# The ToxIC NOSE (Novel Opioid and Stimulant Exposure)

Report #16 from ToxIC's Rapid Response Program for Emerging Drugs

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## ToxIC's Multicenter Projects:
## Novel Substances and Overdose Toxico-Surveillance

### Introduction

The American College of Medical Toxicology (ACMT), a professional medical society, established the Toxicology Investigators Consortium (ToxIC) in 2010 with a multicenter registry of patients cared for at the bedside by medical toxicology physicians. This Core Registry currently receives cases from medical toxicology physicians at 36 medical centers encompassing 61 hospitals.[1] The Core Registry has a diverse collection of cases, ranging from snake envenomations to accidental pediatric exposures to patients presenting after a drug overdose. Mirroring the national rise of the

**The ToxIC Novel Opioid and Stimulant Exposure (NOSE) Reports**

Through the ongoing support of the Opioid Response Network (ORN) since 2020, the American College of Medical Toxicology (ACMT) Toxicology Investigators Consortium (ToxIC) has implemented an enhanced sentinel detector field within the ToxIC Core Registry to identify novel and emerging opioid and stimulant exposures. Once an emerging trend or risk is identified, ToxIC releases a quarterly report.

The goal of this project is to disseminate this novel information to the medical toxicology community as well as the ORN as part of a Rapid Response program.

For more information on the ToxIC Core Registry and data collection, please visit: www.toxicregistry.org

opioid epidemic, opioids now represent the most common exposure reported to the Core Registry.[1,2]

Over the 15 years, ToxIC has expanded well beyond the Core Registry to include more focused projects, many of which center on opioid and stimulant toxicity, opioid withdrawal, and opioid use disorder.[3] The ToxIC NOSE is one such project that seeks to identify novel emerging opioid and stimulant exposures. The purpose of this brief is to inform ACMT and ORN members about ongoing efforts and findings of ToxIC's other focused projects, particularly in relation to the rapidly evolving world of novel synthetic opioids.

## OUD Sub-registry

The Opioid Use Disorder (OUD) Sub-registry is a CDC funded focused data collection within the Core Registry that gathers more information on harm reduction interventions such as initiation of medications for OUD in the hospital setting and discharging patients at high risk of opioid overdose with naloxone prescriptions. All patients reported to the OUD Sub-registry were cared for by medical toxicology physicians during their emergency department (ED) visit or hospitalization that resulted from opioid toxicity and/or withdrawal. Initiated in 2024, over 500 cases have been submitted to date. Further evaluation of this data is forthcoming as it progresses. More information about the OUD Sub-registry can be found here: https://www.acmt.net/toxic-oud-project/

## Fentalog Study

The Fentalog Study started in 2020 as a multicenter toxico-surveillance project titled "Predicting Medical Consequences of Novel Fentanyl Analog Overdose Using the Toxicology Investigators Consortium." The study operates via a partnership between ToxIC and the Icahn School of Medicine under an RO1 grant from the National Institute on Drug Abuse (NIDA) and enrolls patients presenting with a suspected opioid overdose to 10 participating EDs in the United States. Using a diverse geographic network of ToxIC's participating healthcare sites, the study aims to identify risk factors and to characterize novel opioid overdoses.

The Fentalog Study utilizes comprehensive qualitative toxicology blood testing not available within most hospital systems, allowing for unique toxico-surveillance of emerging novel synthetic opioids such as those in the nitazene class and other novel potent opioids (NPOs). NPOs have high potency at the mu opioid receptor in vitro, but scant clinical data is available in the literature. A 2023 publication from the Fentalog Study detected 9 cases of NPOs, including 7 nitazene (isonitazene, metonitazene, N-piperidinyl etonitazene) and 2 brorphine exposures.[4]

This study found in-hospital naloxone dosing to be higher in the NPO group when compared to isolated fentanyl exposures, though the total amount of naloxone administered to these patients was similar. In addition, more severe clinical outcomes were described in the metonitazene exposures specifically, including cardiac arrest and death, compared to other NPOs or fentanyl. A recent Fentalog abstract reported geographic differences in NPO exposures, with a higher burden for patients presenting to participating hospitals in the East Coast.[5] Additional publications and abstracts from the Fentalog Study can be found here: https://www.acmt.net/fentanyl-analog/

The Fentalog Study also includes an interactive dashboard hosted through a collaboration with the Centers for Disease Control and Prevention (CDC), detailing up-to-date statistics on novel opioid exposures, concomitant polydrug exposures, and the presence of adulterants.[6] The dashboard currently reports almost 80% of patients testing positive for fentanyl, often in addition to other illicit substances and adulterants such as xylazine. Stimulant co-exposures with fentanyl are the most common (46%), with a near equal distribution of fentanyl + methamphetamine (26%) and fentanyl + cocaine (25%) exposures reported.[6]

## DOTS Reporting Program

The Drug Overdose Toxico-Surveillance (DOTS) Reporting Program evolved from a continued curiosity of the contribution of individual drugs after a polydrug exposure. The reflection of the "fourth wave" of the opioid epidemic, with stimulant and fentanyl combination overdoses, was detected in the Fentalog Study. However, lingering questions included understanding why individuals were using specific substances together, as well as connecting drug concentrations to clinical presentations and outcomes. The DOTS program, funded by the Food and Drug Administration (FDA), was launched in 2023 to address these knowledge gaps. Detailed patient interviews, clinical data points, and comprehensive quantitative analysis of drug concentrations are obtained in patients presenting with a suspected opioid and/or stimulant overdose at 17 participating sites around the United States.

With over 1000 patients enrolled between April 2023 to September 2024, intriguing results are emerging from the DOTS data. Preliminary data show that while fentanyl, methamphetamine, cocaine and their metabolites remain the most common substances detected, quinine is the next most common substance which is detected in approximately 20% of samples. Quinine, historically an antimalaria drug that blocks sodium/potassium channels and can lead to serious health effects including hearing loss, vision changes, and abnormal heart rhythms. Xylazine, an alpha-2 agonist used as a sedative in veterinary medicine is increasingly detected as an adulterant to fentanyl, detected in 18% of DOTS patients. Additional information including

sociodemographic data and patient reported factors associated with drug use can be found on the DOTS Dashboard: https://www.acmt.net/dots/

## RENDOR Project

The Real-world Examination of Naloxone for Drug Overdose Reversal (RENDOR) Project started in 2024 as a prospective multi-center study that seeks to characterize naloxone's use, risks, benefits, and effectiveness for reversing opioid overdoses in pre-hospital settings. Patients in the pre-hospital setting that receive naloxone or nalmefene by bystanders, non-medical first responders such as police or fire, and/or EMS across 4 sites (San Francisco, CA; Detroit, MI; Portland, OR; and Pittsburgh, PA) are included. Data collected from the EMS patient care record includes naloxone/nalmefene dose, route of administration, person administering each dose, indications, response, and clinical information such as vital signs and outcome. Additional information about the RENDOR Study can be found here: https://www.acmt.net/rendor/

## Future Directions

Additional opioid and stimulant related investigations continue to develop within ToxIC, often born from discoveries or limitations in existing projects, as previously described.

Naloxone administration has been a persistent enigma in the era of fentanyl and novel synthetic opioids. Questions that remain include:

1. Do the more potent novel opioids truly require larger or more frequent naloxone doses? If so, how much and how often?
2. What is the risk of precipitated withdrawal after exposure to novel opioids?
3. With polydrug exposures which may include both opioids and stimulants, what is the risk of unmasking the stimulant's clinical effects after naloxone administration?
4. How are we helping these patients to recover and to prevent another overdose after their acute hospitalization? Are we adequately prescribing or providing discharge naloxone for these patients that are at a high risk of recurring overdose?
5. Are we providing buprenorphine and methadone, or other resources for substance use disorder in those patients presenting with an acute overdose?

ToxIC's ongoing projects will attempt to answer such important questions. The medical toxicology community looks forward to sharing results from these projects and more as we continue to work towards mitigating the rapidly evolving overdose crisis.

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## About the *Opioid Response Network (ORN)*:

**Help is here!** The *Opioid Response Network (ORN)* is your resource for no-cost education, training and consultation to enhance efforts addressing opioid and stimulant use disorders.

*ORN* has consultants in every state and territory to deploy across prevention, treatment, recovery and harm reduction.

**Share your needs via the "Submit a Request" form at www.OpioidResponseNetwork.org.** Within one business day, your regional point person will be in touch to learn more.

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