**Toxicosurveillance of Novel Opioids: Just Screening Tests May Not Be Enough**

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In the last decade, the drug landscape in the United States (US) and throughout much of the world has dramatically changed. This is due, in large part, to the emergence of a variety of new psychoactive substances (NPS), such as novel synthetic opioids (NSO). NSOs include fentanyl as well as a growing number of new fentanyl derivatives; these derivatives are clandestinely synthesized for the illegal market [1, 2]. Fentanyl and many of its analogues are considered particularly risky due to their high potency, their use as cutting or adulterant agents for heroin and other drugs, and their use simply as substitutes for heroin. The illicit use of NSOs has been responsible for the ever-increasing crisis of lethal overdose cases in the US [3].

The timely detection of individual exposure to fentanyl analogues represents a challenging objective because of their typically minuscule concentration in bodily fluids and the chemical variability associated with minor structural changes of the parent drug [4]. Further difficulties include the rapid development of new analogues, their rapid replacement with newly synthetized compounds, and incomplete or lacking pharmacological and structural information. Hence, description of exposures to several NSOs, such as carfentanil, is largely limited to a few case reports [5-7] and preliminary studies testing biospecimens for exposure to fentanyl and some of its analogues post-consumption [8-11]. Certainly, more surveillance studies are needed to assess the diffusion of fentanyl, its analogues, and other NSOs.

In the article from Chhabra et al. [12] published in this issue of the *The American Journal of Drug and Alcohol Abuse*, the authors aimed to describe the prevalence of specific fentanyl analogues and other synthetic opioids via urine specimen testing from living patients presenting to a large healthcare system. Following a preliminary screening test for fentanyl and opiates, a confirmatory analysis for the identification of fentanyl analogues, fentanyl metabolites, and other synthetic opioids,

was performed by means of HPLC-MS/MS. At least one fentanyl analogue or synthetic opioid was detected in 65.3% of referred samples, with 26.0% of samples testing positive for two or more fentanyl analogues. Of note, over one-third of tested samples that screened positive for opiates yet negative for fentanyl were found to contain detectable synthetic opioids, including fentanyl analogues, after confirmatory HPLC-MS/MS analysis. This suggests that either the immunoassay for fentanyl has poor sensitivity or that fentanyl analogues are now beginning to appear without fentanyl being present [8].

This study has limitations in terms of i) time span and geographical coverage, ii) lack of self-report about past use of fentanyl, and iii) missing information about confirmatory fentanyl testing for samples positive for other drugs, such as methamphetamine or cocaine (as evidence now suggests that such drugs can also be adulterated or contaminated with fentanyl [13]). Nevertheless, the results highlight the frequency with which living patients with illicit opioid exposures are now being exposed to synthetic opioids other than fentanyl. Previous studies have shown that people who use illicit substances are often unaware of having been exposed to fentanyl or one of its highly potent analogues, likely as a consequence of heroin adulteration [8, 14-16]. As such, comprehensive and updated testing protocols for large panels of NSOs are now much needed.

Yet, as Chhabra et al. confirm, mere immunoassays are not enough. While on-site screening tests can serve as relatively effective and rapid tools for detecting opioid exposure [17], more advanced testing appears to be needed to detect a wider variety of newer opioids as they reach the illicit market. In addition, it is essential that we try to inform not only patients about their results but also staff in local healthcare systems and addiction treatment centers. A close collaboration between healthcare institutions and reference laboratories would thus be beneficial, provided that the biological samples are appropriately collected and adequate confirmation methods (i.e., targeted HPLC-MS/MS analyses) are made available. Further, it is important that researchers and medical staff attempt to determine what drug(s) patients believe they used, as this informs whether participants used fentanyl analogues intentionally or unintentionally (via adulterated or contaminated drugs) [8].

Finally, effective approaches for opioid screening – particularly those housed within epidemiological studies — are needed to focus on patterns of drug exposure. Such studies could benefit from recent technological developments of analytical instrumentation and methodologies [18]. Therefore, greater investments from the public health system will be crucial to provide more reliable information in terms of toxicosurveillance. This information, in turn, would provide valuable guidance for targeted harm-reduction and treatment approaches.

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