Data-Supported Poly-Drug Use Among Fentanyl Users: A Toxicology Perspective

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After attending this presentation, attendees will be able to discuss the extent to which fentanyl drug users are consuming other substances, including legacy drugs of abuse and novel psychoactive substances (NPS), and the drug classes that are most commonly found in combination with fentanyl.

This presentation will impact the forensic science community by providing comprehensive data regarding patterns and practice of poly-drug use that, in turn, have an impact on policies relating to death investigation and forensic toxicology testing practices, as well as public health and public safety preparedness and response.

The opioid epidemic continues to contribute to morbidity and mortality in the United States, growing and evolving since the increase in prevalence of fentanyl in the heroin supply began around 2014. Following the identification of mixtures of fentanyl and heroin in seized material, laboratories began identifying new variants of fentanyl, often referred to as analogues or derivatives. The number of new fentanyl analogues in the drug supply increased and diversified until the temporary federal "core structure" scheduling of fentanyl related substances by the Drug Enforcement Administration in February 2018. Now, post fentanyl analogue scheduling, the illicit synthetic opioid market has transitioned back to primarily fentanyl, but with evidence of poly-drug use. Based on this observation, this study sought to document patterns of poly-drug use in forensic toxicology casework to determine what substances were most frequently found in conjunction with fentanyl.

Analytical testing was performed via liquid chromatography quadrupole time-of-flight mass spectrometry (LC-QTOF) using a Sciex TripleTOF™ 5600+ (Ontario, Canada) coupled with a Shimadzu Nexera XR UHPLC (Kyoto, Japan). This represents a non-targeted drug testing approach that differs from traditional forensic toxicology testing protocols. Discarded sample vial extracts, primarily collected from testing procedures for the directed analysis of synthetic opioids, were acquired from a large forensic toxicology laboratory (NMS Labs, Willow Grove, PA). All sample extracts were deidentified prior to inclusion in this study. In total, 3,543 sample extracts were analyzed and processed against an extensive, and continuously updated, in-house library database containing more than 700 drugs, including fentanyl, fentanyl metabolites, fentanyl analogues, other synthetic opioids and drugs of abuse, as well as an extensive number of NPS.

The results from comprehensive data processing included the identification of a wide-variety of substances covering all classes and included parent drugs (e.g. fentanyl), metabolites (e.g. norfentanyl), and synthesis precursors (e.g. 4-ANPP) or byproducts (e.g. acetyl fentanyl). For a more accurate determination of drug use, individual identifications were categorized under explicit parent drug groups prior to complex data analysis to determine positivity and combinations. For example, results of fentanyl, norfentanyl, and/or beta-hydroxy fentanyl were all categorized as "fentanyl positive"; 4-ANPP and acetyl fentanyl were not considered for inclusion based on undistinguishable source. Drug classes evaluated included stimulants (e.g. cocaine, methamphetamine, MDMA), opiates/opioids (e.g. heroin, tramadol, buprenorphine),

hallucinogens (e.g. ketamine, phencyclidine), and benzodiazepines (e.g. diazepam, alprazolam), as well as these same classes for NPS.

Overall, 1,301 (36.7%) sample extracts were deemed fentanyl positive. The majority (79.8%) of fentanyl positivity was accompanied by poly-drug use, including the presence of one or more drug of abuse and/or NPS. Fentanyl was found in combination with as many as seven drugs and/or NPS (excluding therapeutics, adulterants, etc.). With respect to drugs of abuse, fentanyl was most commonly found in combination with stimulants (46.0%) and other opiates/opioids (42.8%). Fentanyl was more commonly found in combination with cocaine (26.4%) than methamphetamine (13.1%). Fentanyl combinations with opioids included heroin (28.3%), tramadol (11.1%), and methadone (9.4%). With respect to NPS, fentanyl was most commonly found in combination with synthetic opioids (27.3%) and more rarely found in combination with synthetic stimulants (4.2%), designer benzodiazepines (3.9%), and novel hallucinogen (1.3%).

These results demonstrate the great extent to which fentanyl users are using other substances, either concurrently with or in proximity to their fentanyl use. Fentanyl poly-drug use is significant from forensic toxicology and public health perspectives, as combined drug use creates drug-drug interactions and more complex adverse effect profiles. To better understand poly-drug use, laboratories should consider developing all-inclusive, non-targeted assays for more comprehensive determination of all substances on board at the time of impairment or death.

Keywords: Fentanyl, Poly-Drug, Opioid, NPS, Toxicology