The New Opioid Epidemic: Prescriptions, Synthetics, and Street Drugs

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Opioid users are turning to illicit, ultra-potent synthetic opioids, and those who overdose may not respond to typical doses of naloxone. This review describes the management of patients who use these agents.

Opioid misuse, which often is the result of a prescription written for a very painful condition, has created an epidemic of opioid abuse, addiction, and fatalities across the United States. To reduce the risks from prescribed opioids, regulators and public health authorities have implemented intensive risk mitigation programs, prescription-monitoring programs, and prescribing guidelines.

Clinicians have been encouraged to manage acute and chronic pain more comprehensively. Concurrently, pharmaceutical companies have introduced tamper-resistant formulations, also known as abuse-deterrent formulations, intended to limit manipulation of the contents for insufflation or injection. Although some of these formulations have made tampering difficult, overall they have not effectively reduced inappropriate use or abuse.

All of these interventions have resulted in a reduction in the availability of affordable, commercially available pharmaceutical opioids (**Table 1**). Simultaneously, other prescription opioid users have found that the analgesic or euphoric effects of their prescription opioids were no longer sufficient, due to opioid tolerance and hyperalgesia. Both of these forces are driving opioid users to seek more potent opioid products and higher doses to achieve the desired psychoactive and pain-relieving effects.

For these reasons, many opioid users turned to less expensive, readily available, illicitly produced heroin and potent synthetic opioids—mainly fentanyl derivatives. The increased use of heroin and synthetic opioids has resulted in a sharp rise in overdoses and deaths, which continue to be a daily presentation in EDs throughout the country.

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Authors' Disclosure Statement: The authors report no actual or potential conflict of interest in relation to this article.

DOI: 10.12788/emed.2017.0010

Table 1. Prescription Opioids

Medication
Buprenorphine
Codeine
Fentanyl
Hydrocodone
Hydromorphone
Methadone
Morphine
Oxycodone
Oxymorphone
Tramadol

Table 2. Synthetic Opioids

Medication
Acetyl fentanyl
AH7291
AH7927
Butyr fentanyl
Carfentanil (illicit)
Fentanyl (illicit, nonpharmaceutical fentanyl [NPF])
Furanyl fentanyl
U47700
W18

This review describes the emergence of the new synthetic opioids, and the steps emergency physicians (EPs) can take to identify and manage ED patients who have been exposed to these agents.

Case

A 34-year-old woman with a history of opioid-use disorder was found unresponsive by a family member who immediately called emergency medical services (EMS). Upon arrival, the emergency medical technicians noted the patient's agonal respiration and pinpoint pupils. They immediately provided assisted ventilations via a bag-valve-mask (BVM) and administered 2 mg of intranasal naloxone prior to transport. The patient remained unresponsive, with no improvement in her respiratory status.

Upon arrival at the ED, the patient was still comatose, and her pupils remained pinpoint. Vital signs at presentation were: heart rate, 48 beats/min; blood pressure, 70/40 mm Hg; agonal respiration; and temperature, 98.2°F. Oxygen saturation was 86% while receiving assisted ventilation through BVM. An intravenous (IV) line was established.

What is the differential diagnosis of this toxidrome in the current era of emerging drugs of abuse?

The differential diagnosis of a patient with pinpoint pupils and respiratory depression who does not respond to naloxone typically includes overdose with gamma-hydroxybutyrate, clonidine, or the combined use of sedative-hypnotic agents with ethanol (organophosphate exposure and pontine strokes are two other causes). Naloxone administration may help diagnose opioids as a cause, and, in the past, a lack of response to naloxone was used to help exclude opioids as a cause. However, opioid poisoning should no longer be excluded from consideration in the differential diagnosis when patients are nonresponsive to naloxone. Patients who

combine the use of opioids with another sedative hypnotic or who develop hypoxic encephalopathy following opioid overdose may not respond to naloxone with arousal. Most important, the emergence of ultra-potent synthetic opioid use raises the possibility that a patient may appear to be resistant to naloxone due to the extreme potency of these drugs, but may respond to extremely large doses of naloxone. These new opioids pose a grave public health threat and have already resulted in hundreds, if not thousands, of deaths.[1]

What are novel synthetic opioids?

Unlike heroin, which requires harvesting of plant-derived opium, the novel synthetic opioids are synthesized in laboratories, primarily in China, and shipped to the United States through commercial channels (eg, US Postal Service).[2,3] Over the past few years, novel synthetic opioids have been supplementing or replacing heroin sold on the illicit market.[1] Most of these novel synthetic opioids are fentanyl analogs (**Table 2**) that are purchased in bulk on the "Darknet"—an area hidden deep in the Internet (not discoverable by the common major search engines) that allows users to engage in questionable, even illegal, activities utilizing nontraceable currencies such as Bitcoin.[4]

At the local level, dealers may seek to attract heroin users by adulterating, or even replacing, heroin with fentanyl or novel synthetic opioids, marketing it as a "high-quality" heroin offering more rapid, intense effects. These fentanyl analogs are often hundreds of times more potent than fentanyl, and therefore thousands of times more potent than heroin. Only a miniscule amount increases the perceived potency of the "heroin," allowing dealers to increase their profit margins.

Selling and using novel synthetic opioids leave little room for error, and small dosing miscalculations have resulted in profound overdoses and deaths. Obviously, the quality control, contents, and dose uniformity of illicitly traded products are poor, adding to the risks of use. In some cases, the novel synthetic opioids are pressed into tablets and marketed as diverted prescription opioids or benzodiazepines. In many, if not most, circumstances, intermediary dealers, as well as users, may be unaware of the product's contents.[5,6]

Carfentanil, used as a large-animal tranquilizer, is reportedly 10,000 times more potent than morphine and has recently been implicated in a cluster of deaths of opioid users in the Midwest.[7,8] Other synthetic opioids coming to market were initially developed for laboratory research, including W18, which was identified in Canada; and U47700, an opioid identified on autopsy of the musician Prince[3,9] (**Table 2**).

Novel synthetic opioids can be identified only by specific, specialized assays not available in clinical settings. Because their molecular structures differ substantially from morphine, these compounds skirt identification by standard urine "opiate" drug screens. With the exception of fentanyl, pharmacokinetic data for the use of the majority of these agents in humans is unknown.

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How are patients who present to EDs with an opioid toxidrome managed in practice today?

Classic teaching for the management of opioid-induced respiratory depression in adults is to provide ventilatory support (ie, BVM or intubation) or administer a low dose of naloxone (0.04 mg IV every 2-5 minutes, up to 2 mg) until adequate respirations are restored. This approach is reasonable for patients exposed to heroin or fentanyl, and provides safer reversal in

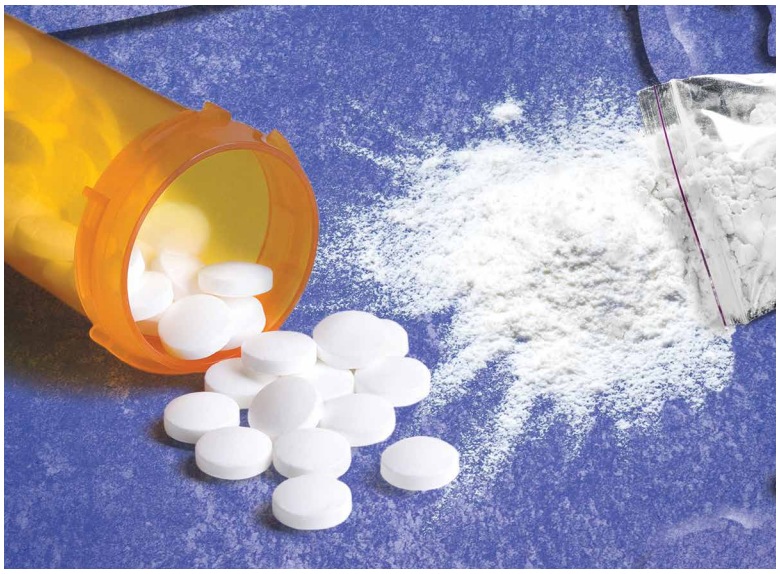
the ED than administration of a large bolus dose of 0.4 or 2 mg naloxone in opioid-dependent patients.

However, patients exposed to novel synthetic opioids may ultimately require higher than usual doses of naloxone to achieve reversal—reportedly IV doses as high as 6 to 10 mg or more.[10] It is not yet fully understood if the need for high-dose naloxone is due to the binding affinity of the opioid or the relatively high dose of opioid administered.

Because the clinical effects of the novel synthetic opioids are generally indistinguishable from those of other opioids, providing respiratory support in the ED remains a critical intervention while awaiting the effect of titrated doses of naloxone. Of concern, though, is that these opioids are so potent that they may cause immediate respiratory arrest, resulting in a more rapid progression to cardiac arrest, limiting the ability to administer rescue breathing or antidote.

In the "bystander" setting, administration of a larger initial dose of naloxone may be reasonable, given the lack of advanced medical supportive care. However, the ability to provide larger doses in these settings is hampered by the accessibility of the antidote. In addition, prehospital-care providers need to consider the possibility of precipitating opioid withdrawal in patients with opioid dependence, which itself can carry significant consequences (eg, aspiration, agitated delirium), as well as the subsequent uncooperativeness of the victim, who may attempt to leave the scene and self-administer an additional dose of opioid or develop recurrent respiratory depression when the naloxone wanes. Since many patients with life-threatening opioid intoxication will suffer long-term consequences if reversal is delayed, the risk of administering high-dose naloxone in the bystander setting generally is worthwhile. However, the risks and benefits of naloxone must still be thoughtfully considered by prehospital-care providers who can provide alternative supportive therapies.

In the ED, the EP must decide whether to intubate the patient directly or first give a brief trial of low-dose naloxone. If a trial of naloxone is unsuccessful at reversing the respiratory depression, dose escalation can be tried while supporting oxygenation and ventilation noninvasively. Administration of naloxone postintubation is not usually necessary or even desired, since respiratory depression, the primary mechanism of death, has been addressed.



Are any special precautions required for health care workers?

Some of the ultra-potent synthetic opioids are available as powders or sprays that can be inadvertently absorbed through the skin (after dissolution in skin moisture) or inhaled.[8] The safety of health care providers and law enforcement personnel who may be exposed to synthetic opioids in this manner is currently unknown, though some law enforcement and public health agencies have published warnings in an effort to be proactively cautious.[8]

While it is highly unlikely that the handling of body fluids of opioid-intoxicated patients poses any health threats, universal safety precautions of wearing dispos-

able gloves should be utilized. As noted, contact with the actual substances may be more concerning, particularly when airborne; in such situations, a particulate mask should also be utilized. Although fentanyl in liquid formulation can slowly enter the skin transdermally (eg, fentanyl patch), there are very limited data to either support or refute the ability of the newer potent opioids to do so. Until more data on these opioid analogs become available, those entering grossly contaminated areas, in which dermal or inhalational exposure is high, should employ a higher level of personal safety precautions.[11] In addition, naloxone should be readily available.

How can we detect novel opioid use?

As noted, there is no ability to specifically detect the use of novel potent opioids in the clinical setting (eg, hospital laboratory); therefore, clinicians must maintain a high level of suspicion and provide care empirically. The ability to make a specific diagnosis is further clouded because a patient who has used a synthetic opioid may have also used certain prescription opioids or heroin, which can be detected by standard testing.

Blood and urine samples obtained early in care and sent to specialized laboratories may provide specific identification. Such testing is typically only done by reference laboratories, health departments, or law enforcement agencies. The information obtained from these analyses may help to understand the epidemiology of novel opioid abuse, prevent others from succumbing to addiction, and determine the cause of related deaths.

Which patients can be safely discharged from the ED after an opioid overdose?

Patients who survive reversal of an opioid overdose, whether from a conventional or novel opioid, are at extremely high risk of subsequent death from continued use, as well as from the initial exposure to a long-acting opioid that outlasts the reversal effects of naloxone. Such patients should undergo a sufficient observation period after the last dose of naloxone has been administered to allow its effects to dissipate. This is likely at least 2 hours, but may be longer in certain individuals. Attempts at establishing a link for the patient to long-term treatment or (where available) providing a naloxone rescue kit and training to patients and their families are worthwhile. Although some data support releasing responsive patients after a short, but safe interval after naloxone administration, the changing landscape of opioid use should prompt reconsideration of such practices.[12]

To whom should suspected opioid overdose patients be reported?

While most EPs are familiar with the management of patients with opioid-induced respiratory depression, atypical cases (eg, patients less responsive to naloxone, those who suffer cardiac arrest) or clusters of suspected cases should always be reported to a regional poison control center (PCC) or health department. The PCC is typically engaged in surveillance and works cooperatively with area EDs and public health officials to track and notify physicians of emerging trends. The epidemiological data derived from reports from a variety of hospitals allow health officials to effectively engage resources for public warnings, facilitate forensic identification of circulating products, and determine any unique clinical information that can then be broadly disseminated.

Case Conclusion

The patient was supported with BVM ventilations. Despite additional titrated IV naloxone (up to a total of 4 mg) the patient was nonresponsive and unarousable. She was intubated, and awoke several hours later. She fully recovered and subsequently was referred to both a harm-reduction and an opioid detoxification program. Analysis of her blood and urine, available several weeks later, confirmed an exposure to U47700.

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