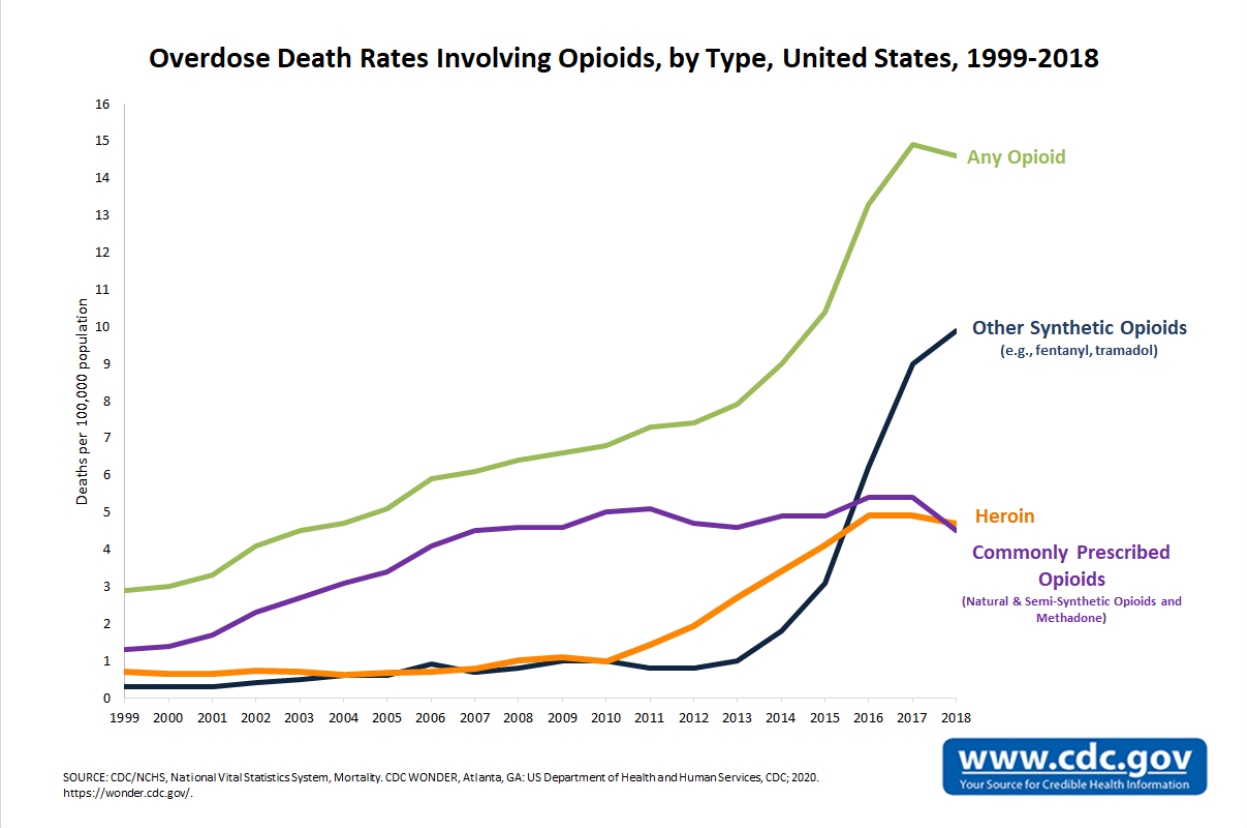
NPS Clinical Update – Designer Opioids and Benzodiazepines August 2020

Novel Psychoactive Substances (NPS) are a diverse group of synthetic substances created to mimic the effects of scheduled or illicit drugs which vary significantly in both toxicity and potency. Synthetic cannabinoids and synthetic stimulants are traditionally the most common classes of NPS abused in the United States;[1] however, other classes of NPS are available and are becoming an area of focus, as they are increasingly identified in drug overdose cases.

Designer Opioids

The most commonly known designer opioids are the fentanyl analogs, sometimes referred to as "fentalogs." While they had been infrequently identified for many years, they became more prominent over the last half-decade in lock-step with efforts to decrease prescribing of opioids. Of all opioid overdoses in 2018, 67% involved a non-methadone synthetic opioid, which the CDC calls primarily fentanyl-like substances.[2] The following graphic illustrates the contribution of synthetic opioids in opioid overdose deaths:



"Plain" fentanyl is identified most frequently in seized drug material, but in many cases it is mixed with other chemicals, including fentalogs. As previously mentioned, the potency of these analogs varies greatly, with some being less potent than fentanyl, while others are much more potent. For example, carfentanil, which is a veterinary sedative for large animals, has been illicitly synthesized and identified

in select overdose death cases.[3] While fentalogs have been the most widely distributed and abused synthetic opioids, newer classes are emerging as regulators begin to limit access through classification of these analogs as Schedule I controlled substances.

One other class of opioids is sometimes labelled "utopioids." This class of compounds was originally studied by the pharmaceutical company Upjohn, but they never made it to the US prescription marketplace. U-47700 has been the most widely detected drug in this class over the last several years and has been found in street drugs known as "pink," "pinky," or "gray death," and in some counterfeit pills intended to mimic prescription drugs. As efforts to regulate U-47700 have increased, other utopioids have been identified in seized drug materials. Within the last year, a new class of opioids sometimes referred to as "nitazenes" have emerged, with isotonitazene being identified in several forensic cases. It can be anticipated that as regulatory efforts continue to focus on classifying individual substances as Schedule I drugs, there will be continued innovation in the illicit drug market to circumvent these efforts, with development of new classes and/or analogs. The following table lists the designer opioids included in testing:

2-Furanyl Fentanyl	Cyclopropyl Fentanyl
2-Furanylbenzyl Fentanyl	Despropionyl p-Fluorofentanyl
3-Methyl Fentanyl	Fluoro Fentanyl
4-Fluoroisobutyryl Fentanyl	Isotonitazene
Acryl Fentanyl	Norcarfentanil
Benzoyl Fentanyl	U-47700
Benzyl Fentanyl	U-48800
Butyryl Fentanyl	Valeryl Fentanyl

Designer Benzodiazepines

Benzodiazepines were first developed in the late 1950's to 1960's with chlordiazepoxide being the first to market in the US in 1960. During this discovery process, thousands of other benzodiazepine structures were synthesized and studied, with only a very small percentage ultimately making it to the prescription marketplace.[4] Even though only a small number of drug candidates ultimately made it to market, benzodiazepines are still widely prescribed today, with varying risks associated with their use/misuse.

The first "designer" benzodiazepines widely reported were phenazepam and etizolam, which are/have been legally marketed by pharmaceutical companies in some countries. As countries began to regulate and schedule phenazepam and etizolam as controlled substances, clandestine laboratories began producing and distributing newer designer benzodiazepines such as diclazepam, flubromazepam, pyrazolam, clonazolam, deschloroetizolam, flubromazolam, nifoxipam and meclonazepam; others have continued to emerge. A July 2020 article in *Pediatrics* has reinforced data from forensic sources showing that flualprazolam is in circulation. In this case series, flualprazolam was identified in biological samples from teenagers who reported to emergency departments after ingestion of a counterfeit alprazolam tablet. The patients showed typical signs of benzodiazepine intoxication but, fortunately, did not require intensive care or antidotal therapy.[5] As with the designer opioids, the potency of designer benzodiazepines relative to prescription benzodiazepines is largely unknown and the true contents of counterfeit tablets is unknown to the ultimate user. The following table lists the designer benzodiazepines included in testing:

Bromazolam	Flubromazepam
Clonazolam	Flubromazolam
Diclazepam	Nitrazolam
Etizolam	Phenazepam
Flualprazolam	

The FDA has pointed out the potential dangers associated with co-ingestion of prescription opioids and benzodiazepines and has required boxed warnings on product literature.[6] Drug testing is one way to identify the co-ingestion of these two drug classes in an objective manner. If patients are ingesting designer opioids and/or designer benzodiazepines, these substances may be more or less likely to result in a similar drug interaction depending on their potencies relative to prescription counterparts. If a provider feels that a patient is at risk for ingestion of these substances and orders a traditional urine drug test, these substances may go undetected. Additionally, these substances may be detected in an immunoassay (IA) test, with a high risk of these presumptive positives being unconfirmed upon confirmatory testing due to lack of designer drug offerings in traditional mass spectrometry testing. The NPS marketplace is constantly evolving in response to regulatory action by various authorities, so definitive testing by mass spectrometry must continually evolve to adjust to these changes and afford providers the opportunity to more completely understand an individual patient's risk factors.

NOTICE: The information above is intended as a resource for health care providers. Providers should use their independent medical judgment based on the clinical needs of the patient when making determinations of who to test, what medications to test, testing frequency, and the type of testing to conduct.

References NPS Clinical Update August 2020

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