CHARACTERIZING THE PRESENCE OF FENTANYL ANALOGUES IN THE UNREGULATED DRUG SUPPLY IN BRITISH COLUMBIA, CANADA

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ABSTRACT

Background: The emergence of fentanyl and its analogues (e.g., carfentanil) have contributed to a rise in overdose-related mortality. The objective of this study was to describe samples containing fentanyl analogues appearing in the unregulated drug supply of British Columbia (BC), Canada.

Methods: Point-of-care drug checking data, using a combination of fentanyl immunoassay strips and Fourier-transform infrared spectroscopy (FTIR), were collected at harm reduction sites in BC between 2017 and 2021. A subset of samples were sent for confirmatory analysis using quantitative nuclear resonance spectroscopy, gas chromatography-mass spectrometry, and/or liquid chromatography-mass spectrometry.

Results: A total of 22916 samples were tested using point of care technologies, with 43% testing positive for fentanyl via fentanyl test strips. 1467 were sent for confirmatory analysis, and of these 854 (58%) tested positive for fentanyl via fentanyl test strips and 84 (6%) contained at least one fentanyl analogue, including: carfentanil (n=61), acetyl fentanyl (n=15), furanyl fentanyl (n=8) and cyclopropyl fentanyl (n=5). Fourteen (16%) samples containing a fentanyl analogue tested negative via fentanyl immunoassay strips and fentanyl was also not detected using FTIR. Fentanyl analogues in all fourteen samples were identified in trace amounts via confirmatory analysis.

Conclusion: Fentanyl analogues were present in the unregulated drug supply and while the risk profiles are known for some, not all are well characterized. These findings underscore the importance of drug checking initiatives for monitoring the unregulated drug market.

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INTRODUCTION

In the last decade, North America has seen a drastic surge in the number of illicit drug toxicity deaths, which can be primarily attributed to an increasingly toxic drug supply.[1,2] In 2020, over 93,000 deaths were associated with drug overdose in the United States, which was nearly a 30% increase from the previous year.[3] Canada's overdose epidemic, which has taken the lives of over 20,000 since 2016,[4] stems from a range of intersecting social, structural and environmental factors, including homelessness, socioeconomic status, unemployment, difficulty accessing addiction treatment which, in turn, have been exacerbated by the adulteration of unregulated drug supplies with fentanyl and fentanyl analogues.[5] The Canadian overdose crisis has had the most significant impact in the province of British Columbia (BC), which in 2020, had the highest rate of opioid toxicity deaths out of all Canadian provinces, at 34.1 per 100,000.[6] In BC, the number of drug overdose deaths involving fentanyl increased dramatically from just 4% in 2012 to 85% in 2020,[7] and this number continues to grow, with 86% of post-mortem toxicology reports detecting fentanyl in the first six months of 2021.[8]

Fentanyl is a potent opioid, 50-100 times more potent than morphine, and is typically used to treat severe pain.[9] With fentanyl saturating the unregulated drug market in recent years, many people who use drugs are now expecting their opioid to contain fentanyl and some are actively seeking fentanyl for use.[10,11,12] Novel analogues of fentanyl (e.g., carfentanil, acetyl fentanyl) have also been appearing more recently in the unregulated drug supply.[8] In particular, carfentanil is an opioid analgesic between 20 and 100 times more potent than fentanyl, which greatly increases the potential risk of overdose.[13] Carfentanil has recently caught media attention as it has been linked to overdose deaths in several Canadian cities.[14,15] In 2021 alone, 137 deaths in British Columbia have involved carfentanil.[14] A similar spike was seen in Ontario in 2019,

with 142 deaths attributed to carfentanil.[15] Given that fentanyl and its analogues range in potency and are often ingested concurrently with other drugs, toxicity and risk of overdose increases.[16] While some analogues have been characterized, there is little information about the pharmacology or toxicity of others, and little is known about how pervasive they are in the unregulated drug market.

Drug checking is a harm reduction intervention that utilizes various technologies to determine what substances are present in the drugs that people intend to consume.[17] The intent is to inform people who use the service of what is in their drugs so they can make informed decisions about consumption and take precautions to reduce the risk of harm.[18,19] Initial results from a drug checking initiative in Vancouver, BC, showed that individuals were ten times more likely to reduce their dose if they obtained a positive test result for fentanyl.[17] Another study in the United States found similar results, where a positive fentanyl test strip result was associated with a positive change in overdose risk behaviour (e.g., using smaller amounts of substance, starting with a low dose and gradually increasing and not using drugs alone).[20] In addition to mitigating risks for individuals who use the service, drug checking initiatives have provided the opportunity to monitor trends in the unregulated drug supply.[21] The objective of this study was to characterize the presence of fentanyl analogues in samples submitted to drug checking facilities in the two most populous cities in BC: Vancouver and Surrey.

METHODS

Described in detail elsewhere,[18,22] drug checking services were first offered in Canada at community harm reduction sites starting in November 2017 [23] offering a two-step point of care service using the Bruker ALPHA or ALPHA II Fourier-transform infrared spectrometers (FTIR)

and BTNX fentanyl immunoassay strips. In brief, FTIR is a non-destructive technique for the identification of compounds within a sample. It is portable and provides results quickly (<5 minutes) with minimal sample preparation. However, given its limit of detection of approximately 3-10%, lesser amounts may go undetected.[24,25] Fentanyl immunoassay strips can detect a lower concentration of fentanyl and its analogues compared to FTIR, but results are qualitative and lack specificity. Thus, the use of these two technologies in combination offsets each technology's limitations when used on its own. In 2018, BTNX benzodiazepine immunoassay strips were introduced to the protocol at point of care to detect benzodiazepines in drug samples given the rise in the prevalence of benzodiazepine adulteration of opioid samples.[26]

A subset of all the samples collected in Vancouver and Surrey were sent to the BC Provincial Toxicology Centre (PTC) or Health Canada's Drug Analysis Service (DAS) for confirmatory analysis. Samples are sent for confirmatory analysis based on current recommendations which include samples with suspected analogues of fentanyl, samples containing benzodiazepines, samples with no FTIR library match, samples with complex mixtures, samples containing new psychoactive substances and any "typical" samples for ongoing evaluation and general surveillance of the drug supply.[27] For confirmatory analysis, the PTC used untargeted gas chromatography and mass spectrometry (GC/MS), and DAS used a combination of untargeted nuclear magnetic resonance spectroscopy, GC/MS and liquid chromatography mass spectrometry. The data collected at point of care and confirmatory analysis are linked via a unique sample ID. The study period for the present study was between May 2018 and July 2021. Providence Health Care/University of British Columbia research ethics approval was obtained for this study as part of a larger drug checking program evaluation.

RESULTS

Point of care drug checking

Between May 2018 and July 2021, a total of 22916 samples were submitted for point of care analysis from 16 drug checking sites in Vancouver and Surrey. The majority of sites are located in Vancouver's downtown eastside, a neighborhood with high levels of drug use, homelessness and poverty. 22324 (97%) were checked with fentanyl immunoassay strips, 22712 (99%) with FTIR and 21184 (92%) with both methods (Figure 1). Of the samples that were checked with both methods and had a positive result for fentanyl using immunoassay strips, FTIR spectroscopy detected fentanyl in 6125 (61%) samples and a fentanyl analogue in 5 (0.4%) samples (all of which were carfentanil). FTIR detected fentanyl co-occurring with carfentanil in 4 (80%) of these 5 samples.

Confirmatory analyses

In total, 1467 samples were sent to partner laboratories for confirmatory analysis. Of these samples, 854 (58%) tested positive for fentanyl via fentanyl test strips. As seen in Table 1, 84 (5.7%) samples that were sent for confirmatory analysis contained a fentanyl analogue, including: Carfentanil (n=56), Acetyl fentanyl (n=15), Furanyl fentanyl (n=8) and Cyclopropyl fentanyl (n=5) (counts are greater than the total [n=84] given that more than one fentanyl analogue may be present in one sample). Interestingly, fentanyl HCl was not detected in 24% of these fentanyl analogue positive samples, suggesting that only fentanyl analogues were present in these samples. Of the 84 samples containing a fentanyl analogue identified by confirmatory analysis, 13 (15%) tested negative via fentanyl strips and FTIR spectroscopy, all of which contained only trace amounts of carfentanil.

DISCUSSION

The present study aimed to examine one crucial aspect of the overdose crisis - fentanyl and its analogues appearing in the unregulated drug supply. We found that of all samples submitted for analysis at point of care, almost half were positive for fentanyl via immunoassay strips, approximately one-third were positive for fentanyl via FTIR and another third were positive for fentanyl using both fentanyl immunoassay strips and FTIR. These point of care technologies were only able to specifically identify fentanyl analogues (i.e., carfentanil) in five samples, missing 15% of the samples where fentanyl analogues (i.e., carfentanil) were detected via confirmatory testing in trace amounts. Of all samples sent for confirmatory testing, the most common fentanyl analogue that was detected was carfentanil, which is of great concern as carfentanil is one of the most potent analogues in circulation.[28]

The risks associated with fentanyl use and the role fentanyl continue to play in the North American overdose epidemic have been thoroughly described,[29,9,30,31,32] Certain fentanyl analogues, like carfentanil, have also been well characterized and recent work has revealed how carfentanil has greatly contributed to overdose mortality.[33,34,35] For example, a study from the United States showed that overdose deaths increased in 2016 and 2017 and declined in 2018, which was associated with a rise and fall of carfentanil availability.[13] There are many other known fentanyl analogues (e.g. acetyl fentanyl, furanyl fentanyl) whose risk profiles have also been described albeit to a lesser degree;[9] however, it is of concern that novel fentanyl analogues (e.g., furanylbenzylfentanyl) continue to appear in the unregulated drug supply. Future research should continue to identify and characterize novel fentanyl analogues, understand its

pharmacodynamics, while monitoring the dynamic unregulated drug supply using drug checking services.

Consistent with previous research,[22] we found that fentanyl analogues, particularly when present in trace amounts, were not identified using point of care technologies. Currently, FTIR specificity is known to be high for fentanyl,[22] but has not been calculated for carfentanil. This poses a number of concerns given that confirmatory analysis is not available in many settings. A major limitation for fentanyl test strips is that we are unable to determine if there is more than one fentanyl analogue present in the sample. It simply identifies the sample as being positive or negative for fentanyl and some analogues.[27] In addition, FTIR does not consistently distinguish between fentanyl and other fentanyl analogues and can only detect these compounds when present in high concentrations and available in reference libraries.[27] Improvement of technologies at point of care or wider availability of confirmatory technologies are necessary to better understand the presence of fentanyl analogues in the unregulated drug supply and its impact on the health outcomes of people who use drugs.

There are several limitations to the present study. First, a non-random subset of samples was sent for confirmatory analysis, which may result in selection bias. Second, when fentanyl analogues are present in the same sample as fentanyl, there is an inability to differentiate between the different compounds using point of care technologies. Because of this, the number of samples containing fentanyl analogues may be greatly underrepresented, as many co-occur with fentanyl.[36] Third, fentanyl test strips are unable to detect more than one fentanyl analogue present in the sample. They simply identify the sample as being positive or negative for fentanyl and/or some analogues. However, they are more sensitive than FTIR and may have detected low concentrations of fentanyl or analogue that FTIR could not detect. Finally, the location of drug

checking sites, primarily in Vancouver's downtown east side, may limit the generalizability of results to the broader unregulated drug market.

In conclusion, we found that in recent years, a number of fentanyl analogues have been detected in drug checking samples in Vancouver and Surrey, BC, Canada. Our findings suggest that some fentanyl analogues may not be distinguishable from fentanyl at point of care using fentanyl test strips and are rarely identified by FTIR. Currently it is unclear if they were not detected because of their chemical structure or because they were only present in trace amounts. Continued efforts to monitor the unregulated drug supply using point of care and confirmatory methods is warranted to better understand this dynamic environment.

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CONFLICT OF INTEREST

The authors have no conflict of interest.

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TABLES AND FIGURES

Table 1. *Number of fentanyl analogs detected using Fourier-transform infrared spectroscopy (FTIR) and confirmatory testing*

Fentanyl Analogue	FTIR (n =22712)	Percentage of FTIR samples positive via FTS	Confirmatory (n = 1467)	Percentage of confirmatory samples positive via FTS
Carfentanil	5	5	56	77
Acetyl fentanyl	0	0	15	67
Furanyl fentanyl	0	0	8	0
Cyclopropyl fentanyl	0	0	5	100
Total	**5**	**100**	**84**	**69**

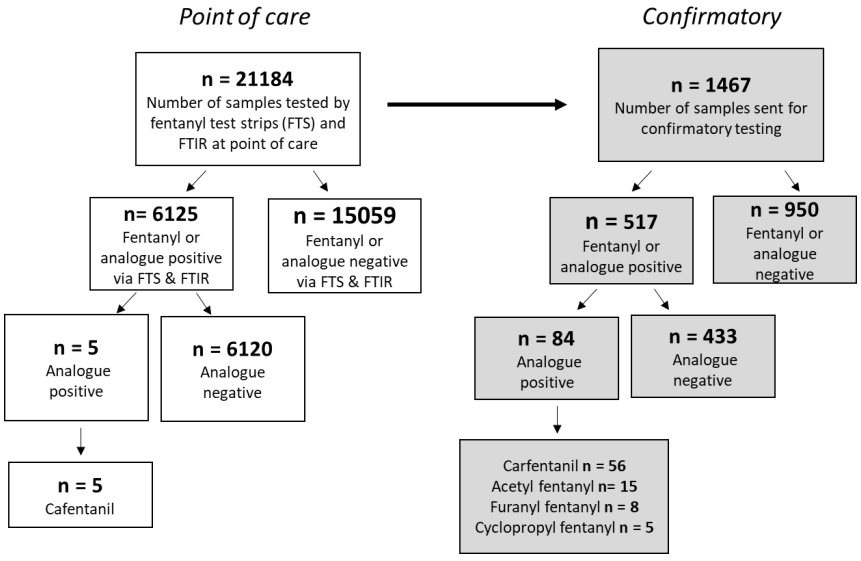

Figure 1. *Number of fentanyl or analogue positive and negative samples detected using point of care and confirmatory technologies*