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EDITORIAL

The Devil Is in the Details but the Details Are Not in NHAMCS

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Given the current epidemic of harmful consequences from prescription opioids and heroin in the USA including 28,647 deaths due to opioids in 2014, naloxone has received widespread attention for use in hospital, prehospital, and bystander settings [1–3]. While naloxone can be a highly effective reversal agent for opioid poisoning, there appears to be a general assumption that it is substantially effective and always safe. This is highlighted by the inclusion of naloxone as part of a "coma cocktail," given indiscriminately to patients with suspected overdose decades ago. Given changes in the opioid pharmacopoeia, this is no longer appropriate [4, 5]. Under optimal circumstances (opioid-naïve patient, no co-intoxicant, shortly after exposure), administration of the opioid receptor antagonist naloxone definitively and safely reverses the dangerous respiratory depression caused by opioids. In the setting of opioid overdose, naloxone is appropriately recommended for those patients with depressed mental status and hypoventilation, often defined as a respiratory rate less than 12/min to maximize sensitivity and specificity of response to the antidote [4]. However, naloxone has never been a risk-free medication. Precipitated opioid withdrawal produces a catecholamine surge that can result in myocardial ischemia or pulmonary edema. Similarly, delirium, severe agitation, and combativeness may occur, as can other, less consequential, effects such as vomiting and diarrhea [6, 7]. Thus, clinicians are increasingly introspective about to whom they administer naloxone in the ED.

In this issue, Frank et al. utilize National Hospital Ambulatory Medical Care Survey (NHAMCS) data to describe the use of naloxone in the ED [8]. Their inclusion criteria were any adult in whom naloxone was among the eight administered medications recorded in NHAMCS or whether any of the three recorded diagnoses were opioid abuse, dependence, or withdrawal. Although it is unclear why the authors included opioid withdrawal in these criteria, it may reflect iatrogenic withdrawal that occurred after a patient was treated with naloxone. Since the authors were most interested in the use of naloxone as an antidote for opioid toxicity, it may have been cleaner to have limited their search criteria to only opioid abuse, overdose, and dependence. There were an estimated 1.7 million visits for opioid overdose over the 10-year period they searched, and naloxone was one of the administered medications recorded by NHAMCS in 16 % of cases. Note that it is not possible from NHAMCS data to decipher why naloxone was administered. It is equally not possible to determine the reason that naloxone was not administered to the vast majority of potential recipients: Did they not manifest respiratory depression? Did they receive prehospital or bystander naloxone? Were they in withdrawal? Were they already intubated? Given the low percentage of naloxone administration, this result may also reflect ED providers being appropriately judicious with the use of naloxone.

Interestingly, of the patients who received naloxone, only 19 % had an opioid-related diagnosis included in the three diagnoses NHAMCS recorded. Explanations for this odd finding include the administration of naloxone to reverse procedural sedation or the use of naloxone as a diagnostic tool in patients with altered mental status or undifferentiated respiratory depression. In patients who present somnolent with respiratory depression, many potential causes exist including

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ethanol, imidazolines, and polypharmacy with various sedative/hypnotic agents, in addition to a host of non-toxicologic reasons (e.g., intracranial hemorrhage, hypoglycemia, encephalitis). Providers, in completing their final assessment, may opt for the less specific, but unassailable, diagnosis of "altered mental status, unspecified" (ICD-10 code R41.82) rather than the likely but unconfirmed diagnosis of "poisoning by other opioids, undetermined, initial encounter" (ICD-10 code T40.2X4A).

Seemingly paradoxically, this study reports administration of naloxone and an opioid medication during the same visit in an estimated 230,000 visits, or 14 % of visits that included naloxone administration. As suggested by the authors to address this apparent contradiction, these scenarios may be due to the decision to treat recrudescent pain after naloxone use or to antagonize an iatrogenic opioid overdose. Additional possibilities abound and include the use of an opioid in a patient intubated for respiratory depression not responsive to naloxone, and sedated with midazolam and fentanyl. Regardless, NHAMCS data severely limits any ability to explain the temporal relationship of the two medications; chart-level data would be necessary.

The NHAMCS database is a powerful tool maintained by the Centers for Disease Control and Prevention that contains a large number of ED visits sampled over many years. It allows researchers to follow the proportion of ED visits over time involving specific diagnoses, procedures, medications, and dispositions in a sample that is nationally and regionally representative. There are important limitations to the use of these data. Two studies have documented significant inaccuracies in the data contained within NHAMCS. In one, NHAMCS reported a positive pregnancy test in only 55 % of cases of ectopic pregnancy while another reported incompatible dispositions (e.g., discharged home and admitted to a non-intensive care bed) for 27 % of cases where intubation was performed [9, 10]. This may occur because medical staff are rarely those extracting NHAMCS data from medical records. Instead, medical records personnel are the primary data extractors and may not be sensitive to the bits of data that are crucial to each case [11]. Additionally, NHAMCS sets a limit on the diagnoses and medications coded for each case at 3 and 8, respectively. Medications administered prior to ED arrival are not coded, and as noted above, the temporal relationship between medications is not recorded.

Increased granularity of these data is vital to make any strong conclusions about naloxone use in America's EDs. The authors concede this when they note that their results are only hypothesis generating. Further detail about the reported cases, including other medications administered and laboratory data, would allow a more nuanced analysis of the results. Serum ethanol concentrations or exposures to other sedative agents would suggest a reason why naloxone was not given. EMS has used naloxone for decades, and more recently, first responders such as police officers, firefighters, and the lay public are able to administer naloxone. Thus, the true number of opioid overdose cases treated with naloxone is far underestimated by NHAMCS data. Dose data is not recorded by NHAMCS, but increased scrutiny of the appropriate naloxone dose has recently shown low doses, titrated from 0.04 mg to start, may be optimal to balance reversal of respiratory depression against precipitated opioid withdrawal, though wide variations in recommended doses are present in the literature [12]. It would be interesting to know if visits when both an opioid and naloxone were given coordinated with higher naloxone doses. If so, this would suggest significant precipitated withdrawal.

It is clear that ED providers are not treating all opioid overdose patients with naloxone, potentially reserving treatment for those meeting established indications, and that naloxone is being administered to patients without opioid toxicity. The details of these cases, including prehospital events, coingestants, laboratory data, and a statement of medical decision-making, can clarify many of the questions raised regarding ED naloxone administration. This granularity though is something that requires a closer evaluation than NHAMCS can provide. We strongly believe that as medical toxicologists we need to be more involved in efforts like these (such as through ACMT's ToxIC), or partner with agencies where these datasets exist, in order to provide more meaningful scholarship and positively impact the care of poisoned patients as we move the specialty into the future.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

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