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Abstract

Overdose due to opioid abuse is an ever increasing problem, especially in the United States, with the last few years seeing a dramatic rise in the number of synthetic opioid-related deaths. The pure opioid antagonist naloxone has been used in a clinical setting as an antidote to opioid overdose for decades. Recent data suggest that the number of patients requiring multiple doses of naloxone is growing likely caused by the increased number of intoxications with potent synthetic opioids such as fentanyl and its derivatives. Treating clinicians in both emergency departments and pre-hospital settings should be aware that they may need to escalate to higher doses of naloxone, with repeat doses or IV infusions required, when treating patients who have overdosed on synthetic opioids. Moving forward, a combination of improved access to naloxone in a pre-hospital setting, an increase in community-based training, including the likely requirement of rapid or higher dose naloxone administration for treatment of synthetic opioid overdose, and a better understanding of the toxicology of high potency synthetic opioids, are required to decrease the number of fatalities stemming from the current opioid crisis.

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The role of naloxone in the opioid crisis

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ABSTRACT

Overdose due to opioid abuse is an ever increasing problem, especially in the United States, with the last few years seeing a dramatic rise in the number of synthetic opioid-related deaths. The pure opioid antagonist naloxone has been used in a clinical setting as an antidote to opioid overdose for decades. Recent data suggest that the number of patients requiring multiple doses of naloxone is growing likely caused by the increased number of intoxications with potent synthetic opioids such as fentanyl and its derivatives. Treating clinicians in both emergency departments and pre-hospital settings should be aware that they may need to escalate to higher doses of naloxone, with repeat doses or IV infusions required, when treating patients who have overdosed on synthetic opioids. Moving forward, a combination of improved access to naloxone in a pre-hospital setting, an increase in community-based training, including the likely requirement of rapid or higher dose naloxone administration for treatment of synthetic opioid overdose, and a better understanding of the toxicology of high potency synthetic opioids, are required to decrease the number of fatalities stemming from the current opioid crisis.

KEYWORDS

Opioid; naloxone; fentanyl;
EMS; heroin; overdose


The United States, sadly, is in the midst of an opioid epidemic. Data released by the National Center of Health Statistics in December 2017 show that deaths from opioid overdose exceeded 42,000 in 2016, an increase of more than 27% on 2015 [1] with increases seen for all classes of opioids (Figure 1). Of greatest concern, however, is the rapid increase in the number of deaths from synthetic opioids, such as fentanyl and its derivatives. An agonist at all opioid receptors fentanyl is fifty to a hundred times more potent than morphine [2,3] with respiratory depressant effects that peak in 5–15 min and a dose-dependent duration of action [4]. Synthetic opioid deaths doubled from 9580 in 2015 to 19,413 in 2016 and contributed to the accelerated rise in opioid deaths since 2013 (Figure 1) [1]. The trend appears unabated in 2017. In Ohio during January–February 2017 90% of the 281 unintentional overdose fatalities tested positive to the presence of fentanyl with the majority of decedents testing positive to more than one type of fentanyl derivative [5].

The US Government recently acknowledged the opioid crisis at both a state and federal level, with six states taking the additional step of declaring the issue a state of emergency [6]. Both Alaska and Maryland specifically acknowledged the role synthetic opioids are playing, and five of the six states used their emergency declaration to

promote an increase in access to the opioid antidote naloxone [6]. The approaches taken to promote this improved access to naloxone vary greatly by state and local area. Some of the programs introduced include: the training and education of emergency medical services, law enforcement personnel and lay-persons; supply of naloxone to emergency medical services and law enforcement agencies; lay-person access to naloxone via pharmacy without a prescription; and programs to directly supply naloxone to addicts upon institutional release [6,7].

Clinicians have used the opioid antagonist naloxone as an antidote to opioid overdose for decades. As a competitive antagonist at the μ -opioid receptor it effectively reverses clinical signs of opioid intoxication. However, naloxone can precipitate withdrawal effects in opioid-addicted individuals. The US Food and Drug Administration (FDA) approved its use as an intravenous, intramuscular, or subcutaneous injection of naloxone hydrochloride in 1971, and more recently in the form of the Evzio[®] auto-injector in 2014, designed for intramuscular or subcutaneous administration, and Narcan[®] Nasal Spray, designed for intranasal administration, in 2015.

The recent approval and increased availability of intranasal naloxone products has altered the pre-hospital

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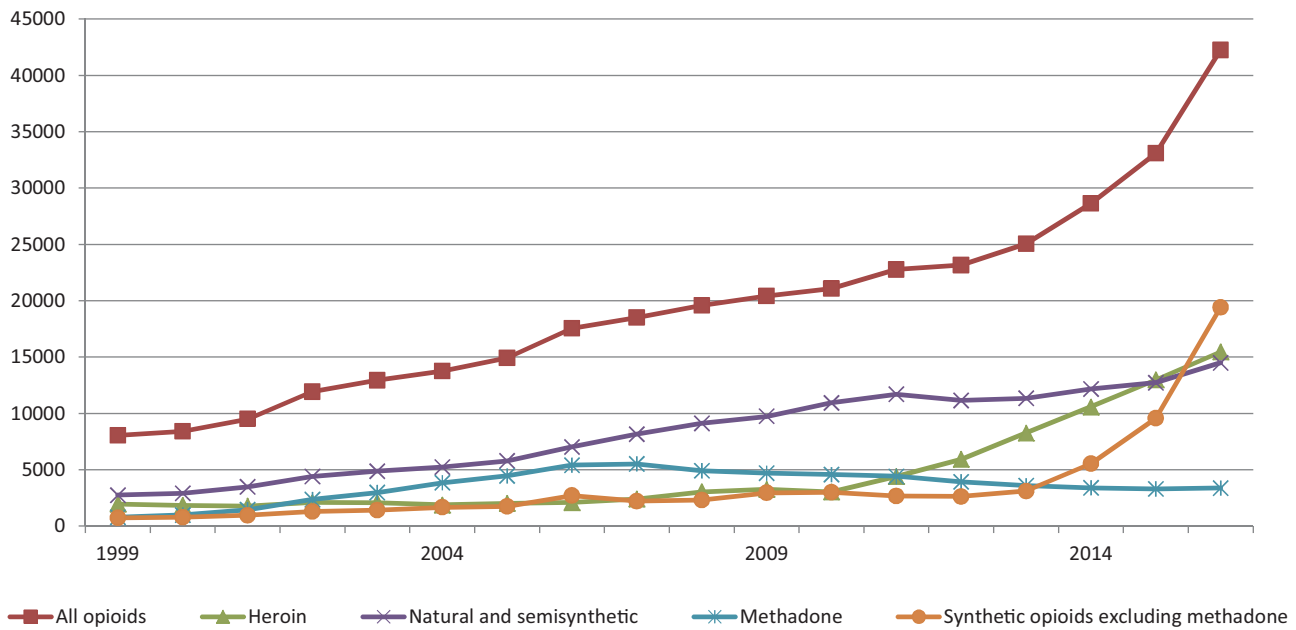


Figure 1. Drug overdose deaths in the United States, 1999–2016, by opioid category. Deaths involving more than one drug may be counted in more than one category. Data taken from the NCHS Data Brief, December 2017 [1].

care setting in the past few years. Lay-persons are able to regularly administer these products as they eliminate the risk of needle-stick injury. However, the prices of both Narcan[®] Nasal Spray (~\$US135 for a two pack) [8] and the Evzio auto-injector (~\$US3800 for a two pack) [8] are hindrances to their use. Claims from the Narcan[®] Nasal Spray manufacturer that the drug is affordable as “80% of current prescriptions have a co-pay of \$20 or less” [9] are unlikely to accurately represent the current pricing situation as opioid addicts who are not able to purchase naloxone due to its prohibitive cost are not reflected in these statistics. Continuing to ease access to naloxone, including a decrease in price, allowing non-prescription supply and providing training for both lay-persons and advanced life support providers is a critical step in the attempt to decrease the number of deaths stemming from the opioid epidemic.

US National Emergency Medical Service data show that the number of patients requiring multiple naloxone

doses is trending upwards [10] likely as a result of increasing intoxication with synthetic opioids. Literature evidence of cases involving higher than usual doses of naloxone is summarized in Tables 1 (case studies) and 2 (retrospective case series). Gussow 2016 suggested that protocols starting with very low doses or naloxone (<0.4 mg) may need to be rethought, providing anecdotal evidence that patients with presumed carfentanyl exposure required up to 18 mg of naloxone to reverse the effects of opioid intoxication [11]. The general conversational nature of this report with no analytical analysis or data provided shows the importance of ensuring unusual cases are fully reported in the literature with naloxone doses and full toxicological blood and urine screening results in order to better inform changes to naloxone dosage protocols.

The FDA currently recommends an initial dose of 0.4–2 mg of naloxone via IV or IM, with some emergency medical service protocols recommending the

Table 1. Case studies involving higher than usual doses of naloxone in patients with synthetic opioid intoxication.

Ref.	Patient	Drug	Naloxone dose	Outcome
[12]	23-year-old female, unresponsive, 4 breaths/min	U-47700 insufflated and IV	2 mg IN – no response; 2 mg IV – response (4 mg total)	Discharged next day; LC-MS drug confirmation
[13]	36-year-old male, altered mental status, pinpoint pupils, GCS = 6	Vaping “synthetic opium” shown to contain acetylfentanyl	2 mg IV – awoke but eventually mental status declined; 2 mg IV – again roused but mental status declined; 2 mg IV followed by 1.5mg/hour infusion (>7.5 mg total)	Admitted to ICU; Identity of drug determined through website of sale
[14]	24-year-old male, hypotension, hypoxic respiratory failure	Street purchased hydrocodone/acetaminophen tablets shown to contain fentanyl	2 mg IN + 1 mg IV – no significant response (3 mg total)	Eighteen further patients over eight days, one death, 3/18 received ≥ 5 mg naloxone total bolus dose, 4/18 received a naloxone infusion

Table 2. Retrospective case series involving higher than usual doses of naloxone to treat patients with suspected synthetic opioid intoxication.

Ref.	Study description	Naloxone administered	Summary of findings
[15]	Observational case series; Chicago, IL; ED data; Opioid overdoses 5 April–6 Dec	Twenty-six cases; 0.4–12 mg IV naloxone; average 3.36 mg	6/26 patients required >6 mg IV naloxone; 0.4 mg effectively reversed patient toxicity in only 15% of ED cases; even with some initial doses of 2 mg IV no patients experienced significant withdrawal
[10]	Data analysis of NEMSIS 2012–2015; naloxone use only; comparison of single vs. multiple naloxone administration (MNA)	2012: 95,012 patients received naloxone; 14.49% MNA 2015: 173,016 patients received naloxone; 18.24% MNA	MNA increased 25.8% from 2012 to 2015; odds of MNA were the highest in north-eastern US, which is consistent with increased use of fentanyl; no data on administration route
[16]	Survey study; April 2016 MA; adults who had used opioids (<2 months) and witnessed or survived an opioid overdose (<6 months)	83% of survey respondents reported that ≥ 2 naloxone doses (likely 2 mg/2ml) were required in cases of suspected fentanyl overdose	~2/3 of opioid overdose deaths in south-eastern MA (Oct 2014–Mar 2015) involved fentanyl [44% in Oct 2014 to 76% in Mar 2015]

lower end of this dosing regimen [17,18]. However, in cases of an unknown intoxication with opioids resulting in poor or incomplete response to naloxone, or known intoxication with synthetic opioids, clinical staff may need to escalate to higher doses more quickly than they would have previously with opioids such as heroin. In addition, multiple doses or intravenous infusions are often required as fentanyl and its derivatives have a longer biologically active half-life than naloxone [4].

In the face of the rising opioid epidemic, the obvious difficulty facing clinical staff is that often they do not know identity of the opioid causing the intoxication. A number of illicit opioids, including fentanyl, do not produce a positive result on a standard drug urine screen and staff have to rely solely on the opioid toxidrome to identify cases of suspected opioid intoxication. Adding to this complexity is the fact that the 200 known synthetic derivatives of fentanyl, some of which are up to 10,000 times more potent than morphine, are increasingly sold as heroin or in combination with heroin without the knowledge of the user [19,20]. We suggest beginning with smaller doses of naloxone (0.4 mg IV), followed by a rapid escalation to higher doses (2 mg) if no response is observed within 2–3 min.


Pre-hospital settings would likely require similar protocols with lay-persons or emergency medical personnel administering naloxone via the intramuscular or intranasal route. It is therefore important to ensure an explicit explanation of the likely higher doses of naloxone required for treatment of synthetic opioid in education and training programs. Additionally, treating staff need access to adequate volumes of naloxone to deal with this eventuality.


Moving forward we require improved access to naloxone in the pre-hospital setting, increased community-based training including the likely requirement of rapid/higher dose naloxone administration for treatment of synthetic opioid overdose, and a better understanding of the toxicology of high potency synthetic opioids, to reduce the number of fatalities stemming from the current opioid crisis.

Disclosure statement

The authors report no conflicts of interest.

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