North America is currently facing an opioid epidemic. Opioid overdose deaths have increased 200% since 2000, and in 2014, 28,647 drug-poisoning deaths were attributed to some type of opioid. Multiple sources of opioids contribute to this growing problem and include prescription opioids (including natural and semisynthetic opioids, eg, oxycodone, hydrocodone), methadone, and other synthetic opioids (eg, fentanyl, tramadol); heroin; and other illicit opioids produced in clandestine laboratories. These illicitly produced opioids include nonpharmaceutical fentanyl, fentanyl analogues (eg, acetylfentanyl), and novel synthetic opioids, such as U-47700. The increased incidence of toxicity related to synthetic opioids is highlighted by the case report in this issue by Armenian et al, who describe a case of opioid toxicity related to fentanyl and U-47700 in a patient who believed she was receiving “Norco.”

To understand the concerns about nonpharmaceutical fentanyl requires some background about the opioid epidemic. Prescriptions for opioid analgesics paralleled an increase in opioid abuse and fatalities between 2002 and 2010, leveling off from 2011 to 2013. However, drug overdose deaths involving natural and semisynthetic opioids, including the most commonly prescribed opioid pain relievers, oxycodone and hydrocodone, increased by 9% between 2013 and 2014. Increased prescriber education and public awareness of the true harms of opioid overprescribing has likely contributed to improvements in prescribing practices. Additionally, local and regional interventions have led to decreased prescribing and subsequent diversion of prescription opioids. However, as the availability of prescription opioids has decreased, the use and availability of other opioids has increased. This is clearly demonstrated by the significant increase in heroin use in several regions of the United States between 2010 and 2013. In fact, heroin overdose death rates increased 26% from 2013 and 2014 and have more than tripled since 2010. But even more concerning, between 2013 and 2014 the death rates for synthetic opioids, excluding methadone (eg, fentanyl), increased by 80%, largely because of increased use and abuse of nonpharmaceutical fentanyl.

Nonpharmaceutical fentanyl is produced in clandestine laboratories and is primarily sourced from Mexico; fentanyl analogues and precursor chemicals are obtained from distributors in other countries, including China, Germany, and Japan. In late 2013 and 2014, the Drug Enforcement Administration National Heroin Threat Assessment Summary noted spikes in overdose deaths related to fentanyl and its analog, acetylfentanyl, and in March 2015, the agency issued nationwide alerts that identified fentanyl as a significant threat to public health and safety. Nonpharmaceutical fentanyl is often sold to users who believe they are receiving heroin, oxycodone, or other drugs of abuse, including stimulant drugs such as Methyleneoxyamphetamine (MDMA, “ecstasy”) and cocaine. In fact, many pills being sold as counterfeit oxycodone are made to resemble OxyContin or Roxicodone, and even Xanax, with nearly identical markings and colors. In July 2015, the Drug Enforcement Administration New Jersey Tactical Diversion Squad identified an illicit organization that was distributing counterfeit Roxicodone pills that were in fact 40% acetylfentanyl. Subsequent testing of similar Roxicodone pills from the same organization in December 2015 revealed that the pills now contained 60% pharmaceutical grade fentanyl citrate. Not surprisingly, many long-term opioid abusers who present with unintentional fentanyl overdoses believe they were purchasing oxycodone or another drug of abuse, and the significantly different potency and pharmacokinetics of fentanyl contributed to opioid toxicity. The case described by Armenian et al is similar and highlights another example in which counterfeit pharmaceuticals that are made to look like legitimate ones contain a different opioid from the active...
compound the user is seeking, therefore leading to toxicity.\(^2\)

In addition to nonpharmaceutical fentanyl, there are myriad other novel synthetic opioids that continue to emerge on the illicit drug market.\(^10\) Many of these drugs were initially developed in research laboratories as opioid agonists for analgesic use but were never brought to market for use in human beings. As such, most of the novel synthetic opioids do not have any human pharmacokinetic or pharmacodynamic data available. One such example is the W-series research opioids (W1 to W32), specifically, W-18, developed in 1981 at a Canadian university. Although early reports suggest that W-18 has 100 times the potency of fentanyl, true pharmacologic and potency data are lacking.\(^10\)

Recently, in Ohio, multiple overdoses and deaths of patients who believed they were purchasing heroin were attributed to the ultrapotent fentanyl derivative carfentanil.\(^11\) The synthetic opioids MT-45 and AH-7921 were first reported to the National Forensic Laboratory Information System in 2013.\(^1\) MT-45 has been associated with 28 deaths reported to the European Monitoring Centre for Drugs and Drug Addiction since 2013 and 2 reported deaths in the United States.\(^1\) The abuse potential of AH-7921 was identified in 2012, when it was isolated in a seized sample purchased on the Internet, and it has been increasingly used in Japan, the United States, and Europe.\(^14,15\) Abuse of AH-7921 has accounted for at least 16 deaths between 2012 and 2013,\(^16\) including one in the United States.\(^17\) An isomer of AH-7921, U-47700, is the new compound reported by Armenian et al\(^2\) and is now present in the illicit drug marketplace; it already has one recent report of death related to its use.\(^18\) Legislators are seeking to gain control over the spread of this dangerous drug, and recently the Kansas Bureau of Investigation released a public health warning after a number of unintentional drug overdose deaths in Kansas during the past month related to the use of U-47700.\(^19\) Several states, including Ohio, Wyoming, Georgia, and Kansas, are taking steps to have U-47700 placed under emergency scheduling to make consumption, possession, and distribution illegal. In addition, anecdotally, many medical toxicology program directors from across Canada and the United States have reported presumed cases of U-47700 exposures and deaths; analytical studies are sorely missing.

The production of novel synthetic opioids represents an ever-changing process as illicit drug manufacturers work to remain one step ahead of legislation with the introduction of novel and as yet unregulated compounds. The manufacture, distribution, possession, and improper use of drugs is overseen by the Controlled Substances Act, a drug policy enacted by the Food and Drug Administration in 1970.\(^20\) Similar to the current situation facing legislators, illicit drug manufacturers in the 1970s and 1980s sought ways to produce “legal highs,” that is, drugs with physiologic and pharmacologic effects similar to those of illegal drugs, but with slight structural modifications to avoid legislative control. An amendment to the Controlled Substances Act in 1986, the Controlled Substances Analogue Enforcement Act, specifies that “a controlled substance analogue shall, to the extent intended for human consumption, be treated, for the purposes of any Federal law as a controlled substance in schedule I.”\(^20\) This act classified a drug as an analogue if the chemical structure is substantially similar to that of a controlled substance in schedule I or II; the drug has stimulant, depressant, or hallucinogenic effect on the central nervous system that is substantially similar to or greater than effects of a controlled substance in schedule I or II; and the drug is received with the intent of gaining stimulant, depressant, or hallucinogenic effects similar to those of schedule I or II drugs. In a seemingly tongue-in-cheek manner, many synthetic drugs are labeled as “not for human consumption,” “research chemical,” “legal high,” or another way that is intended to detract attention from law enforcement and to suggest compliance with the Controlled Substances Act.

The introduction of novel synthetic compounds poses several issues, including limited analytical methods for detecting and monitoring these substances. As shown in the related case report,\(^2\) suspicion for the presence of a novel drug is often initiated by experienced recreational drug users who concede that their drug experience was somehow different from normal. Additionally, a significant increase in opioid overdoses, particularly in patients with routine urine drug screens that are negative for opioids, suggests that fentanyl or another novel synthetic opioid is present.\(^21\) Case reporting remains important to keep the medical community updated on epidemiologic trends and unique aspects of specific drugs. Unique toxicities have indeed been reported, including alveolar hemorrhage with butyrfentanyl and ototoxicity with MT-45.\(^22\)

How is the emergence of novel synthetic opioids going to change the approach of the emergency physician in patients presenting with presumed opioid intoxication? It’s not. External stimulation should be attempted in all patients, along with external ventilatory support (eg, bag-valve-mask device) for those with profound hypoventilation. Anticipatory titration of naloxone with the goal of restoring ventilatory drive remains the mainstay for patients who do not respond in a sustained fashion to the above. As opioids appear with various potencies, receptor affinities, and street concentrations emerge, one can only speculate about the doses of naloxone required for reversal. Because controlled studies are unlikely, this remains to be determined on a case-by-case and drug-by-drug basis. It is...
unlikely that any hospital laboratory is capable of onsite testing, but specialized laboratories, health departments, and other governmental agencies may be interested.

It is likely that the opioid epidemic, particularly overdoses and deaths, will continue to progress as newer, more potent opioids emerge. Legislators must be willing to enact broad-based legislation that rapidly adds all new synthetic opioid agonists to schedule I in a manner similar to the Synthetic Drug Abuse Prevention Act of 2012, which focused on synthetic cannabinoids. Of course, without effective public education and adequate enforcement, the latter of which is particularly controversial, the incentive to create, distribute, and use unique opioids will far exceed the risk threshold.

Emergency physicians and the public should be aware of the rapidly increasing incidence and severity in toxicity from illicit opioids. Thoughtful questioning in the emergency department can often reveal the type of drug, which can be reported to law enforcement or public health personnel. Without this information, even lethal cases may go undetected. Through public education, public health intelligence, and law enforcement efforts, we can curb the use and deaths from opioids. In the ever-changing opioid drug market, there continues to be a cat-and-mouse game that legislators must play with illicit drug manufacturers. Unfortunately, we continue to see novel synthetic opioids emerge in the illicit drug market, with unknown potencies and unique adverse effects, to be sold among the masses of designer drugs that are “not for human consumption.”

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