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Research Paper

An outbreak of novel psychoactive substance benzodiazepines in the unregulated drug supply: Preliminary results from a community drug checking program using point-of-care and confirmatory methods

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ABSTRACT

Background: From mid-2018, an increase in novel psychoactive substance (NPS) benzodiazepines was noted on surveillance of the unregulated drug market around Vancouver, British Columbia, Canada. The rise was concordant with an outbreak of atypical overdoses suspicious for benzodiazepine adulteration of unregulated opioids. This study sought to describe the number and type of NPS benzodiazepines in a sample drawn from a community drug checking program during this period, and to explore accuracy of point-of-care drug checking technologies when compared to confirmatory methods in this sample.

Methods: Point-of-care drug checking data using fentanyl and benzodiazepine test strips as well as Fourier transform infrared spectroscopy were gathered at harm reduction sites in the Vancouver area from October 2018 to January 2020. A convenience subsample underwent confirmatory testing with gas chromatography-mass spectrometry, liquid chromatography-mass spectrometry, or quantitative nuclear magnetic resonance spectroscopy.

Results: Of 159 samples with both point-of-care and confirmatory results, 24 (15.1%) contained at least one NPS benzodiazepine, including etizolam ($n = 18$), flubromazolam ($n = 3$), flualprazolam (4), and flubromazepam ($n = 1$). Of 114 confirmatory samples expected by participants on self-report to contain opioids, 18 (15.8%) contained some NPS benzodiazepine, with 16 (14.0%) containing both an NPS benzodiazepine and an opioid, always fentanyl. False positive and negative rates were 15.5% and 37.5% for test strips, and 3.9% and 91.7% for FTIR, respectively. Combined together, false positive and negative rates of point-of-care methods were 17.8% and 29.2%.

Conclusions: NPS benzodiazepine adulteration in an unregulated drug supply sample reveals new risks compounding ongoing harms associated with the synthetic opioid epidemic. Given substantial false positive and false negative rates noted in our sample for point-of-care detection methods, cautious use of combined point-of-care methods, routinely paired with confirmatory drug checking may aid in early detection and monitoring of unregulated drug markets and inform targeted harm reduction strategies and health policy approaches.

Introduction

North America is in the midst of an unprecedented public health crisis, with extreme levels of morbidity and mortality related to opioid overdose – particularly involving high-potency synthetic opioids such as fentanyl and its analogues. In Canada, more than 16,343 apparent opioid-related deaths occurred between January 2016 and March 2020, with a national death rate of 10.1/100,000 in 2019

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(Special Advisory Committee on the Epidemic of Opioid Overdoses, 2020). In British Columbia (BC), the Canadian province most affected by the opioid overdose epidemic, the opioid-related death rate was nearly twice the national average for 2019, at 19.8/100,000 (Special Advisory Committee on the Epidemic of Opioid Overdoses, 2020), with 82.8% of unregulated drug toxicity deaths between 2016 and 2019 involving fentanyl or analogues (British Columbia Coroners Service, 2020). While the harms related to this crisis continue, new concerns are mounting about the emergence of novel psychoactive substance (NPS) benzodiazepines in unregulated drug markets, particularly as potential adulterants in drugs sold as unregulated opioids (Lysyshyn & Ahamad, 2019; Vescera, 2019a; Wadhwani, 2019).

Novel psychoactive substances are considered by the United Nations Office on Drugs and Crime (United Nations Office on Drugs and Crime, 2013) to be "substances of abuse, either in a pure form or a preparation, that are not controlled by the 1961 Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but which may pose a public health threat". The clandestine nature of NPS production and rapid development, coupled with their often ambiguous legal status and varied marketing channels (often being sold online as research chemicals or household products) make tracking and studying these drugs difficult (Winstock & Wilkins, 2011; Zawilska & Andrzejczak, 2015). Regulation and intervention efforts aimed at enforcement or reduction of supply are similarly challenging (Seddon, 2014; Winstock & Wilkins, 2011). Harms directly attributable to NPS are unique to each drug class, with broad groups being: "synthetic cannabimimetics, synthetic cathinones, phenethylamines, piperazines, ketamine- and phencyclidine-type substances, tryptamines, benzofuranes, and opioids" (Zawilska & Andrzejczak, 2015).

Less frequently considered, NPS benzodiazepines were first reported by the European Monitoring center for Drugs and Drug Addiction (EMCDDA) in 2007 (Manchester, Lomas, Waters, Dempsey & Maskell, 2018). While early NPS benzodiazepines (e.g., etizolam) had market approval in a few selected countries (e.g., India, Italy, Japan), they were frequently found as unregulated substances in other countries (Marin & van Wijk, 2019; World Health Organization, October, 2019a). Since the first reports of these substances, other NPS benzodiazepines with no history of market approval started to emerge, and have steadily increased in prevalence (EMCDDA, 2018; Manchester et al., 2018). Between 2011 and 2016, 209 reports of NPS benzodiazepines were made to the UNODC via the Early Warning System (EWS; Zawilska & Wojcieszak, 2019). Over 50% of documented NPS benzodiazepines have been detected between 2015 and 17 (EMCDDA, 2018; Manchester et al., 2018; Marin & van Wijk, 2019). There are currently 27 NPS benzodiazepines under observation by the EMCDDA (Bäckberg, Pettersson Bergstrand, Beck & Helander, 2019). Monitoring from the US National Poison Data System revealed a 330% increase in single-agent exposure to these substances from 2014 to 2017 (Carpenter, Murray, Dunkley, Kazzi & Gittinger, 2019), and recent data from Scotland indicate a majority of the country's increase in benzodiazepine-detected deaths in 2016 were attributable to NPS benzodiazepines, particularly etizolam (EMCDDA, 2018). Established drug checking programs that provide regular analysis on changing patterns and emerging substances such as the Welsh Emerging Drugs and Identification of Novel Substances (WEDINOS), report an increase in the prevalence of flualprazolam and high proportions of etizolam in tested samples, particularly as substances sold as diazepam or alprazolam (WEDINOS, 2019). Many NPS benzodiazepines are inexpensive and easily obtainable online through vendors selling them for research purposes, or via the darkweb (Manchester et al., 2018; Marin & van Wijk, 2019). As with other benzodiazepines, co-ingestion of NPS benzodiazepines and opioids presents heightened risks secondary to the compounded effects of combined respiratory depression and sedation (Jones, Mogali & Comer, 2012; Zawilska & Wojcieszak, 2019).

As a diverse group, the NPS benzodiazepines have varying, and to some extent, still unknown pharmacologic and toxicologic profiles (EMCDDA, 2018). The mechanism of action of all benzodiazepines, resulting in varying levels of anxiolysis, euphoria, muscle relaxation, sedation, amnesia, hypnosis, and anticonvulsant effects comes from differential allosteric binding of the molecules to one of several sites on the $GABA_a$ receptors (El Balkhi, Monchaud, Herault, Géniaux & Saint-Marcoux, 2020). These effects, the relative potencies, as well as side effects such as respiratory depression and ataxia of the various NPS benzodiazepines, have been posited to result from specific configuration and type of molecular side-chain functional groups and their relative position on the benzene and diazepine rings (El Balkhi et al., 2020). For some NPS benzodiazepines such as flubromazolam, their quick absorption, very high receptor affinity, combined with unknown off-target effects, carry potentially elevated risks over traditional pharmaceutical benzodiazepines (Łukasik-Głębocka et al., 2016). Owing to their varied structure and unclear metabolism, NPS benzodiazepines have a wide range of effective doses and duration of action, with potential harms resulting from early dosing prior to peak effects and accumulation (Zawilska & Wojcieszak, 2019).

The presence of NPS benzodiazepines in current unregulated drug supplies is unclear, particularly with respect to their role as adulterants. With surveillance data confirming NPS benzodiazepines in the drug markets of Vancouver, BC and surrounding-areas (Lifelabs, 2019; Marmel & Lysyshyn, 2019), and with concerns from local health and harm reduction service providers, as well as people who use drugs, over an emerging pattern of complex overdoses related to likely NPS benzodiazepine-opioid co-ingestion (Hennig, 2019; St. Denis, 2019; Vescera, 2019a), work was undertaken to better ascertain the extent of NPS benzodiazepines in the local unregulated drug market. The present study sought to describe the results of an expanded drug checking program evaluating the first reported outbreak of NPS benzodiazepine adulteration of an unregulated drug supply, and explore the potential accuracy and utility of various drug checking technologies, both at point-of-care and through confirmatory laboratories.

Methods

This study expanded on drug checking efforts that were initially established in 2017 at harm reduction centres, including supervised consumption sites (SCS) and overdose prevention sites (OPS), in Vancouver, BC (Tupper, McCrae, Garber, Lysyshyn & Wood, 2018) and extending into the nearby city of Surrey, BC. As in the previous study, designed to explore the feasibility of harm reduction-based drug checking services in the detection of fentanyl adulteration, participants could voluntarily access point-of-care drug checking services via Bruker ALPHA or ALPHA-II Fourier transform infrared (FTIR) spectrometers in combination with fentanyl test strips (BTNX, Markham, ON, Canada). This was later expanded to include benzodiazepine strips in October 2018, after circulating counterfeit alprazolam ("fake Xanax") was detected and found to contain fentanyl but no benzodiazepine (Vancouver Coastal Health, 2018). Manufacturer's product insert for the Rapid Response Single Drug Benzodiazepine Test Strip indicates these strips utilize oxazepam as a calibrator, with a cut-off of 300 ng/ml, and have been validated to detect 22 benzodiazepines in urine samples (BTNX Inc., N.D.). More details can be found in Supplemental Table 1. While it is acknowledged that the test strips employed in the current study were not initially designed for use with raw, dissolved drug samples, previous drug checking initiatives have employed the same technique for application with fentanyl test strips with good results (Green et al., 2020; McCrae et al., 2019; Tupper et al., 2018). At commencement of this study, detection of NPS benzodiazepines by existing test strip technology was unclear. A recent analysis examining the use of similar test strips for detection of NPS benzodiazepines concluded that both flualprazolam and flubromazolam appear to be detected at concentrations similar to alprazolam, a prescription benzodiazepine intended to be detected by these strips (Shapiro et al., 2020). Minimum detectable concentration for etizolam was higher than those for these former NPS benzodiazepines, but still

within range of useful detection in the setting of drug checking. In this study, there was no observed cross-reaction with fentanyl. With respect to point-of-care detection of NPS benzodiazepines by FTIR technologies, multiple reference libraries are utilized, which contain both prescription (i.e. alprazolam) and NPS benzodiazepines (i.e. flubromazolam). Infrared spectra were analyzed using the Bruker OPUS software and compared against available reference libraries (i.e., TICTAC ATR-FTIR Drug Library, the Bruker ATR-FTIR Pharmaceuticals Library, the Scientific Working Group for the Analysis of Seized Drugs (SWGDRUG) Infrared Library, and our own developed reference library). Specifically, our own reference library was generated based on available samples from the drug checking service, whereby those that were of relatively high purity and confirmed by partnering laboratories were added on an ongoing basis. It is a documented limitation of FTIR that substances present in low concentrations are difficult to detect, particularly when in combination with others (Tobias, Shapiro, Wu & Ti, 2020).

In Canada, legal exemptions permit the lawful operation of drug checking services and handling of drugs for such purposes as those described in this study. As in previous related drug checking work (Tupper et al., 2018), point-of-care testing took place in a two-step process, with a small sample (2–3 mg) of participants' drugs analyzed by FTIR before then being dissolved in water. Test strips were added to the dissolved sample, and a combined result was recorded. In the present study, a convenience subset of samples was collected based on specimens submitted for drug checking that were discarded, not reclaimed, if the client requested further analysis, or in cases that were clinically suspicious for benzodiazepine overdose (e.g. where participants reported protracted loss of consciousness inconsistent with opioid toxicity alone). These samples were then sent to partnering laboratories for confirmatory testing at the BC Provincial Toxicology center (PTC and/or at Health Canada's Drug Analysis Service (DAS). Samples were sent to confirmatory laboratories based on availability of laboratory resources or the location from where the sample was collected (with some drug checking sites more frequently submitting to PTC, and others to DAS, for example). Of those samples sent for confirmatory testing during the study period, seven found to contain NPS benzodiazepines were sent to both confirmatory sites. Five (71.4%) were confirmed at both sites, and two (28.6%), were only detected at one of either site.

At PTC, samples were analyzed using an Agilent 6890 N gas chromatograph in split mode coupled to an Agilent 5975C mass selective detector, which was run with electrospray ionization (EI) in positive mode and scanned from 40 to 600 m/z. A single point calibration curve using the certified reference standards (Cerilliant Corporation, Round Rock, TX) for the drugs listed in Supplemental Table 2 was run with every batch of samples and 0.1 mg/mL prazepam (Cerilliant Corporation) was added to all samples and controls as an internal standard. Relative Retention Time (RRT) was accepted with deviations of up to ±5% when compared to a reference standard. Drugs were identified using commercial libraries provided by Cayman Chemicals (Ann Arbor, MI) and SWGDRUG. Drugs identified by mass spectral libraries were considered detected if the retention times of the unknowns matched those of the reference standards/calibrators. If a drug that is not included in Supplemental Table 2 was identified, it was considered to be a tentative finding until it could be verified in house by a certified reference standard.

At Health Canada DAS, samples were initially screened using a Bruker Ascend 400 MHz NMR with Broadband Prodigy Cryoprobe running an in-house multivariate quantitative algorithm, or and Agilent 5977A GC–MS using EI. This allows for determination of the presence of unidentified components in a mixture via qNMR, with some limited sensitivity depending upon the analyte. When coupled with a GC–MS technique, Total Ion Current (TIC), designed to capture most forensic street drugs, novel compounds were flagged for additional analysis. For GC–MS employed at DAS, the RRT is not required, however, select samples with low level compounds may be analyzed on a GC with flame ionization detector to increase sensitivity. In these circumstances, RRT would be required also with a ± 5% acceptance criteria to Eicosane as an internal reference. Positively identified analytes were confirmed using a Waters Acquity Liquid Chromatography System coupled to a Xevo Quadrupole Time-of-Flight (QTOF) mass spectrometer, which targets the analytes listed in Supplemental Table 3. The LC-QTOF/MS employed was an ultra-performance LC-QTOF/MS instrument utilizing UNIFI software to capture all data throughout each run of analysis. While the underlying method is a fentanyl opioid/benzodiazepine targeted method, if any unknown is identified by NMR or GC–MS data reprocessing in UNIFI allows the operator to re-examine the data specific to the new compound. The LC-QTOF/MS method is qualitative and, as such, the Reporting Limit and RRT is based on response of Propanolol as an internal standard. The window of acceptance for RRT is 10% (± 5%), and must be greater than the response factor, with ranges between 0.099 for Ketazolam and 0.562 for Temazepam, calculated at 20 ng/mL for each Benzodiazepine standard. The accurate mass should be within ± 2 mDa for the precursor ion and within ± 5 mDa for the product ions. The DAS laboratory is a Forensic Drug Testing laboratory and as such methods and techniques, including reporting requirements, are designed to meet the needs of Canadian enforcement agencies in support of the Controlled Drugs and Substances Act.

Testing using benzodiazepine test strips took place from October 2018 to January 2020 at eight harm reduction sites in Vancouver and Surrey, BC, with confirmatory testing samples being sent from five sites between two health authorities (3 in Vancouver, 2 in Surrey). A subset of samples underwent confirmatory testing but no testing by benzodiazepine test strips. Data were collected anonymously, without demographic or other identifying information. Ethics approval was obtained through the Providence Health Care/University of British Columbia Research Ethics Board.

Given the reality of NPS benzodiazepine adulteration in the unregulated drug market in the region under study, we aimed to present exploration of the potential accuracy of these technologies. In this analysis, we first collapsed 'point-of-care' testing into a single entity. A True Positive was considered if the result was positive on *either* test strips or FTIR with a confirmatory finding of NPS benzodiazepines. Likewise, as an amalgamated measure, a False Positive on point-of-care was considered if *either* test strip or FTIR returned positive, but the sample was confirmed negative for NPS benzodiazepines. On the other hand, a True Negative was considered if *both* test strips and FTIR returned negative, and were confirmed negative on subsequent analysis.

Results

During the study period, 1368 samples were checked at point-of-care using both benzodiazepine test strips and FTIR. Of these, 159 also underwent confirmatory testing, with 120 being sent to DAS, 65 sent to PTC, and 26 to both labs, and were therefore included in the present analysis. Study flow and sample inclusion are presented in Fig. 1.

NPS benzodiazepines in primary sample

Table 1 presents the 159 samples that underwent both point-of-care and confirmatory testing, categorized by participant report of expected substance. Of these, 24 (15.1%) yielded a positive result for NPS benzodiazepines via confirmatory testing methods, with none of them being expected by participants to be a NPS benzodiazepine. Specifically, among these 24 samples, participants expected their samples to primarily contain fentanyl ($n = 15$), alprazolam ($n = 5$), an indeterminate opioid ("down"; $n = 2$), heroin ($n = 1$), and an unknown substance ($n = 1$). NPS benzodiazepines confirmed in the study included etizolam ($n = 18$), flualprazolam (4), flubromazolam ($n = 3$), and flubromazepam ($n = 1$), with two confirmatory samples containing more than one NPS benzodiazepine (etizolam with each flubromazolam and flubromazepam). Confirmatory and point-of-care analyses of samples with confirmed NPS benzodiazepines are summarized in Table 2.

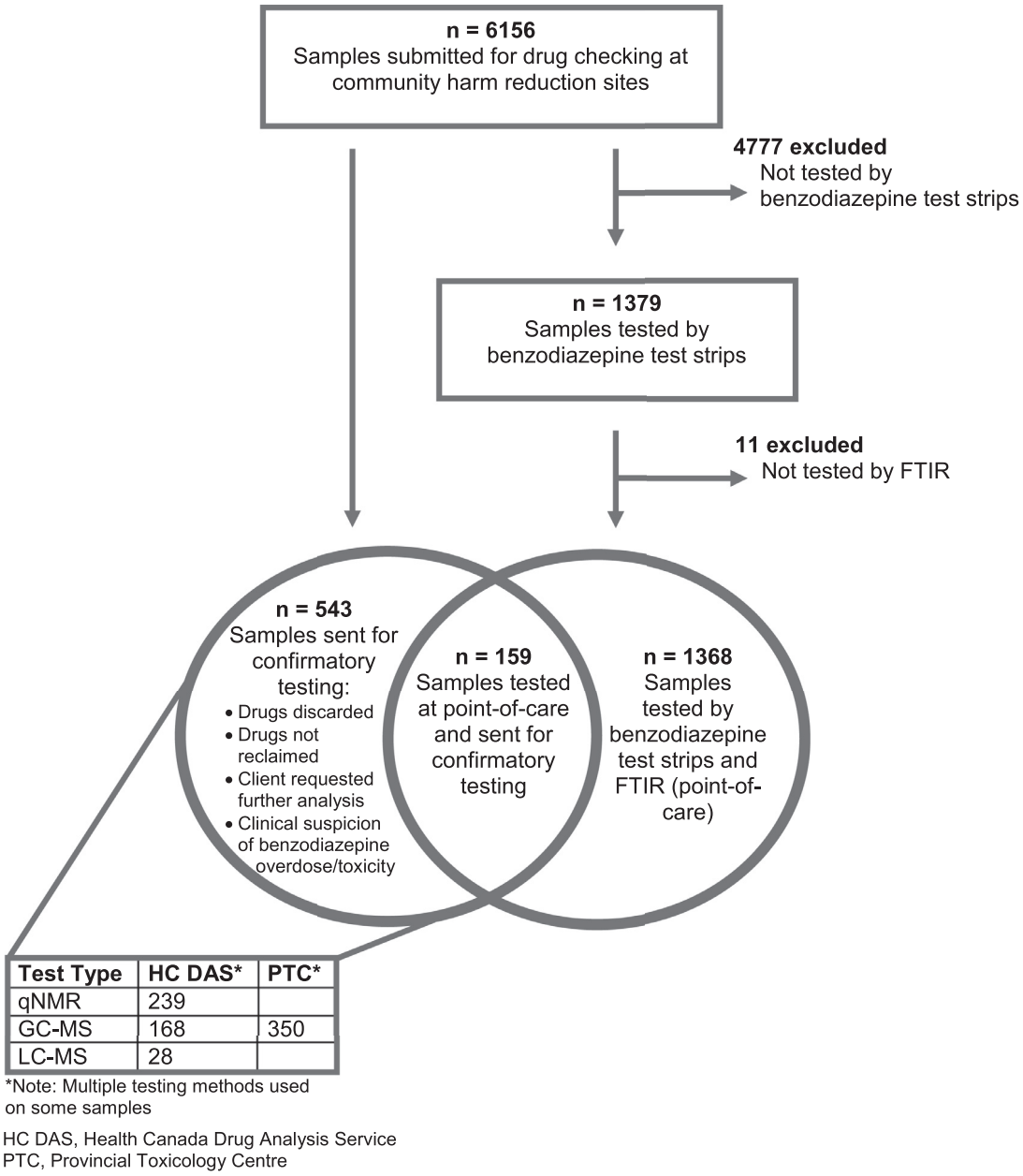

Fig. 1. Benzodiazepine drug checking procedural flow.

NPS benzodiazepines and opioids

Of the 159 samples with point-of-care and confirmatory data, 114 (71.7%) were thought by participants to primarily contain opioids (fentanyl, 'down', heroin, carfentanil, or oxycodone). Of these 114 samples, 18 (15.8%) were found by confirmatory testing to contain at least 1 NPS benzodiazepine, with 16 (14.0%) containing both an NPS benzodiazepine and an opioid. Two (1.8%) of 114 opioid-anticipated samples contained NPS benzodiazepine, but no opioid on confirmatory testing. Specific to the described outbreak, of the 24 samples which tested positive for NPS benzodiazepines on confirmatory testing, 17 (70.1%) also contained an opioid, always fentanyl, and in one case both fentanyl and carfentanil.

Point-of-care accuracy & error

Details pertaining to the accuracy of each point-of-care method are presented in Table 3. Overall, 6 (3.8%) out of the 159 samples that underwent both point-of-care and confirmatory testing were confirmed to contain typical benzodiazepines (alprazolam and temazepam, each detected by test strips), but no NPS benzodiazepines. Acknowledging that the BTNX benzodiazepine test strips were not specifically designed to detect NPS benzodiazepines, but with recent evidence of cross-reactivity supportive of use in point-of-care drug checking settings (Shapiro et al., 2020), we present the following detection values based on the assumption of some ability of these strips to detect NPS benzodiazepines, and to gauge potential accuracy of these technologies.

Of the remaining 153 samples, 40 (26.1%) had a positive benzodiazepine point-of-care result (n = 35 test strips, n = 7 FTIR, n = 2 test strips and FTIR). Of these 40 samples, 23 (57.5%) revealed no NPS benzodiazepine on confirmatory testing (point-of-care false positive rate [FPR]=17.8%). Of the 113 samples which returned negative results on both point-of-care methods, 7 (6.2%) were confirmed to contain an NPS benzodiazepine (point-of-care false negative rate [FNR]=29.2%, where

Table 1
Benzodiazepine and NPS benzodiazepine positivity by participant-reported expected drug type ($N = 159$).

Drug expected	n (% of total confirmatory samples)	Benzodiazepine** test strip positivity, n (% of positive samples per substance)	FTIR† NPS positivity, n (% of positive samples per substance)	Confirmatory test†† NPS positivity, n (% of positive samples per substance)
Fentanyl	90 (56.6%)	25 (27.8%)	2 (2.2%)	15 (16.7%)
Alprazolam	17 (10.7%)	6 (35.3%)	2 (11.8%)	5 (29.4%)
Down* - Unknown	12 (7.5%)	5 (41.7%)	2 (16.7%)	2 (16.7%)
Carfentanil	5 (3.1%)			
Heroin	5 (3.1%)			1 (20.00%)
Ketamine	5 (3.1%)			
Cocaine	4 (2.5%)			
MDMA	3 (1.9%)			
2C-B	1 (0.6%)			
Acetaminophen/Oxycodone	1 (0.6%)			
Fentanyl and Heroin	1 (0.6%)	1 (100.0%)		
Methamphetamine	1 (0.6%)			
Temazepam	1 (0.6%)	1 (100.0%)		
Unknown	13 (8.2%)	3 (23.1%)	1 (7.7%)	1 (7.7%)
TOTAL	159 (100.0%)	41 (25.7%)	7 (4.4%)	24 (15.1%)

2CB, 4-Bromo-2,5-dimethoxyphenethylamine.
MDMA, 3,4-Methyl enedioxy methamphetamine.
* 'Down' is a term used by participants to denote a substance containing an unregulated opioid, with 'down-unknown' being an indeterminate opioid.
** May detect NPS benzodiazepines and non-NPS benzodiazepines.
† Fourier transform infrared spectroscopy (point-of-care).
†† Confirmatory includes positive finding of any NPS benzodiazepine in one or more of GC–MS, LC-MS, and qNMR testing.

Table 2
Active constituents of samples that tested positive for NPS benzodiazepine on confirmatory testing ($n = 24$).

Sample	Expected drug	Benzodiazepine test strip	Substance(s) identified in FTIR analysis	Substance(s) identified in confirmatory analysis
1	Alprazolam	Negative	Etizolam	Etizolam
2	Alprazolam	Negative	Etizolam	Etizolam
3	Alprazolam	Positive	Uncertain Match	Flubromazolam
4	Alprazolam	Negative	Uncertain Match	Melatonin, Etizolam
5	Alprazolam	Negative	No Library Match	Etizolam
6	Fentanyl	Positive	Fentanyl, Caffeine	Caffeine, Fentanyl, Flualprazolam, Methamphetamine
7	Fentanyl	Positive	Caffeine	Fentanyl, Caffeine, 4-ANPP, Flubromazepam, Etizolam
8	Fentanyl	Positive	Methamphetamine, Caffeine	Caffeine, Methamphetamine, Fentanyl, Carfentanil, Etizolam
9	Down* – Unknown	Positive	Caffeine	Caffeine, N-phenylpropanamide, Fentanyl, Etizolam
10	Down* – Unknown	Positive	Caffeine, Uncertain Match	Caffeine, Methamphetamine, Fentanyl, N-phenylpropanamide, Flualprazolam
11	Fentanyl	Positive	Caffeine	Caffeine, Fentanyl, Etizolam
12	Fentanyl	Negative	Caffeine	Caffeine, Phenacetin, Etizolam, Fentanyl
13	Fentanyl	Negative	Caffeine	Caffeine, Flubromazolam, Etizolam, Phenacetin, Fentanyl
14	Fentanyl	Positive	Caffeine	Caffeine, Fentanyl, Etizolam, Phenacatin, Methamphetamine
15	Fentanyl	Positive	Caffeine	Caffeine, Methamphetamine, Phenacetin, Etizolam, Fentanyl
16	Fentanyl	Positive	Caffeine	Caffeine, Etizolam, Phenacetin, Fentanyl
17	Fentanyl	Positive	Caffeine	Caffeine, Phenacetin, Etizolam, Methamphetamine, Fentanyl
18	Fentanyl	Negative	Caffeine	Caffeine, Fentanyl, Etizolam
19	Fentanyl	Positive	Fentanyl, Caffeine	Caffeine, Flubromazolam, Fentanyl
20	Fentanyl	Negative	Caffeine, Uncertain Match, Fentanyl or Analog	Caffeine, Fentanyl, Etizolam
21	Fentanyl	Positive	Caffeine	Flualprazolam, Methamphetamine, Caffeine
22	Fentanyl	Positive	Uncertain Match, Caffeine	Methamphetamine, Caffeine, Flualprazolam
23	Heroin	Negative	Caffeine	Caffeine, Phenacetin, Fentanyl, Methamphetamine, Etizolam
24	Unknown	Positive	Caffeine, Uncertain Match	Methamphetamine, Etizolam, Fentanyl, Caffeine

4-ANPP, 4-anilino-N-phenethyl-piperidine.
* 'Down' is a term used by participants to denote a substance containing an unregulated opioid, with 'down – unknown' being an indeterminate opioid.

Table 3
Point-of-care accuracy and error for NPS benzodiazepine detection.

	Positive at Point-of Care				Negative at Point-of-Care			
	Strips($n = 35$)	FTIR($n = 7$)	Both($n = 2$)	Either($n = 40$)	Strips($n = 118$)	FTIR($n = 146$)	Both ($n = 113$)	Either($n = 151$)
Confirmed positive, n (%)	15 (42.9%)	2 (28.6%)	0 (0.0%)	17 (42.5%)	9 (7.6%)	22 (15.1%)	7 (6.2%)	24 (15.9%)
Confirmed negative n (%)	20 (57.1%)	5 (71.4%)	2 (100.0%)	23 (57.5%)	109 (92.4%)	124 (84.9%)	106 (93.8%)	127 (84.1%)

$N = 153$; samples with both point-of-care and confirmatory data, with 6 samples removed that were confirmed to contain only typical benzodiazepines (alprazolam, temazepam).

true positive is considered positive test strip or FTIR result with confirmed NPS benzodiazepine).

Test strips successfully detected benzodiazepines in 62.5% (15/24) of the confirmed NPS benzodiazepine-positive samples. Frequency of detection was higher when flualprazolam, flubromazolam, or flubromazepam were present in a sample (87.5%, n = 8) and lower when etizolam was the only benzodiazepine present (50.0%, n = 16). Of the 35 samples with positive benzodiazepine test strip results, 20 (57.1%) had no NPS benzodiazepines on confirmatory testing (test strip FPR=15.5%). Of 118 samples with negative benzodiazepine test strip results, 9 (7.6%) contained NPS benzodiazepines on confirmatory testing (test strip FNR=37.5%).

Of the 7 samples positive on FTIR, 5 (71.4%) had no NPS benzodiazepines on confirmatory testing (FTIR FPR=3.9%). Of 146 samples with negative FTIR results, 22 (15.1%) were found to contain NPS benzodiazepines on confirmatory testing (FTIR FNR=91.7%). FTIR spectroscopy identified 2 samples that contained etizolam on confirmatory testing, which were negative on test strips.

NPS benzodiazepines in confirmatory-only subsample

During the study period, 383 samples which did not undergo benzodiazepine strip testing were sent for confirmatory analysis. Ten (2.6%) of these samples returned positive results for NPS benzodiazepines (nine contained etizolam, and one contained both etizolam and flualprazolam). Of note, each of the ten samples also contained a high-potency synthetic opioid, with three containing fentanyl, four containing carfentanil, two containing both fentanyl and carfentanil, and one containing fentanyl and furanyl UF-17. FTIR spectroscopy results on these ten samples were all negative for NPS benzodiazepines. Taken with those samples which also underwent point-of-care testing for benzodiazepines, the total number of samples with confirmed NPS benzodiazepines (n = 34), represents 6.3% of the 543 samples sent for confirmatory testing during the study period.

Discussion

While benzodiazepines have been documented as adulterants in unregulated opioids on rare occasions in the past (Broséus, Gentile & Esseiva, 2016), to our knowledge this is the first report of a sizeable outbreak of NPS benzodiazepines in the context of a continuing opioid overdose epidemic, due to adulteration of the unregulated drug market with fentanyl and other highly potent synthetic opioids. This study found an overall positivity of NPS benzodiazepine occurrence amongst confirmatory samples obtained at harm reduction-based drug checking services of 6.3% over a 15-month period. Results of the present study are consistent with earlier surveillance data indicating the emergence of multiple NPS benzodiazepines as unanticipated adulterants in the unregulated drug supply in Vancouver since mid-2018 (Lifelabs, 2019; Marmel & Lysyshyn, 2019).

Reasons for the emergence of NPS benzodiazepines as potential adulterants in unregulated drug markets are unclear. Multiple motivations have been posited for purposeful co-ingestion of benzodiazepines with opioids, where benzodiazepines may serve to 'heighten' or prolong the 'high' associated with opioid use, to cope with opioid withdrawal symptoms, or to control the 'descent phase' of opioid intoxication. Where people who use opioids also use other substances, benzodiazepines may be ingested to balance side effects of these (e.g. stimulants), augment intoxication (e.g. alcohol), or incidentally as self-medication for co-occurring negative affective states or psychiatric illness experienced by people who use opioids (EMCDDA, 2018; Manchester et al., 2018; Zawilska & Wojcieszak, 2019). It may also be prudent to consider the role of drug market economics, with cheap, easily available NPS benzodiazepines adulterating opioids for the perception of similar effects at lower total costs to suppliers.

Consistent with analysis of recent local public health data (Marmel & Lysyshyn, 2019), as well as emerging regional reports of complex overdoses, characterized by prolonged loss of consciousness and lack of responsiveness to naloxone administration, suspicious for opioid-benzodiazepine co-ingestion (Hennig, 2019; Vescera, 2019a; Woo, 2019), a sizeable proportion of samples thought to contain opioids in the current study were confirmed to contain NPS benzodiazepines (15.8%). A majority of the samples confirmed to contain NPS benzodiazepines also contained high-potency opioids such as fentanyl or carfentanil (70.1%).

The risks of harm associated with combined opioid-benzodiazepine ingestion relate to their separate but synergistic mechanisms of action which may result in profound sedation and respiratory depression, potentially causing death (Jones et al., 2012; Zawilska & Wojcieszak, 2019). The described constellation of prolonged, non-responsive loss of consciousness with accompanying memory loss places individuals at elevated risk, with some reports of associated theft and sexual assault during overdose (Hennig, 2019). Unique to people with opioid use disorder (OUD) seeking opioid agonist therapy (OAT), concerns have also been raised about the potential for benzodiazepine toxicity to interfere with therapeutic OAT dosing, as providers may mistakenly attribute drowsiness to supratherapeutic doses of methadone, buprenorphine, or slow-release oral morphine (Lysyshyn & Ahamad, 2019). This could conceivably lead to undertreatment of OUD, increasing risk of unregulated opioid use and associated harms. Additionally, anecdotal evidence suggests that persons seeking substance use detoxification and recovery services may face unanticipated barriers to care (and consequent increased risks of harm), in settings where positive benzodiazepine test results preclude access. Use of NPS benzodiazepines may also include harms secondary to the lack of rigorous clinical safety testing that licensed pharmaceuticals are subject to (Manchester et al., 2018). As more NPS benzodiazepines emerge, further unanticipated harms may be attributable to metabolites which remain active and for longer durations (Manchester et al., 2018; World Health Organization, October, 2019b).

Harm reduction efforts targeted specifically to NPS benzodiazepines have not been fully explored. For example, while the benefits of Take Home Naloxone (THN) programs in reducing opioid-related mortality are well-established (Irvine et al., 2018), the role of GABAa antagonist flumazenil in NPS benzodiazepine overdose is unclear (Bäckberg et al., 2019; Bohnenberger & Liu, 2019; Carpenter et al., 2019). However, it is unlikely that flumazenil can play a role similar to that of THN in the context of overdoses involving NPS benzodiazepines. This is primarily due to the increased risk of adverse effects following administration of flumazenil such as seizure - a risk which is heightened by co-ingestion of pro-convulsants, chronic benzodiazepine use, and underlying seizure disorder (Bohnenberger & Liu, 2019; Sivilotti, 2016). Additionally, flumazenil's intravenous route of administration likely precludes it from being a point-of-care harm reduction tool.

While the presence of NPS benzodiazepines has consistently been rising (Carpenter et al., 2019; EMCDDA, 2018), the potential role of these substances as adulterants, exemplified in the described outbreak, represents a new phenomenon, and should remain at the fore of consideration for public health, harm reduction, and care providers. Owing to the increased risk associated with combined opioid-benzodiazepine toxicity, employment of harm reduction strategies for people who use drugs (PWUD) such as not using alone, using a test dose, and having naloxone readily available remain of great importance (BC Centre for Disease Control Harm Reduction Programs, 2020). As NPS benzodiazepines continue to emerge in unregulated drug markets, municipal, healthcare, and community advocacy leaders have pointed to 'safer supply' initiatives as one means of mitigating some of the potential associated harms (Vescera, 2019b).

Drug checking has also previously been posited as one possible method to mitigate harms associated with an unregulated and evolving drug market and associated toxicity with synthetic opioids

(Karamouzian et al., 2018; Laing, Tupper & Fairbairn, 2018). Pilot drug checking efforts suggest participants may be more likely to decrease dosage of use if results were positive for fentanyl adulteration, thus potentially reducing overdose risk (Karamouzian et al., 2018; Krieger et al., 2018; Peiper et al., 2019). However, further research into the applicable value of various drug checking services is advisable, as deterrents to using these services have been identified by PWUD in marginalized settings including having to give up some amount of drug for testing, time to complete testing, ambivalence following positive results, and prioritized trust in the relationship with established drug dealers (Bardwell, Boyd, Arredondo, McNeil & Kerr, 2019; Bardwell, Boyd, Tupper and Kerr, 2019).

Limitations

While this study offers insight into a new and concerning outbreak of NPS benzodiazepine adulteration in Vancouver's unregulated drug supply, it has some limitations. First, as drug checking services are entirely voluntary, these findings may not be representative of the broader unregulated market. Similarly, persons accessing harm reduction services may differ systematically in their drug selection and use patterns, further undermining generalizability. Second, although the relatively small subsample sizes may under- or over-estimate the true false positive and false negative rates associated with each point-of-care testing technique, the high rates found in this study highlight concerns about the accuracy of current point-of-care drug checking methods for NPS benzodiazepines. Specifically, point-of-care immunoassay-based tests (e.g. test strips) for benzodiazepines have been designed to test urine for standard metabolites of common benzodiazepines such as oxazepam and nordiazepam (Moeller, Kissack, Atayee & Lee, 2017), potentially producing false negatives when samples containing NPS benzodiazepines or other specimen types are used (i.e. diluted drug samples). Similarly, as the benzodiazepine test strips in this study are not specifically designed to detect NPS benzodiazepines, any associated accuracy data for detection of these substances should be approached with care. However, several reviews have cited good cross-reactivity for NPS benzodiazepines on standard immunoassay screens (Manchester et al., 2018; Marin & van Wijk, 2019; Shapiro et al., 2020). In addition, etizolam is reportedly not soluble in water (World Health Organization, October 2019a), with others reporting difficulty dissolving any of the NPS benzodiazepines identified in this study sample without the use of sonic agitation and vortexing (Shapiro et al., 2019), which could lead to false negative results. FTIR technologies are limited in their ability to detect small quantities of target substance, particularly in combined mixtures (Tobias et al., 2020), which may account in part for the relatively low detection rates in our study. That said, confirmatory quantitative techniques were undertaken to address potential limitations of point-of-care technologies, underscoring the essential role of confirmatory methods of analysis in the complete understanding of drug market trends with respect to the emergence of NPS benzodiazepines. However, as noted above, the composition of NPS benzodiazepines are changing rapidly, which may itself result in a greater chance that the newest of these substances may not be detected in targeted assays used in confirmatory analyses.

Conclusions

This study presents findings of the first drug checking initiative specifically responding to public health concerns related to an outbreak of NPS benzodiazepines in the Vancouver-area unregulated drug supply. The identification of NPS benzodiazepines in the drug supply can help raise alarms in the context of rapidly shifting drug markets, and offers supportive data in corroboration of community-based reports of clusters of atypical overdoses. The advent of NPS adulteration of high-potency synthetic opioids is of particular concern. As we consider the multifactorial etiology of the current North American opioid epidemic, we must remain vigilant to the myriad potential harms that may still arise, given the unregulated and unpredictable nature of unregulated drug supplies. Results from this study underline that, while point-of-care drug checking technologies may provide some information pertaining to novel or harmful constituents in shifting unregulated drug markets, the use of these technologies may be limited in their ability to reliably detect NPS benzodiazepines, and that continued combined use of confirmatory methods is required in order to mitigate potential harm that might result from over-reliance on less accurate point-of-care methods. Given these noted limitations, and the unclear establishment of direct benefit to people accessing drug checking services at point-of-care, such limitations should be reviewed with service users, and emphasis placed on consistent implementation of other harm reduction techniques. Further research into the accuracy and utility of point-of-care methods for reliable detection of NPS benzodiazepines is warranted, as is the impact of point-of-care results on the drug taking behaviours of people accessing these services. In this fashion, drug checking may still play a valuable individual and public health role, potentially supporting informed decision-making for PWUD around dose adjustments and other harm reduction practices, in addition to the generation of more robust public health surveillance data which may contribute to greater health policy responsivity and focus in efforts to prevent further drug-related harms. Ongoing drug checking efforts and monitoring will be indispensable in determining whether the presence of NPS benzodiazepines in local drug markets represents a transient anomaly, or a more ominous trend.

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Declaration of Competing Interest

All authors declare no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.drugpo.2021.103169.

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