

## THE BURDEN OF FENTANYL AND FENTANYL ANALOGUES

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**Overview:** The appearance of illicit fentanyl and fentanyl analogues in Baltimore is associated with a drastic increase in both fatal and nonfatal opioid overdoses. The gross potency of fentanyl compared to heroin has increased the danger of these drugs, especially to those who are functional heroin users and those who have recently relapsed. Despite a number of public health efforts, we are seeing an increasing number of fentanyl-related deaths and there is an increasing burden on the emergency departments (EDs) throughout the University of Maryland Medical System.

**Fentanyl:** Marketed as Fentanyl, Duragesic, Sublimaze, IUPAC: N-phenyl-N-[1-(2-phenylethyl)piperidin-4-yl]propanamide.

**Medical Use<sup>1</sup>:** Indicated for the management of acute pain in hospitalized patients (i.e., post-operative and cancer break-through), chronic pain in opioid-tolerant patients, and for the sedation of ventilated patients.

**Properties<sup>2</sup>:** Synthetic, lipophilic mu-opioid receptor antagonist with analgesic and anesthetic properties. Thought to be 80 times more potent than morphine and hundreds of times more potent than heroin. Not generally a part of hospital drug screens, usually only detected as a part of a research study.

**Route of administration<sup>4-6</sup>:** intravenous, intramuscular, inhaled, sublingual (under the tongue), per os (by mouth), transdermal (through the skin)

**Excretion<sup>7</sup>:** 75% via urine within 72 hours, with less than 8% as unchanged drug

**Analogues/related synthetics<sup>8,9</sup>:** carfentanyl (**10,000x** potency of morphine), U-47700 (7x potency of morphine), synthetic cannabinoids (“Scooby Snacks”, “K2”, “Spice”)

**Illicit Production<sup>3</sup>:** Illegally produced in China and Mexico and shipped via post to the US. Fentanyl powders are often mixed with other drugs (heroin) and insufflated or injected, or they are pressed into pills and passed off as prescription opioids (e.g. oxycodone). Fentanyl has begun to replace heroin for a number of reasons: it is cheaper to produce, more compact and therefore easier to distribute, it can be diluted (“cut”) further to increase profits, or it can be mixed with heroin to create a stronger product.

**Toxicity:** As the concentration of fentanyl in the blood increases, users will experience deepening sedation, decreasing respiratory rate, and increasing respiratory acidosis. As the acidosis increases, fentanyl that was bound to proteins in the blood is released, further increasing the concentration of the drug. Eventually acidosis and hypoxia lead to cardiac arrhythmias and brain injuries and death.

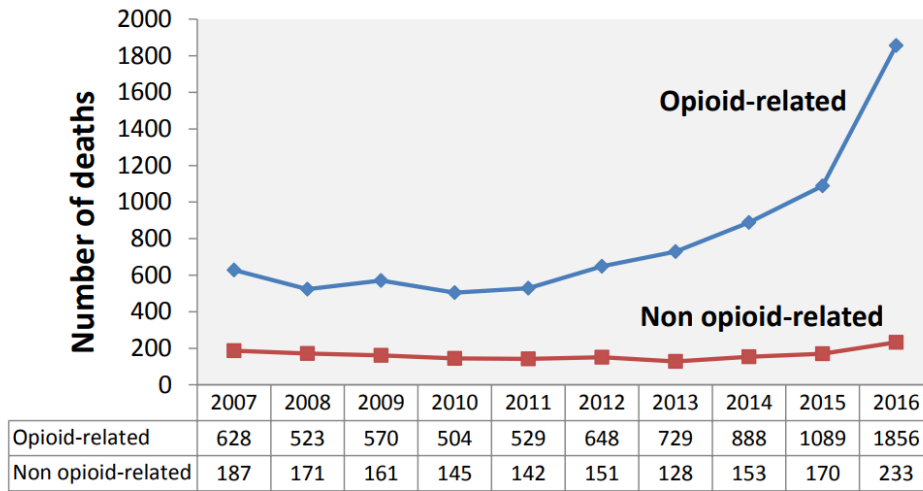
**Overdose Reversal:** Naloxone (trade name Narcan) is a competitive mu-receptor antagonist, meaning it will attach to the same receptor as opioids like fentanyl. However, it does not transmit the same biological signal and will not have the same physiological effects, essentially blocking the effects of the opioid.

Naloxone is effective against fentanyl and carfentanyl. But strength of these new opioids is such that naloxone is less effective and must be administered in much larger doses to affect a reversal of an overdose, especially compared to heroin. Naloxone generally lasts in the body longer than heroin, so one or two doses of naloxone is usually sufficient to reverse most heroin overdoses. Naloxone has a shorter duration of action than fentanyl, so often multiple doses, or a continuous infusion of naloxone, is required to ensure a patient doesn't become somnolent again. If a patient experiences a severe overdose and has respiratory depression for an extended length of time, late administration of naloxone may help to bring the patient's respiratory rate back into the normal range, but it will not undo any brain injury the patient may have suffered.

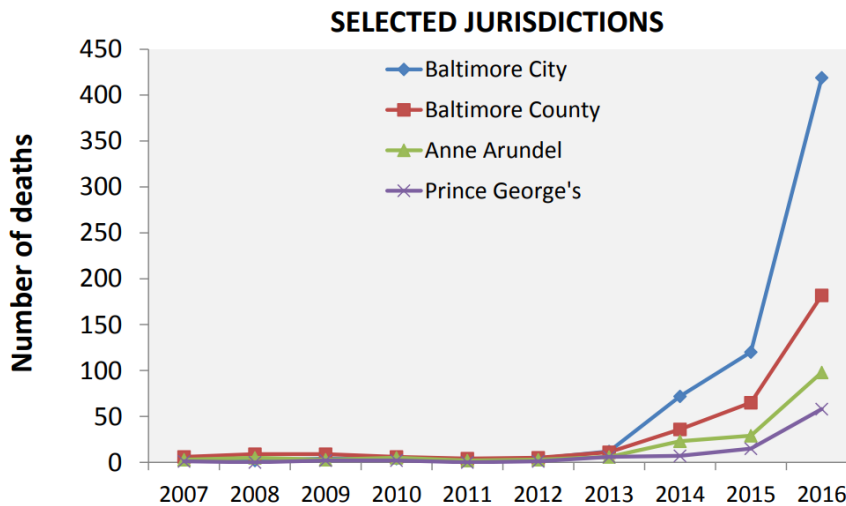
**The Opioid Problem in Maryland and Baltimore City<sup>12-14</sup>:** 2016 saw 1,856 opioid-related deaths in Maryland (Figure 1), with more than 400 of those in Baltimore City (Figure 2). For context, Baltimore gained national prominence in 2015 when we had a record number of 344 homicides. 2017 appears to be on the same trend. Fentanyl deaths have increased drastically, and fentanyl is now implicated in as many deaths as heroin (Figure 2). Sixty-three percent of fentanyl-related deaths in 2016 occurred in combination with heroin, 26% in combination with alcohol, and 23% in combination with cocaine. Carfentanyl had not been detected as the

cause of any deaths in Baltimore City when they began testing it in 2016. However, it has been identified as the cause of 48 deaths in 2017.

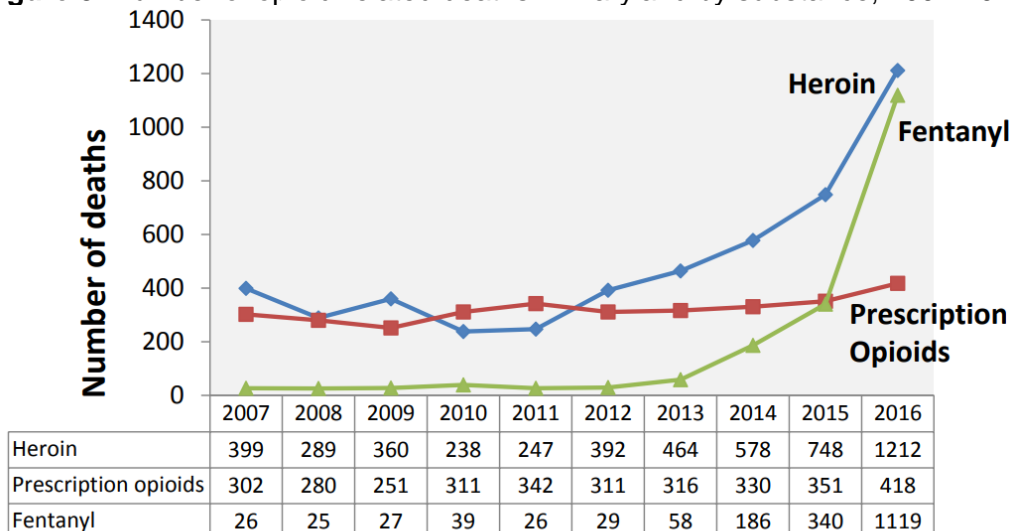
**Figure 1.** Number of Opioid- and Non-Opioid Related deaths in Maryland, 2007-2016



**Figure 2.** Fentanyl Deaths by Selected Jurisdictions in Maryland, 2007-2016



**Figure 3.** Number of opioid-related deaths in Maryland by substance, 2007-2016



\*Total opioids include heroin, prescription opioids, and illicit forms of fentanyl.

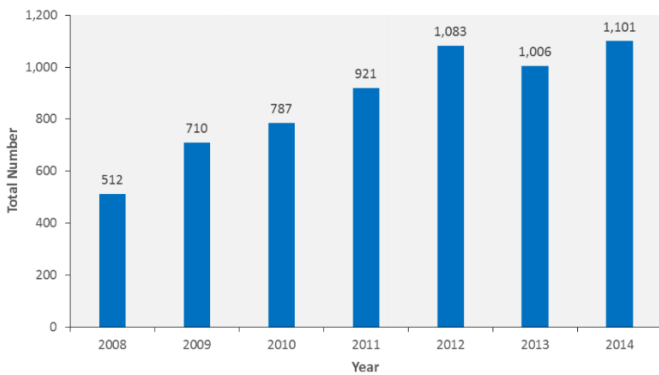
**The Burden of Illicit Fentanyl on Emergency Departments in Maryland<sup>10,11</sup>:** A number of challenges have come about as fentanyl and fentanyl analogues arrived on the drug scene of Baltimore, Maryland. These include a rising number of overdoses in vulnerable populations, increasing numbers of overdoses spikes, overdoses requiring hospital admission and advanced life support, and atypical responses to naloxone.

To maintain the close to the same level of euphoria and potency as heroin, fentanyl has to be diluted to a much greater degree. This dilution is not done by professionals, and the cutting agents often clump, so the dilution process is imperfect. Users frequently buy several doses at once. But if they do not re-mix the amount they have bought prior to using, one of their purchased “doses” may be mostly inactive diluent with the next being highly concentrated. Furthermore, many end users will have a specific stable dose or dollar amount that they have bought for years. They will buy their usual amount, not knowing that fentanyl has been added, and accidentally overdose. This effect also extends to those users who have recently relapsed, as they may buy what they remember to be their previous usual dose of heroin, but get fentanyl instead and overdose. In addition, there is also a market for stronger drugs that provide a stronger experience, and fentanyl accelerates this pathway towards fatal overdose.

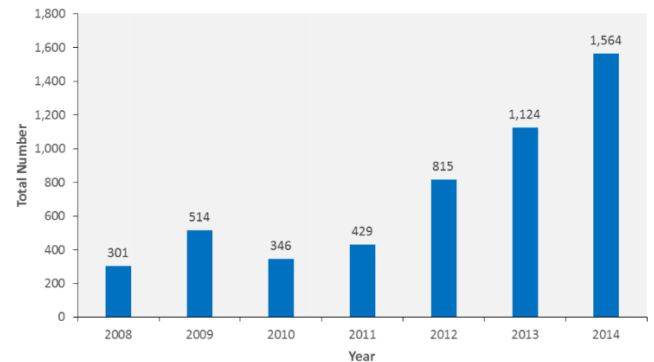
We have also seen an increase in the number of patients ED visits related to fentanyl (Figures 4A and 4B). Note that the data presented is for ED visits related to prescription opioids and heroin, not fentanyl.

Unfortunately, the data for fentanyl-related ED visits is not available. But given the overlap between these opioids, these figures illustrate the observed trend. The increasing number of visits has led to an increase in the costs associated with treating this population (Figures 5A and 5B). Anecdotally, clinicians have also seen an increasing number of overdose patients who need to be put onto a ventilator (a breathing machine).

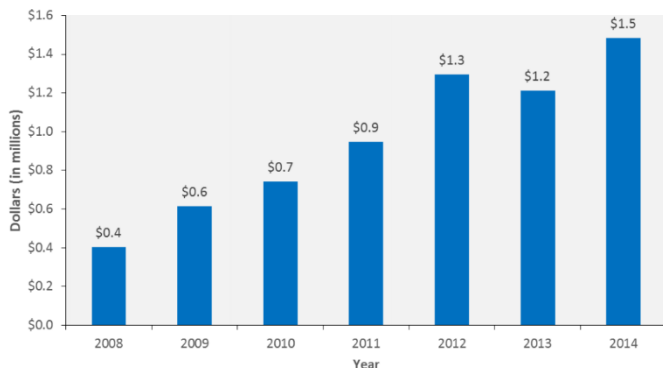
**Figure 4A. Total Number of Prescription Opioid-related Emergency Department Visits: Maryland, 2008-2014**



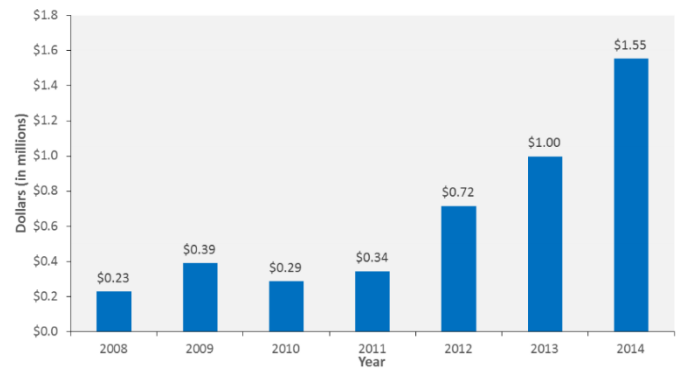
**Figure 4B. Total Number of Heroin-related Emergency Department Visits: Maryland, 2008-2014**



**Figure 5A. Total Charges for Prescription Opioid-related Emergency Department Visits: Maryland, 2008-2014**



**Figure 5B. Total Charges for Heroin-related Emergency Department Visits: Maryland, 2008-2014**



Lastly, as fentanyl has become more common in Baltimore, clinicians have seen an increase in overdose spikes and atypical responses to naloxone. Over the last summer, on two separate occasions, more than 25 people were rushed to area hospitals over the course of afternoon with what appeared to be an opioid overdose. Patients will state this is typical when a batch of stronger-than-usual product is sold. In addition, many of the apparent opioid overdoses involved in these spikes developed agitated delirium (distinct from acute withdrawal) after receiving naloxone. This pattern of response to naloxone is atypical and suggests some other adulterants are present in combination with the opioid. Many of these patients become violent and paradoxically, require sedation immediately after being revived with naloxone. Patients will later say they used Spice/K2. This atypical response is new and is a clear threat to the safety of health care workers attempting to care for these patients.

**Conclusions:** The illicit use of fentanyl and fentanyl-analogues has increased the number of fatal and nonfatal opioid overdoses in Baltimore City and Maryland State. As physicians, it is more difficult to revive patients suffering from fentanyl overdoses and it is more dangerous when we do so. We have seen a rise in the number of opioid-related ED visits and the costs of caring for these individuals has increased. It is our opinion that fentanyl has had a strongly negative impact on our patients and the medical system as a whole.

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