JPPT | Invited Commentary

Pediatric Overdose Deaths Increase as the Fourth Wave of the Opioid Epidemic Creates a Perfect Storm

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ABBREVIATIONS DEA, Drug Enforcement Administration; FA, fentanyl analog; IMF, illicitly manufactured fentanyl; MOR, mu-opioid receptor

KEYWORDS fentanyl; nitazenes; opioid epidemic; opioid overdose; pediatric

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The Storm Front

The confluence of multiple factors including 1) an increase in clandestinely produced polydrug products; 2) clandestinely produced press pills; 3) illicitly manufactured fentanyls (IMFs) and 4) identification of novel mu receptor agonists ("nitazenes") has resulted in a "perfect storm" and an increase in pediatric-related opioid overdose deaths. Drug overdose deaths accounted for 107,081 deaths in the United States in 2022.[1] Two-thirds of these overdose deaths were the result of synthetic opioids, namely IMFs.[1] In 2023, a total of 3,651 Ohioans died because of an opioid overdose, 98% of which were attributed to fentanyl.[2] In 2022, a total of 68 children overdosed on opioids in Ohio. Of these pediatric overdoses, 59 (86.8%) were attributed to IMFs, a trend which has been increasing since 2014. The number of pediatric overdoses to date for 2023 indicates that IMFs accounted for 98% of pediatric drug overdoses. Most deaths were among those in the 15- to 19-years-of-age group (Figure 1).

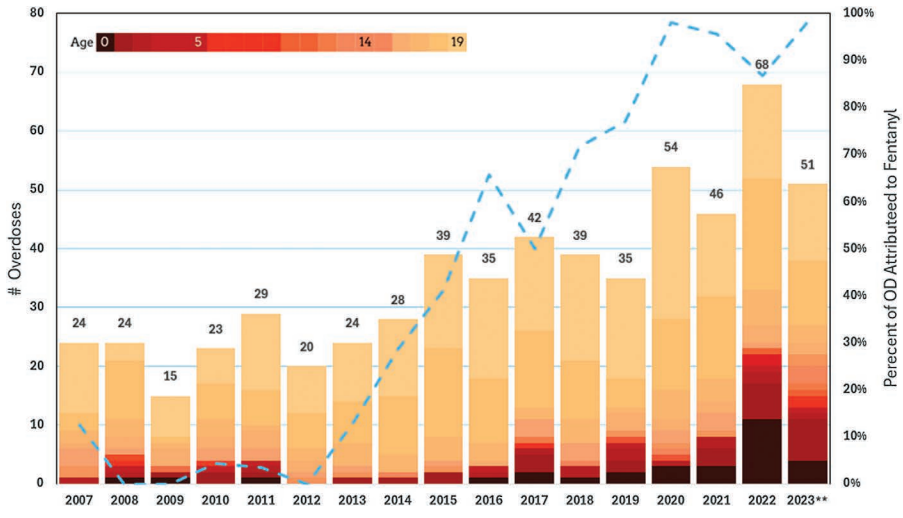
The pediatric opioid-related overdose death trends in Ohio are similar to those at the national level, where fentanyl has been reported to account for 94% of pediatric overdoses with the 15- to 19-year-old age range being the most affected in 2021.[3] A recent study examining opioid exposure reports to the America's Poison Centers for pediatric patients aged one month to six years revealed that illicit opioids and fentanyl exposures increased from 65 in 2016 (1%) to 398 in 2023 (14.0%).[4]

The opioid epidemic has now been described in 4 waves: The first wave began in the 1990s with prescription opioids contributing to most overdose deaths. The second wave began in 2010 with heroin contributing to the largest percentage of overdose deaths. The third wave began in 2013 with the movement toward clandestinely produced fentanyl and synthetic forms of fentanyl,[5] and the recently suggested "fourth wave" of the opioid overdose crisis is characterized by a combination of polydrugs.[6] Subsequently, the Drug Enforcement Administration (DEA) launched the "One Pill Can Kill" campaign in response to the number of counterfeit "pressed" tablets having a polydrug mixture.[7] Many of these counterfeit tablets are clandestinely produced to appear to be alprazolam (Xanax, Viatris, Canonsburg, PA), oxycodone (M30), or hydrocodone tablets.[8] However, most were found to contain IMFs, other opioids, or benzodiazepines.[7] The DEA further reports that 7 of 10 counterfeit tablets contain a lethal dose of fentanyl.[7] These counterfeit tablets are difficult to differentiate from authentic drugs (see examples in Image 1) and can be in rainbow colors that could be enticing to young children.[9] In 2022, the Ohio Bureau of Criminal Investigation received 5,633 polydrug submissions, with IMFs being identified in 89.3% of the submissions combined with cocaine, heroin, methamphetamine, or a synthetic benzodiazepine.

Illicitly Manufactured Fentanyls

IMFs are a group of compounds that includes fentanyl analogs (FAs) and non-pharmaceutical fentanyl. Fentanyl analogs are structurally similar to fentanyl but differ by the addition, removal, or substitution of a functional group to the fentanyl core structure as in the case of cyclopropylfentanyl and *para*-fluorofentanyl (Figure 2). While the prevalence of FAs has dramatically increased in recent years, the first instances of fatal overdoses attributed to FAs date back to 1979 when alpha-methylfentanyl or "China White" was first seen in autopsy reports.[10,11] Subsequently, in 1984, 3-methylfentanyl emerged and other FAs continued to emerge on the drug market, which led to the passing of the Federal Analogue Act in 1986 as an addition to the Controlled Substances Act. This legislation ensured that any compound structurally similar to a Schedule I or II drug would also be scheduled. However, this began the debate as to what constitutes a "structurally similar" compound. Clandestine laboratories then began to modify FAs in order to circumvent federal drug laws

Figure 1. Ohio pediatric opioid overdose numbers 2007–2023. Source: Ohio Department of Health mortality data warehouse[2]. **2023 data are considered partial and may be incomplete.



OD, overdose.

Image 1. Counterfeit oxycodone tablets (A, C) compared with authentic oxycodone tablets (B, D). Pictures of counterfeit tablets were generously provided by the chemistry section of the Ohio Bureau of Criminal Investigation. Pictures of authentic oxycodone tablets were pulled from Drugs.com.[19]

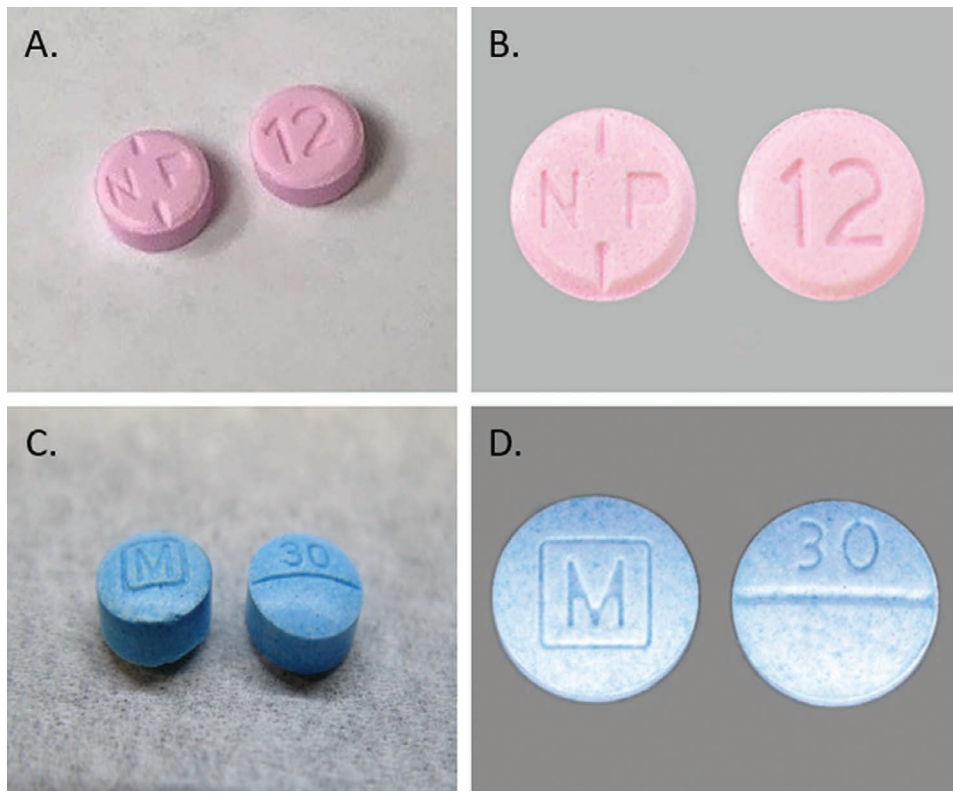


Figure 2. Structures of fentanyl (left), cyclopropylfentanyl (middle), and *para*-fluorofentanyl (right). Differences from fentanyl drawn in red, 4-phenylpiperidine pharmacophore drawn in blue.

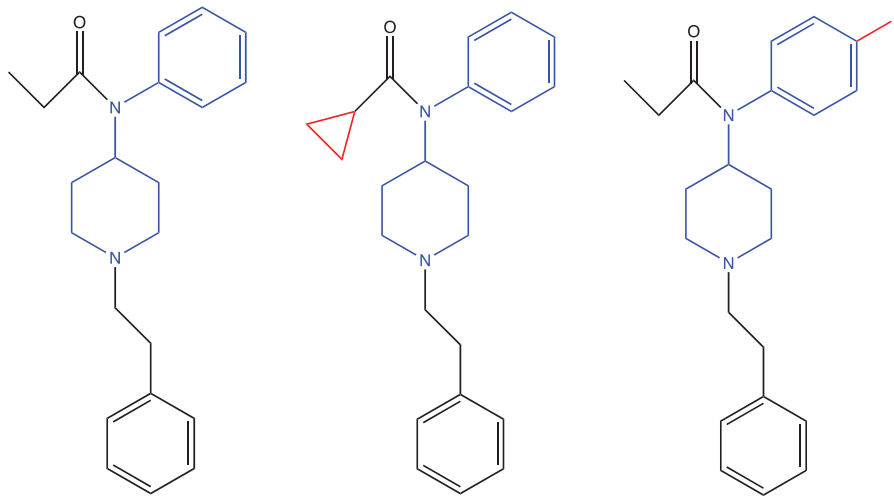
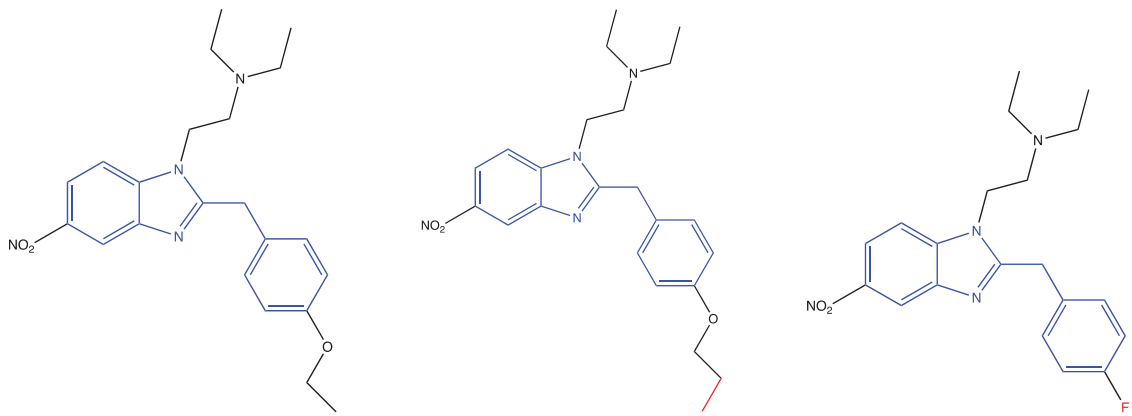


Figure 3. Structures of etonitazene (left), protonitazene (middle), and flunitazene (right). Differences from etonitazene drawn in red, 2-benzylbenzimidazole pharmacophore drawn in blue.



and the "structurally similar" portion of the Federal Analogue Act.[10,11] While structurally different, all FAs are similar in that they share the same pharmacophore or core chemical scaffold required for binding to the mu-opioid receptor (MOR).

All FAs, IMFs, and opioids in general contain a 4-phenylpiperidine pharmacophore (Figure 2). The nitrogen-containing piperidine ring forms a critical ionic bond with an aspartic acid residue located in the third transmembrane region of the MOR, which is a classic G-protein–coupled receptor.[12,13] Other key components include an aniline and phenethyl benzene ring as well as a hydrogen bond donating and/or accepting group.[11] Fentanyl exhibits all of these critical components for binding to the MOR. As new FAs were scheduled, clandestine laboratories would begin modifying the structure to circumvent the "structurally similar" portion of the law.[10,11] While these changes did create new compounds, these new compounds still contained the fentanyl pharmacophore and therefore retained MOR activity. In some cases, the changes can even increase MOR activity and risk of toxic effects as in the case of carfentanil.[14] While structurally different from fentanyl, every FA still possesses the same potential and even greater potential for toxicity so long as the pharmacophore is present.

The "Frankenstein Opioids"

A classwide ban of FAs in 2018, whether existing or yet to be synthesized, led to the Schedule I assignment of all FAs, which then led to the emergence of non-fentanyl MOR agonists such as the nitazene class

of compounds.[15] Nitazene compounds (Figure 3), which are also referred to as "Frankenstein opioids," were first synthesized in the late 1950s but have re-emerged from clandestine laboratories in recent years.[16] To date, 20 nitazenes have been identified in the United States, 10 of which are Schedule I controlled substances and none of which have approved medical uses.[17] These compounds can vary in potency and are from 20 to 50 times more potent than fentanyl, leading to an increased potential for toxic effects.[18] While not containing the prototypical 4-phenylpiperidine pharmacophore of FAs, all of the nitazene compounds do contain a 2-benzylbenzimidazole pharmacophore (Figure 3).

Storm Warning

Pediatric health care providers are currently in the middle of this "perfect storm." Clandestine chemists continue to synthesize IMFs and nitazenes with unknown and difficult-to-predict pharmacologic and toxicologic characteristics. These novel agents are then pressed into counterfeit tablets that resemble prescription drugs and/or candy. Subsequently, pediatric-related opioid-related overdose deaths have continued to rise. This commentary serves as a "storm warning" to those caring for pediatric patients.

Article Information

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