

# The Potential Threat of Acetyl Fentanyl: Legal Issues, Contaminated Heroin, and Acetyl Fentanyl “Disguised” as Other Opioids

John M. Stogner, PhD\*

\*Corresponding Author. E-mail: [johnstogner@uncc.edu](mailto:johnstogner@uncc.edu).

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Acetyl fentanyl (*N*-[1-phenethylpiperidin-4-yl]-*N*-phenylacetamide) is one of countless novel psychoactive substances that have emerged within the American and international drug scene within the last decade. Although some agents such as *Salvia divinorum* and *Mitragyna speciosa* are natural botanicals newly “discovered” by entrepreneurs who package and market fortified versions of the plant product as a “legal high,” the potentially most problematic novel psychoactive substances are newly introduced synthetic compounds such as acetyl fentanyl. Whether discovered in a laboratory as a part of legitimate scientific pursuits or created as a part of a manufacturer’s quest to tweak an existing compound enough to avoid regulation, these compounds often reach users through legitimate retail outlets, Internet Web sites, and street dealers. A variety of synthetic cannabinoids, 3,4-methylenedioxypropylvalerone (MDPV; referred to as “bath salts”), and mephedrone (also referred to as bath salts) were recently problematic before bans; acetyl fentanyl use is still in its infancy, but may eventually follow a similar trajectory.

One common feature of novel psychoactive substance use is the speed at which the drugs emerge as problematic substances. Often “head shop” patrons and Internet-savvy shoppers become aware of these compounds before extensive information appearing in either criminological or medical journals. Thus, experimentation often precedes the development of legal and clinical protocols, forcing law enforcement officers and emergency medical professionals to react to situations for which they are unprepared. Given the lag between cases presenting themselves and that information appearing in print in an academic outlet, several months of increasing use may pass before the medical community becomes adequately prepared to deal with potential overdoses. Initial detection of a novel drug may hinge on poison center call data—an information source that was invaluable when synthetic cannabinoids and bath salts were emerging—but poison center data may be less useful for novel drugs such as acetyl fentanyl that are disguised as or mixed with other substances unbeknownst to the actual users or their physicians. Other early warning detection systems such as Psychonaut, ReDNet, and Drug Early Warning System also have

utility, but delays inevitably exist in getting information to physicians who feel overwhelmed and unprepared for dealing with novel psychoactive drugs. The recent survey by Lank et al<sup>1</sup> of emergency physicians indicated that only 20% felt prepared for dealing with acute novel drug intoxication or overdose. Furthermore, relatively common novel drugs were completely unknown to more than half of the respondents, and all reported a desire for more information and training.

The purpose of this article is to minimize the delay in preparation for one potentially emergent drug. The number of potentially problematic compounds is countless, but through the use of experiences and education in the field of criminology it is possible to forecast which drugs are likely to become an issue. Acetyl fentanyl, a slight variant of fentanyl, is one such drug.

Acetyl fentanyl is an opioid analgesic with no recognized medical uses. Studies suggest that it is 5 to 15 times more potent than heroin<sup>2</sup> and associated with euphoria, altered mood, drowsiness, miosis, cough suppression, constipation, and respiratory depression.<sup>3</sup> Acetyl fentanyl, typically administered intravenously, may serve as a direct substitute for heroin or pharmaceutical-grade opioids among dependent users.<sup>3</sup> The Rhode Island State Health Laboratories attributed a series of 2013 deaths of illicit drug users to acetyl fentanyl. A similar outbreak occurred in Pennsylvania<sup>4</sup> and, more recently, in several southern states.<sup>5</sup> Acetyl fentanyl may have also contributed to deaths elsewhere but have been mistakenly attributed to heroin or fentanyl use, given that enzyme-linked immunosorbent assay screening followed by confirmatory gas chromatography–mass spectrometry is required to confirm that acetyl fentanyl was the toxic agent<sup>4</sup> and this testing is not commonly performed.<sup>6</sup> Nonfatal acetyl fentanyl cases may similarly be attributed to heroin because patients would present as if experiencing a heroin overdose and respond similarly to naloxone, albeit that a larger dose may be required.<sup>4</sup> Users are unlikely to report their use outside of a medical emergency and may not even know that they have used the substance because acetyl fentanyl may be deceptively sold as heroin or mixed with heroin.

What makes acetyl fentanyl potentially problematic is its legal status. It is not scheduled under the Controlled Substance Act but is considered an analogue of fentanyl.<sup>3</sup> Thus, acetyl fentanyl

exists in a legal gray area: it is considered illicit if intended for human consumption, but it evades regulation if packaged with the qualifier “not for human consumption.” Analogues regulated in this way present a challenge for law enforcement and prosecutors because products that are clearly intended for recreational use sidestep regulations if their marketed purpose is something else (eg, bath salts, plant food, potpourri).<sup>7</sup> Though legal precedent does not yet exist, present legislation and experience suggest that a large quantity of an analogue, such as acetyl fentanyl, would be immune to regulation as long as it was titled, labeled, and stored as a product with industrial or nonhuman research purposes.

This creates the potential for acetyl fentanyl to increasingly reach users through street sales whether sold as acetyl fentanyl or disguised or mixed with other substances. Clever and well-informed drug distribution networks will likely take advantage of the “analogue loophole.” They may profit, in terms of decreased legal repercussions, from replacing or cutting a highly regulated drug with acetyl fentanyl. Though acetyl fentanyl would certainly be considered illicit when packaged for individual street sales, there are fewer risks in transporting and storing it compared with heroin. Dealers may eventually mix heroin and acetyl fentanyl before selling the product to better deceive users (as suggested by most mortality reports also indicating the presence of heroin), but use of this stronger product reduces the amount of heroin needed to maintain their present level of distribution. Anecdotal evidence also suggests that acetyl fentanyl may be packaged as pills and sold on the streets as oxycodone for the same reasons.

Head shops and other similar retail outlets are also potential, though less likely, points of distribution. Analogues of banned substances were available in tobacco outlets, labeled as potpourri, cleaners, plant food, bath salts, and even “ladybug attractant” very recently in the United States. Though these outlets formerly sold synthetic cannabinoids and, in some states, continue to sell products such as *S divinorum*, the likelihood of widespread over-the-counter acetyl fentanyl sales is minimal. Whether motivated by humane concerns for their customers or the fear of negative publicity and legal action, the majority of these establishments have avoided selling the strongest novel drugs in the past. MDPV was sold only in limited outlets, whereas sales of synthetic cannabinoids, *S divinorum*, and kratom are more common. Some recreational drug users who visit head shops pride themselves on the scope and breadth of their drug-related experiences. These individuals are likely to request and purchase any new product sold as a legal high,<sup>7</sup> but most head shop clientele seem interested only in cannabis replacements and hallucinogens.

The mixing of compounds and unknowing users is at the heart of the potential acetyl fentanyl problem. Heroin users may obtain and administer packages that they believe is heroin and experience severe consequences if the package contains only the more potent acetyl fentanyl or a mixture of acetyl fentanyl and heroin. Clinicians should realize that these individuals may present in emergency departments in much the same manner as heroin overdose victims (lethargic and disoriented, with shallow

breathing, bradycardia, and hypotension) and, if conscious, may claim that they used heroin or oxycodone rather than acetyl fentanyl. However, unless the acetyl fentanyl and heroin were mixed, standard screens would deny use of heroin. If enzyme-linked immunosorbent assay for fentanyl is available and used, it would suggest the patient used fentanyl rather than acetyl fentanyl (gas chromatography–mass spectrometry is required to differentiate between the two).<sup>4</sup> Clinicians may initially attribute an overdose of acetyl fentanyl–contaminated heroin solely to heroin, further complicating the issue because acetyl fentanyl would not be specifically investigated as the culprit, particularly if the event had already been attributed to heroin. Fortunately, the clinical course of action for opioid overdoses does not depend on the exact compound. Roberts<sup>6</sup> stressed that naloxone remains appropriate, noting that higher doses are likely required for acetyl fentanyl but cautioning that clinicians may want to avoid large doses until after the patient fails to respond to standard doses.

Clinicians should suspect acetyl fentanyl was the causal agent if a patient unresponsive to standard naloxone doses was revived by a megadose or responds to naloxone but screens negative for heroin.<sup>6</sup> Given the potential for localized overdose outbreaks after consumption of poorly mixed or diluted batches of acetyl fentanyl–contaminated heroin, clinicians should report suspected acetyl fentanyl cases and request confirmatory gas chromatography–mass spectrometry. Because dilution or mixing would likely occur in large batches later distributed to multiple users in a short period, acetyl fentanyl overdoses may come in waves; if multiple acetyl fentanyl overdoses are confirmed (or even suspected) in an area, emergency medical administrators should be prepared to increase staffing and naloxone supplies until the immediate concern passes.<sup>4</sup>

As long as acetyl fentanyl remains unregulated specifically and not simply as an analogue, there remains motivation for organized drug distribution networks to replace or partially replace heroin with it. As a result, emergency medical professionals will likely see an upswing in what on the surface appears to be heroin overdoses. Because of acetyl fentanyl’s smaller potential user base, it would not be reasonable to expect the drug to become as widespread as other novel drugs such as synthetic cannabinoids, but physicians still need to remain vigilant for acetyl fentanyl and be aware that cases presenting as heroin overdoses may be more complex.

The significant potential for overdose associated with acetyl fentanyl justifies the attention of medical research and, perhaps more important, policy reform. It is likely that public outcry over publicized tragic accidents will eventually lead state, and later federal, governments to specifically schedule acetyl fentanyl and close the legal loophole as they did for drugs such as MDPV. However, a more pertinent course of action would be to schedule acetyl fentanyl proactively in accordance with the potential for harm. Given that the drug’s potential as a medicinal tool has not been fully investigated, such regulation should make allowances for legitimate scientific research. This, of course, is a drug-specific reaction, and handling acetyl fentanyl in this way will not

prevent another analogue from initially existing in a similar legal gray area. Though there may be logistic and regulatory challenges, the elimination of the exemption for products containing an analogue of a controlled substance when labeled “not for human consumption” appears to be the most effective solution to the issue more broadly.

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*Supervising editor:* Richard C. Dart, MD, PhD

*Author affiliations:* From the Department of Criminal Justice and Criminology, University of North Carolina at Charlotte, Charlotte, NC.

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