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Invited review

# Fentanyl, fentanyl analogs and novel synthetic opioids: A comprehensive review

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ABSTRACT

Deaths from opioid use are increasing in the US, with a growing proportion due to synthetic opioids. Until 2013, sporadic outbreaks of fentanyl and fentanyl analogs contaminating the heroin supply caused some deaths in heroin users. Since then, fentanyl has caused deaths in every state and fentanyl and its analogs have completely infiltrated the North American heroin supply. In 2014, the first illicit pills containing fentanyl, fentanyl analogs, and other novel synthetic opioids such as U-47700 were detected. These pills, which look like known opioids or benzodiazepines, have introduced synthetic opioids to more unsuspecting customers. As soon as these drugs are regulated by various countries, new compounds quickly appear on the market, making detection difficult and the number of cases likely underreported. Standard targeted analytical techniques such as GC-MS (gas chromatography mass spectrometry) and LC-MS/MS (liquid chromatography tandem mass spectrometry) can detect these drugs, but novel compound identification is aided by nontargeted testing with LC-HRMS (liquid chromatography high resolution mass spectrometry). Fentanyl, fentanyl analogs and other novel synthetic opioids are all full agonists of varying potencies at the μ-opioid receptor, leading to typical clinical effects of miosis and respiratory and central nervous system depression. Due to their high affinity for μ-opioid receptors, larger doses of naloxone are required to reverse the effects than are commonly used. Synthetic opioids are an increasingly major public health threat requiring vigilance from multiple fields including law enforcement, government agencies, clinical chemists, pharmacists, and physicians, to name a few, in order to stem its tide.

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**Contents**



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**Abbreviations**

| | |
|---|---|
| 4-ANPP | 4-anilino-N-phenethyl-4-piperidine; ANPP |
| 4Cl-iBF | 4-chloroisobutyryfentanyl |
| 4F-iBF | 4-fluoroisobutyrfentanyl |
| AEI | Advanced electronic information |
| AMF | alpha-methylfentanyl |
| CBP | US Customs and Border Protection |
| CDC | Centers for Disease Control |
| CDSA | Controlled Drug and Substance Act (Canada) |
| CNS | central nervous system |
| DEA | US Drug Enforcement Agency |
| DTO | Drug trafficking organization |
| ED | Emergency department |
| ELISA | enzyme-linked immunosorbent assay |
| EMCDDA | European Monitoring Centre for Drug and Drug Addiction |
| FDA | US Food and Drug Administration |
| GC-MS | gas chromatography mass spectrometry |
| ICU | intensive care unit |
| IN | intranasal |
| IV | intravenous |
| LC-HRMS | liquid chromatography high resolution mass spectrometry |
| LC-MS/MS | liquid chromatography tandem mass spectrometry |
| MDA | United Kingdom Misuse of Drugs Act |
| NPF | non-pharmaceutical fentanyl |
| THF-F | tetrahydrofuranfentanyl |
| US | United States |
| USPS | US Postal Service |
| UNODC | United Nations office on drugs and crime |

## 1. Introduction

The death rate due to opioid analgesics nearly quadrupled in the US from 1999 to 2011 and was responsible for 33,091 deaths in 2015 (Rudd et al., 2016). The increased demand for opioids has led to the increased availability of heroin and the proliferation of real and counterfeit opioid pills in the illicit drug market. Synthetic opioids such as fentanyl, fentanyl analogs, and other novel compounds such as U-47700 and MT-45 are an emerging public health threat, detected in white heroin, black tar heroin, and pills. Although some are banned by the US DEA and international drug agencies, clandestine manufacturers are able to produce drug analogs at a faster rate than these compounds can be controlled, or scheduled, a process that requires lengthy evidence gathering by drug agencies. Detection requires specialized testing and clinicians need to have a strong index of suspicion to recognize the possibility of a synthetic opioid causing respiratory depression, altered mental status, miosis, and the other hallmarks of opioid toxicity in patients. In this review, we discuss the multifactorial aspects of fentanyl, fentanyl analog, and novel synthetic opioids in regards to epidemiology, legal status, pharmacology, detection, and care of the poisoned patient.

## 2. Methods

### 2.1. Search strategy

A systematic search for articles about synthetic opioids, including fentanyl, fentanyl analogues, and other novel psychoactive substances, was conducted in PubMed on May 1, 2017. A broad search technique was used in order to encompass all subject areas detailed in this review, and irrelevant articles were excluded from the results. Preliminary searching in Embase and Google Scholar did not yield additional unique results; therefore, the search was limited to PubMed. Cited reference searching and grey literature searching in Google were used to identify additional articles and government reports. To gain current information about trafficking and legal status, which were less likely to be found in scholarly journals, Google was searched for governmental documents pertinent to the topic. Google searches were also performed for websites selling drugs and drug production equipment. Detailed search strategies can be found in Appendix 1.