-flow nasal cannula, but not additional doses of naloxone. Desaturations can naturally occur while sleeping and often elicit a response from medical providers even when not clinically important. This effect is likely magnified as length of stay increases. The majority (64.3\%) of patients in this study had 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. Length of stay may be a confounder, as patients who stay in a medical environment longer may be more likely to receive additional care, some of which may meet the preestablished criteria for AEs. It is unlikely that the cases of transient mild hypoxia in patients not requiring additional naloxone or ventilatory support that occurred in this study would have resulted in a clinically important adverse outcomes if left untreated. However, it was reasonable that providers treated these patients with supplemental oxygen at the time, because transient hypoxia is a retrospective diagnosis.

When the prediction rule was used in tandem with the provider impression, it improved overall sensitivity and decreased overall specificity. Using a two-step process of provider impression followed by application of a prediction rule is not uncommon in emergency medicine. Early discharge among patients whom the provider feels are at low risk for an AE and who pass the clinical prediction rule is a rational approach that in this study population yielded a 96.0\% negative predictive value.

Some authors recommend a 2-hour observation,\textsuperscript{16} and others recommend a 4- to 6-hour period of observation.\textsuperscript{2} At the time of the study, the general practice at the study hospital was to observe patients with suspected parenteral opioid overdose for at least 4 hours following naloxone administration. 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 we typically observe patients for in our department following naloxone administration. Also of note, although that patient was bradypneic, with a respiratory rate of 8 breaths/min, her pulse oximetry on room air was normal.

Similar to the original derivation study, 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. This limitation should be taken into consideration by providers when assessing patients with opioid toxicity using the prediction rule. Patients presenting after IV injection or insufflation of an opioid likely experience peak drug effect prior to or shortly after arriving in the ED. In these cases, reemergence of toxicity should occur rapidly as naloxone is metabolized. However, oral overdose of opioids can result in altered absorption with delayed emergence or reemergence of
toxicity. Additional data are needed to assess the role of the prediction rule in this patient population.

Patients included in the study population were presumed to have used opioids based on the administration of out-of-hospital naloxone. Urine testing was not obtained to analytically confirm the presence or type of opioid in these cases. It is unknown if a majority of patients presenting after IV opioid use were exposed to heroin, fentanyl, or another synthetic opioid analog. The kinetics of these drugs are still largely unknown, although a window of observation beyond the duration of effect of naloxone would seem reasonable after IV or insufflation of an unknown opioid.

Clinical prediction rules are best for answering binary questions, such as can a condition be ruled out or is a patient safe for discharge. However, it is critically important that they only be used for the condition for which they are intended when patients have multiple acute conditions. For example, in this study, one patient with a normal 1-hour evaluation required incision and drainage, IV antibiotics, and admission for abscesses. In this case, the provider appropriately evaluated and treated the infectious condition independent of the outcome of the prediction rule. Finally, the performance of any clinical prediction rule is only as good as the availability of the data and the providers who are applying the rule. In two cases in which the prediction rule failed to predict an AE, the provider evaluated the patient as normal using the rule, despite the presence of a low SpO\textsubscript{2} recorded in the nursing notes.

Patients who are determined to be low risk may still experience complications after discharge. Therefore, discharge instructions and medications are important steps for risk mitigation. Patients should be advised not to use drugs or alcohol following an opioid overdose. Mixing opioid drugs with other drugs like cocaine or benzodiazepines may be particularly problematic. Patients should also be provided with materials outlining local resources for the treatment of opioid use disorder and with a take-home naloxone kit when appropriate. These steps may further mitigate potential complications in low-risk patients. At-home observation by a responsible adult who has naloxone and who is able to summon 9-1-1 in the cases of delayed sequelae makes intuitive sense.

Concerns over the legal and social implications of illegal drug use often lead a patient to want to leave the ED early. Risk stratifying a patient based on the results of their 1-hour evaluation may inform shared decision-making conversations between providers and patients with decision-making capacity. The ideal duration of observation for patients whom fail the 1-hour rule remains unclear.

Applying the prediction rule for patients for whom providers have a low clinical suspicion for AEs is a reasonable approach for risk stratifying patients for early discharge following naloxone administration for suspected opioid overdose. The rule should be used with caution in cases of known oral or mixed overdose.

**LIMITATIONS**

Unlike the derivation study, the design of this study did not include patient follow-up by phone. This is balanced by the fact that patients did remain in the ED longer than in the derivation study. Like the derivation study, this study did not limit its inclusion criteria based on the drug used or route of administration. Therefore, it is not possible to specifically determine the performance of the rule among patients following parenteral opioid overdose. Some of the patients treated with naloxone for presumed opioid overdose may not have actually overdosed on opioids.

Unlike the derivation study which based the timing of the 1-hour evaluation on the last naloxone administration, this study based the timing of the 1-hour evaluation on the first prehospital naloxone. This difference in design is unlikely to have affected the performance of the rule, because repeat doses of naloxone were frequently clustered together over a short period of time.

The prediction rule and provider impression had similar performance characteristics. The treating provider’s clinical impression was asked immediately after assessing the six components of the rule and this likely influenced the provider’s gestalt. In our city, EMS transports a disproportionate number of overdose patients to the study hospital, due in part to the availability of specialized substance abuse and psychiatric services at the study hospital. As a result, providers have more frequent exposure to overdose patients, which may improve their ability to identify patients at risk for adverse outcomes when compared to providers who see overdose patients less frequently.

**CONCLUSION**

This prediction rule appears to be a useful tool for identifying suspected opioid overdose patients treated
with naloxone who are safe for discharge after 1 hour. The adverse events identified in patients with normal examinations following naloxone administration for parenteral opiate overdose were generally minor and unlikely to be life-threatening. This study suggests the rule works when naloxone is administered intranasally and in a population where synthetic opioids are more common than in the original study. Further study is needed to determine the exact performance characteristics of the rule in the context of overdoses of various drugs, drug combinations, and routes of administration subgroups.

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References


