Drug and Alcohol Review

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Understanding the Emergence and Impact of Novel Synthetic Opioids and How to Reduce Associated Harms

The Detection of Novel Nitazene-Class Opioids in Unregulated Drug Markets in Canada

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ABSTRACT

Introduction: Nitazenes, a highly potent class of synthetic opioids, have emerged in Canadian unregulated drug markets. We report on their presence and composition, along with overdose trends.

Methods: Samples were obtained from January 2019 to July 2024 from two drug checking services (Toronto's Drug Checking Service (TDCS) and drug checking partners affiliated with the British Columbia Centre on Substance Use (BCCSU)) and national police seizure data from Health Canada's Drug Analysis Service (HC-DAS). Overdose data were retrieved from the Office of the Chief Coroner for Ontario from January 2019 to December 2022 and included deaths in which a nitazene was present. We conducted Cochran-Armitage test and logistic regression trend analyses to assess trends over time.

Results: Of 668,486 samples, 4074 (0.61%) contained nitazenes: 532 from drug checking services (489 (0.07%) from TDCS; 43 (0.01%) from BCCSU) and 3542 (0.53%) from police seizures (HC-DAS). Twelve unique nitazenes were detected. Common co-occurring drugs included caffeine, benzodiazepine-related drugs and fentanyl and fentanyl-related drugs. Nitazenes were expected in 3 (< 1%) of 532 drug checking samples. Of 14,103 samples from TDCS, 886 (6.28%) were associated with an overdose, among which 76 (8.58%) contained nitazenes. Of 8719 opioid deaths in Ontario and 1803 in Toronto, nitazenes were present in 79 (0.91%) and 33 (1.83%), respectively. Significant trends ($p < 0.001$) in nitazene detections and overdoses in Toronto, as well as nitazene detections across Canada, were observed, increasing prior to and peaking in January–March 2022, followed by reductions.

Discussion and Conclusions: The presence of nitazenes in Canada requires enhanced overdose prevention responses and drug market monitoring.

Key Point Summary

- Nitazenes are circulating across Canada, indicating a concerning trend that suggests enhanced harm reduction responses, health care provision and overdose prevention given their high potency, unexpected detection and co-occurrence with other central nervous system depressants.
- Diverse nitazenes were detected in samples of unregulated drugs across multiple Canadian jurisdictions. Common co-detected drugs among samples containing nitazenes included caffeine, benzodiazepine-related drugs, as well as fentanyl and fentanyl-related drugs.
- While we did not establish a direct causal relationship between nitazenes and overdose deaths, we did observe similar patterns of increasing nitazene detections and overdoses over time.
- This demonstrates the dynamism of Canada's unregulated drug markets and the need for a comprehensive and public health-oriented drug market monitoring approach.

1 | Introduction

The rising incidence of fatal opioid overdose in Canada is a public health crisis [1, 2]. Between January 2019 and March 2024, Canada reported 36,182 apparent opioid toxicity deaths,[1] with the crude rate per 100,000 increasing from 9.9 in 2019 to 21.1 in 2023 [3, 4]. This surge is largely attributed to the contamination of unregulated drug markets with high potency and toxic compounds, particularly fentanyl and its analogues [5].

Among these are novel and potent synthetic opioids of the benzimidazole subclass (herein referred to as 'nitazenes') [6–8]. Synthesised in the 1950s as potential analgesics, nitazenes were never marketed due to their potency and potential for dependence [9]. The first marked wave of nitazene detections in unregulated drug markets occurred in 2019 when isotonitazene was identified in Europe, the United States (US) and Canada [10]. Since then, nitazenes have been detected in other unregulated drug markets, including in Brazil [11] and the United Kingdom [10]. A growing number of nitazenes have been internationally scheduled [12], and in Canada, nitazenes are classified as Schedule I substances in the *Controlled Drugs and Substances Act* [13]. Given their similar or higher affinity for mu-opioid receptors than other potent opioids, nitazenes can contribute to life-threatening overdose potential [8], particularly given that they are as much as 12 times as potent as fentanyl [14]. Considering their increasing prevalence and contribution to overdose risk, understanding market patterns of nitazenes is essential to effective public health strategies for overdose prevention.

Nitazenes have been identified by drug checking services (DCS) in British Columbia and Ontario, the two Canadian provinces most significantly impacted by overdose mortality [15]. DCS provide people who use drugs with information on the chemical composition of their drug samples to facilitate more informed decision-making, while simultaneously providing insight into the unregulated drug supply by aggregating data on the composition of drug samples [16]. Nitazenes have also been detected in drug seizures by law enforcement across Canada [17]. Our study aimed to report market patterns involving nitazenes in unregulated drug markets across Canadian settings, including their presence and composition, co-occurring drugs, discrepancies between expected and actual contents and overdose trends.

2 | Methods

Data for this study were collected from 1 January 2019 to 31 July 2024. Drug sample data were provided by Toronto's Drug Checking Service (TDCS), Health Canada's Drug Analysis Service (HC-DAS) and the British Columbia Centre on Substance Use (BCCSU). Data from the Office of the Chief Coroner (OCC) for Ontario were included to investigate the presence of nitazenes in opioid toxicity deaths. Descriptions of datasets, including the scope of their geographic region, are outlined below.

TDCS: A full description of the service has been previously reported, as has the protocol and rationale for its evaluation [18]. Data were collected from 10 October 2019, the service's launch date, to 30 June 2024. Results were obtained from chemical analyses of substance (i.e., 10 mg of powder, crystals, rocks or a pill, blotter or a small amount of liquid) or used drug equipment (i.e., cooker, filter or leftover liquid from a syringe) samples voluntarily and anonymously submitted in-person and free of charge at community collection sites. Samples were analysed with in-lab developed protocols for targeted and/or nontargeted drug identification using high performance liquid chromatography-high resolution mass spectrometry and gas chromatography–mass spectrometry techniques at clinical laboratories within St. Michael's Hospital and the Centre for Addiction and Mental Health. These technologies provide precise information about which drugs are found, as well as information regarding drug concentration. Self-reported survey data on previous nonfatal overdoses and drug expectation from service users at the time of sample collection were also included. Participation in the survey was voluntary among service users of TDCS, and respondents were not compensated. For this study, overdoses were defined by survey responses at the time of sample collection to TDCS indicating that a sample was previously associated with an overdose. Nitazene overdoses were similarly defined as samples reported to be associated with an overdose as part of survey responses during sample collection for TDCS, and in which any nitazenes were detected by TDCS.

2.1 | HC-DAS: Data From Samples Submitted by Law Enforcement Officials Across Canada

HC-DAS operates laboratories across Canada that analyse suspected illegal drugs seized by Canadian law enforcement agencies and samples submitted by public health partners. For the purposes of this study, only data from seized samples are included in results from HC-DAS. HC-DAS uses advanced and

standardised analytical methods to analyse exhibits that are submitted to its laboratories. All HC-DAS laboratories are accredited (International Organization for Standardization 17,025) and every method used by Health Canada is recognised internationally as meeting or exceeding technical requirements for drug analysis [19]. Multiple analytical methods, such as liquid extraction and liquid or gas chromatography, are often needed to confirm the presence of controlled substances. HC-DAS performs qualitative analysis for all exhibits submitted to determine whether controlled substances are present [19]. Analysis data for drug samples was retrieved from Health Canada's Laboratory Information Management System with the date of detection aggregated at the monthly level. Data are complemented by qualitative descriptions of samples provided by laboratory analysts, which include information regarding the sample's colour, texture and form (e.g., pill, powder, blotter, etc.) and any distinguishing features.

2.2 | BCCSU: Data From Drug Checking Samples Across British Columbia

Data were collected from samples submitted in-person and by mail to BCCSU's affiliated drug checking partners within the province of British Columbia. All sample types (i.e., substances, used drug equipment) and drug categories were eligible. Self-reported drug expectation data were also collected for samples. A nonrandom, convenience subset of samples, initially analysed through point-of-care primarily using Fourier-transform infrared spectrometry and immunoassay strips, were submitted for confirmatory analysis through HC-DAS laboratories. This subset included only samples submitted as substances, specifically those suspected to contain fentanyl analogues or benzodiazepines, without a match in the Fourier-transform infrared library, complex mixtures, new psychoactive substances, and any 'typical' samples for ongoing evaluation and general surveillance (e.g., typical samples refer to samples that are most commonly detected in British Columbia, particularly those that co-present with fentanyl and benzodiazepines) [20].

2.3 | OCC for Ontario: Overdose Mortality Data Across Ontario

The OCC conducts death investigations to ensure every death is thoroughly examined; fatal overdose data from the OCC are therefore generated from decedent files that are administratively captured as part of routine death investigations. Data were obtained as part of a data sharing agreement with the OCC covering accidental opioid toxicity deaths from 1 January 2019 to 31 December 2022. OCC toxicology reports identified substances detected at the time of death. For this study, opioid overdose deaths were defined as deaths in which OCC toxicology reports identified any opioid as present at the time of death, including cases where opioids were and were not attributed to death. Nitazene deaths were similarly defined as opioid deaths in which OCC toxicology reports identified any nitazene as present at the time of death, including cases where nitazenes were and were not attributed to death. Deaths in Toronto, extracted from the broader Ontario dataset, include the location where the death occurred.

2.4 | Data Analysis

Findings were stratified by data source, and descriptive statistics were generated on market patterns involving nitazenes including their presence and composition (TDCS, HC-DAS and BCCSU), co-occurring drugs (TDCS, HC-DAS and BCCSU), discrepancies between expected and actual contents (TDCS and BCCSU), as well as nitazene overdoses (TDCS) and deaths (OCC). Nitazene detections from TDCS and BCCSU were grouped into 3-month intervals to address statistical issues related to months with zero nitazene detections. The first 3-month interval was 2020/11–2021/01, and the final 3-month interval was 2024/05–2024/07. We calculated the proportions of samples with nitazenes detected, along with 95% confidence intervals (CI), and converted the proportions into percentages. Quarterly TDCS self-nonfatal overdose and OCC administratively captured fatal overdose data, as well as self-reported nonfatal overdose data for specific nitazenes from TDCS, were suppressed when cell counts were less than six to protect client anonymity, to protect patient privacy and comply with provincial legislation [21]. The Cochran-Armitage test, a sensitive test for trend detection [22], was performed to evaluate whether there was a significant difference in the proportions of nitazene detections and overdoses between quarters for TDCS data, and in the proportions of nitazene detections between quarters for HC-DAS data. The results of the Cochran-Armitage test did not detect significant differences, so we opted to employ nonlinear logistic regression to examine the relationship between time and nitazene detections and overdoses [23]. The base model formula was specific as follows:

$$\text{logit}(P(Y=1|\,t)) = \text{In}\left(\frac{n(t)}{1-n(t)}\right) = \beta_o + \beta_1 t + \beta_2 t^2 + \beta_3 t^3$$

where $pi(T) = P(Y=1|T)$ is the probability that the substance is detected at time t; beta_0 is the intercept and beta_1, beta_2 and beta_3 are the regression coefficients for the linear quadratic and cubic terms, respectively. We tested for curvilinear relationships using a sequential model-building approach. We first entered the linear time variable, followed by the quadratic term, and finally the cubic term. An a priori significance level of alpha = 0.05 was used to determine the inclusion of higher-order terms. Marginal effect analysis was used to assess the effect of time on the predicted probability of nitazene detection and overdoses, with the significance level set at 0.05 [24]. To interpret the results of the nonlinear logistic regression model, we calculated Average Marginal Effects (AME). This was done because of the nonlinear nature of the cubic model and because the effect of time on the predicted probability is not constant. While regression techniques generate estimates of probabilities related to outcomes, AMEs provide a single summary measure by estimating the marginal effect at each observed time point and averaging these effects. This allowed us to present a more robust and representative summary of the overall time effect compared to the marginal effect at the mean or predicted probabilities [25]. Trend analysis was not performed on BCCSU data due to the nonrandom nature of the sampled data. Trend analysis was not feasible on OCC data due to a small sample size of nitazene deaths. All analyses were done using R V4.4.1. Ethics approval was obtained via the Unity Health Toronto Research Ethics Board.

3 | Results

From 1 January 2019 to 30 July 2024, a total of 668,486 samples were analysed across the three agencies: 14,103 (2.11%) by TDCS; 533,968 (79.88%) by HC-DAS and 120,415 (18.01%) by BCCSU. Of these, 4074 samples (0.61%) contained nitazenes: 489 (0.07%) by TDCS; 3542 (0.53%) by HC-DAS; and 43 (0.01%) by BCCSU. Additionally, a total of 886 TDCS samples (6.28%) were associated with an overdose, among which 76 (8.58%) contained nitazenes. Our sequential testing process revealed that the cubic model provided the best fit. The results of this process for the HC-DAS data are exemplary: the transition from a linear to a cubic model resulted in a substantial reduction in the Akaike Information Criterion, falling from 1643.3 (linear) to 960.3 (quadratic), and finally to 783.5 (cubic). The downward trend in Akaike Information Criterion, alongside our a priori significance testing, confirms that the cubic model provides the best fit for the data. Similar results were generated for all other data sources. Figure 1 presents percentages and 95% CIs per quarter for nitazene-containing samples among all samples for each agency, and nitazene overdoses among all reported overdoses for TDCS.

3.1 | TDCS

During the study period, TDCS analysed 14,103 samples. The majority were submitted as drugs ($n = 10{,}787$; 76.49%), followed by used drug equipment ($n = 3316$; 23.51%). Nearly half of samples ($n = 6943$; 49.23%) were expected to be opioids, most often fentanyl ($n = 6286$; 90.54%). Of all samples, 886 (6.28%) were reported to be associated with an overdose. Nitazenes were detected in 489 (3.47%) samples. Of those, the majority were submitted as drugs ($n = 313$; 64.01%), while the remainder were used drug equipment ($n = 176$; 35.99%). Among samples reported to be associated with an overdose, 76 (8.58%) contained nitazenes. Nitazenes were among the top five drug groups detected in samples reported to be associated with an overdose, which also included fentanyl ($n = 696$; 78.56%), benzodiazepine-related drugs ($n = 519$; 58.58%), fentanyl-related drugs ($n = 272$; 30.7%) and veterinary tranquillisers ($n = 102$; 11.51%).

Trends in nitazene detections and overdoses show a similar pattern from the beginning of the study period to December 2022 (the most recent date for which overdose mortality data were available). The first nitazene detection and nitazene overdose occurred in February 2021, as shown in Figure 1. The Cochran-Armitage test indicated a significant trend in both nitazene detections and overdoses over time ($p < 0.001$). The logistic regression model also indicated that the cubic term was statistically significant ($p < 0.0001$), and it was therefore retained as our final model. a significant cubic relationship between time and nitazene detections as well as nitazene overdoses ($p < 0.001$), as shown in Figure 1. AME analysis assessed the changes in the probability of nitazene detection and overdose over time. From Q1 2021 to Q4 2021, the probability of detecting nitazenes steadily increased (AME = 0.02; 95% CI 0.01, 0.02). This trend peaked in Q1 2022 and then declined (AME = −0.002; 95% CI −0.004, −0.0002) until the end of the study. From Q1 2021 to Q3 2021, the probability of nitazene overdose steadily increased (AME = 0.07; 95% CI 0.04, 0.12). This trend peaked in Q4 2021 and then declined (AME = −0.007; 95% CI −0.01, −0.001) until the end of the study. The trend in nitazene detections precedes the trend in nitazene overdoses by approximately one-quarter.

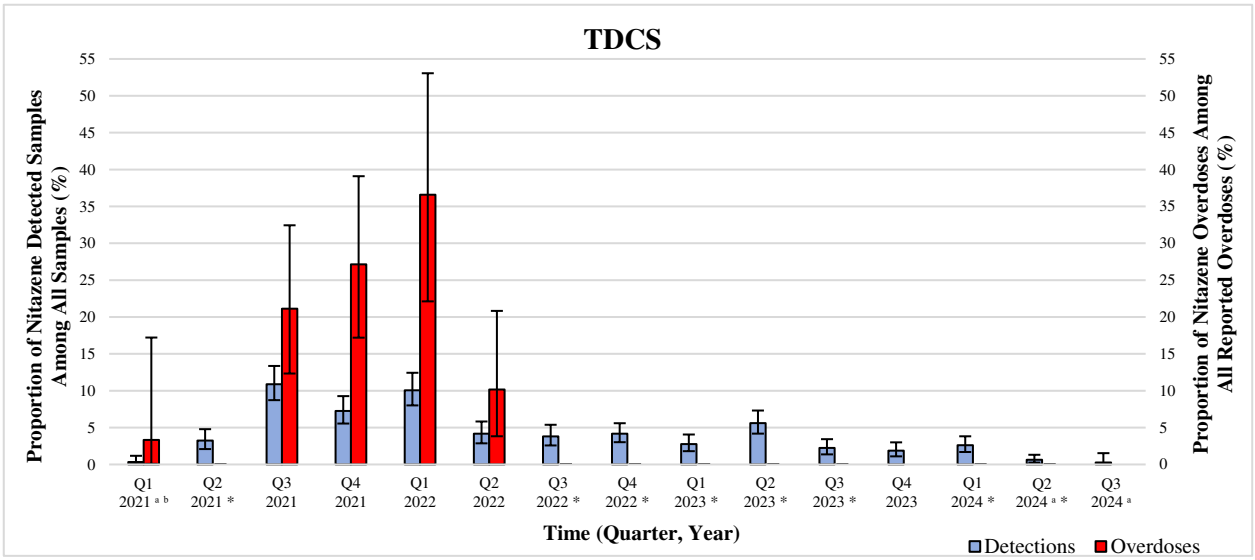
The majority of nitazene-containing samples ($n = 453$; 92.64%) were expected to be an opioid and only two (0.44%) of such samples were specifically expected to be a nitazene. Fentanyl was the most commonly expected opioid in such samples ($n = 417$; 92.05%), followed by oxycodone ($n = 18$; 3.98%), carfentanil ($n = 4$; 0.88%), hydromorphone ($n = 4$; 0.88%), heroin ($n = 3$; 0.66%), hydrocodone ($n = 2$; 0.44%), oxymorphone ($n = 1$; 0.22%), 'down' (i.e., a sample of unknown opioids [$n = 1$; 0.22%]) and methadone ($n = 1$; 0.22%). Other than expected opioids, 7 (1.43%) nitazene-containing samples were expected to be 3,4-methylenedioxymethamphetamine (MDMA), one (0.2%) was expected to be cocaine, and one (0.2%) was expected to be crack cocaine. Of the remaining nitazene-containing samples, seven (1.43%) were expected to be a combination of psychoactive substances and 20 (4.1%) had no expectation reported.

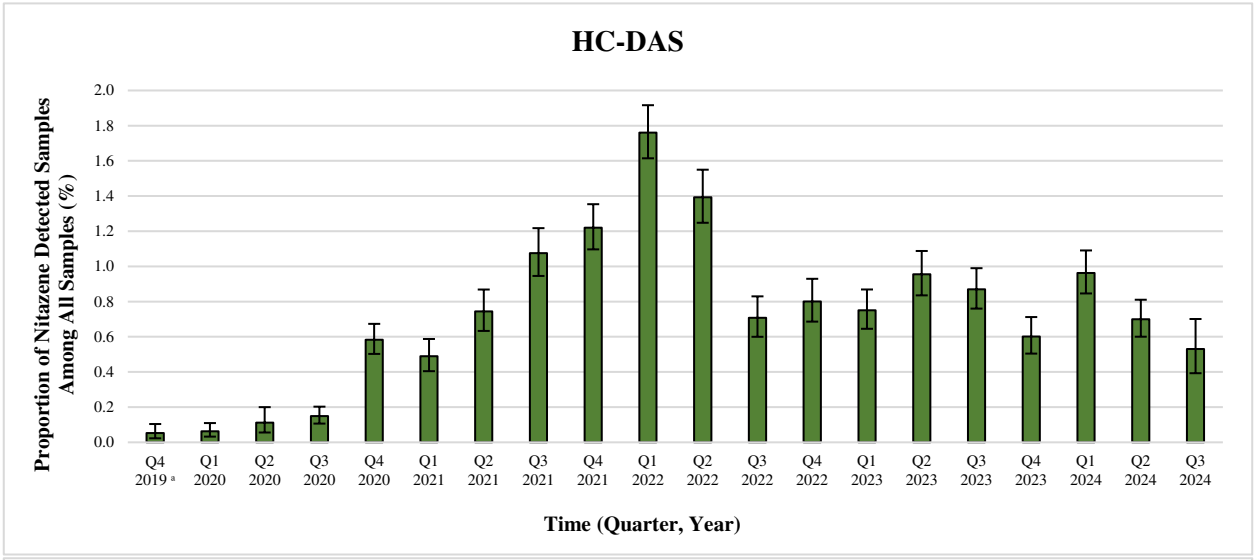
One or more nitazenes were detected in 13.91% ($n = 68$) of nitazene-containing samples. Ten different types of nitazenes were identified, totalling 574 nitazene detections across 489 samples containing nitazenes. The number of samples containing specific nitazenes, date of first identification, sample type, as well as reported expectation and overdose association upon submission, are presented in Table 1. In samples containing nitazene, 36% ($n = 176$) did not contain other substances. In nitazene-containing samples with other compounds detected (64%; $n = 313$), the most common were benzodiazepine-related drugs ($n = 188$; 60.06%), caffeine ($n = 234$; 74.76%), fentanyl ($n = 215$; 68.69%), fentanyl-related drugs ($n = 68$; 21.73%), xylazine ($n = 33$; 10.54%) and other opioid-related drugs ($n = 4$; 1.28%).

3.2 | HC-DAS

During the study period, HC-DAS laboratories analysed 533,968 samples, with a relatively even annual distribution. Samples were submitted in Ontario ($n = 187{,}513$; 35.12%), Quebec ($n = 159{,}352$; 29.84%), British Columbia ($n = 73{,}437$; 13.75%), Alberta ($n = 68{,}506$; 12.83%), Manitoba ($n = 14{,}531$; 2.72%), New Brunswick ($n = 9794$; 1.83%), Saskatchewan ($n = 9015$; 1.69%), Nova Scotia ($n = 6513$; 1.22%), Newfoundland and Labrador ($n = 2844$; 0.53%), Prince Edward Island ($n = 1112$; 0.21%), the Northwest Territories ($n = 640$; 0.12%), the Yukon ($n = 622$; 0.12%) and Nunavut ($n = 89$; 0.02%).

Nitazenes were detected in 3542 (0.66%) samples. Samples were primarily described as powders ($n = 1841$; 51.98%) or tablets ($n = 1615$; 45.6%). The first nitazene detection by HC-DAS in Canada occurred in November 2019, with two samples in Quebec. The quarterly percentages of nitazene detections in all samples are illustrated in Figure 1. The Cochran-Armitage test indicated the proportions of nitazene detections were different over time ($p < 0.001$). The logistic regression model indicated a significant cubic relationship between time and nitazene detections ($p < 0.001$), as shown in Figure 1. From Q4 2019 to Q4





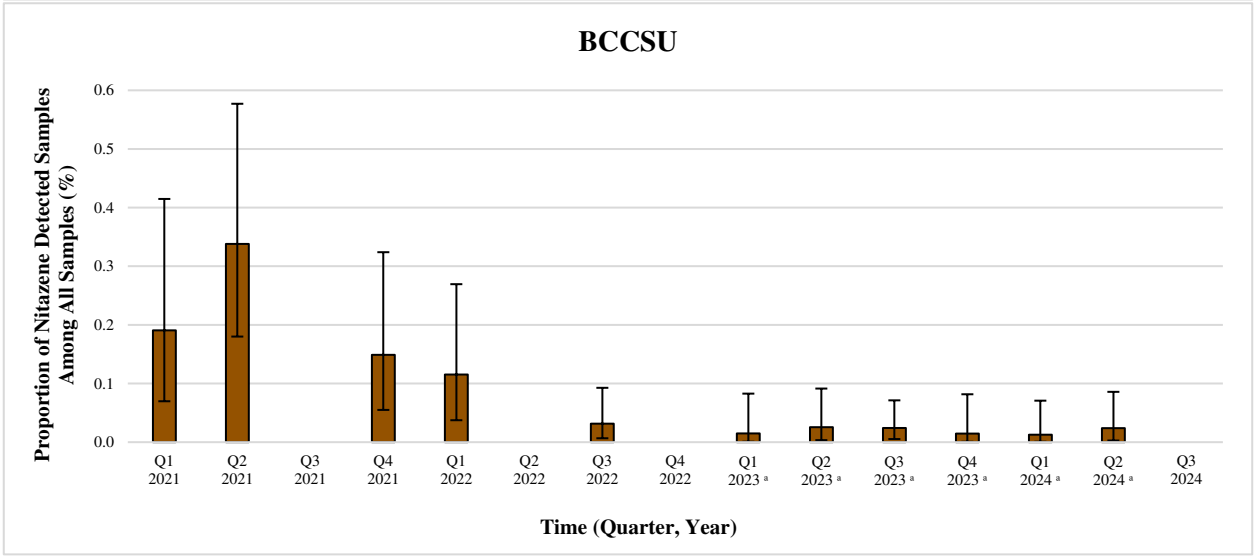


FIGURE 1 | Legend on next page.

FIGURE 1 | Proportions and 95% confidence intervals (CI) of nitazene detections among all samples per agency, and nitazene overdoses among all reported overdoses for TDCS, over time from the date of first detection. The y-axis varies per graph given varying distributions across data sources. In each graph, 'all samples' refers exclusively to the samples checked by the respective agency and not the total samples checked across the study. For TDCS, 'all reported overdoses' refers to samples reported to be associated with an overdose as part of survey responses during sample collection and 'nitazene overdoses' refers to samples reported to be associated with an overdose as part of survey responses during sample collection and in which any nitazenes were detected. Q1, quarter 1; Q2, quarter 2; Q3, quarter 3; Q4, quarter 4. [a]The lower 95% CI for nitazene detected samples approaches but does not reach zero. [b]The lower 95% CI for nitazene overdoses approaches but does not reach zero. *Nitazene overdose data are suppressed because of small cell size. BCCSU, British Columbia Centre on Substance Use; HC-DAS, Health Canada's Drug Analysis Service; Q1, quarter 1; Q2, quarter 2; Q3, quarter 3; Q4, quarter 4; TDCS, Toronto's Drug Checking Service.

2021, the probability of detecting nitazene steadily increased (AME = 0.001; 95% CI 0.001, 0.002). This trend peaked in Q1 2022 and then declined (AME = −0.0003; 95% CI −0.0005, −0.0002) until Q4 2023.

A total of 12 types of nitazenes were identified, with 8.47% ($n = 300$) of nitazene-detected samples containing more than one type. The number of samples per nitazene detected overall and per province, as well as the month and province of first identification, are presented in Table 2. Data acquired did not include the number of samples exclusively containing nitazenes. However, common co-detected drugs among samples containing nitazenes were caffeine ($n = 1775$; 50.11%), fentanyl ($n = 1419$; 40.06%), dimethyl sulfone ($n = 897$; 25.32%), benzodiazepine-related drugs including etizolam ($n = 571$; 16.12%), flubromazepam ($n = 244$; 6.89%), flualprazolam ($n = 241$; 6.8%) and bromazolam ($n = 219$; 6.18%), as well as xylazine ($n = 193$; 5.45%) and para-fluorofentanyl ($n = 187$; 5.28%).

3.3 | BCCSU

During the study period, BCCSU and affiliated partners analysed 120,415 samples. Of these, 2340 samples were forwarded to HC-DAS laboratories for confirmatory analysis. Nitazenes were detected in 43 samples (0.04%), with the first nitazene detected in January 2021. The percentage of nitazene detections was highest in Q2 2021 after which detections decreased, and there were no nitazene detections in Q3 2021, Q2 2022 and Q4 2022, as depicted in Figure 1.

Only one (2.33%) of the nitazene-containing samples among those that were sent for confirmatory analysis was expected to be a nitazene. The most expected drug on submission was 'down' ($n = 16$; 37.21%), followed by fentanyl ($n = 13$; 30.23%). Samples were also commonly submitted as unknown substances ($n = 10$; 23.26%), with a smaller percentage expected to be diazepam ($n = 2$; 4.65%) or heroin ($n = 1$; 2.33%). A total of six types of nitazenes were identified, and more than one nitazene was detected in 4.65% ($n = 2$) of nitazene-containing samples. The number of samples per nitazene detected, date of first identification, reported expectation and substance appearance are presented in Table 3. Among 43 samples containing nitazenes, 21 (48.8%) exclusively contained nitazenes. Co-detected drugs among samples containing nitazenes including caffeine ($n = 17$; 39.53%), benzodiazepine-related drugs ($n = 15$; 34.88%) and fentanyl ($n = 15$; 34.88%), diphenhydramine ($n = 2$; 4.65%), phenacetin ($n = 1$; 2.33%), methamphetamine ($n = 1$; 2.33%) and cocaine ($n = 1$; 2.33%).

3.4 | OCC for Ontario

From 1 January 2019 to 31 December 2022, there were 8719 opioid deaths in Ontario, and 1803 (20.68%) of these occurred in Toronto. Deaths in which nitazenes were present (hereafter referred to as 'nitazene deaths') in Ontario accounted for 79 (0.91%) of the provincial opioid deaths, and nitazene deaths in Toronto accounted for 33 (1.83%) of the city's opioid deaths. Figure 2 presents percentages and 95% CIs per quarter for nitazene deaths among all opioid deaths in both Toronto and Ontario.

After the first Ontario nitazene death in Q3 2020, nitazene deaths were not reported again until Q2 2021, as shown in Figure 2. The largest percentage of Ontario nitazene deaths occurred in Q1 2022 ($n = 25$; 4.4%). Aside from this quarter, Q3 2021 ($n = 20$; 3.07%), Q4 2021 ($n = 17$; 2.63%) and Q2 2022 ($n = 6$; 1.18%), the percentage of nitazene deaths per quarter remained below 1%. Among the Ontario nitazene deaths, 33 occurred in Toronto (41.77%). While the first Toronto nitazene death was in 2021, the largest percentage of deaths also occurred in Q1 2022 ($n = 9$; 8.82%), followed by Q3 2021 ($n = 9$; 6.87%), Q4 2021 ($n = 8$; 5.44%) and Q2 2022 ($n =$ suppressed). The remaining percentage of nitazene deaths per quarter fell below 2%. These patterns in Ontario and Toronto nitazene deaths aligns with the trend in TDCS nitazene detections and overdoses, the trend in HC-DAS nitazene detections across Canada, and the pattern of HC-DAS nitazene detections in Ontario, where each increased until peaking in Q1 2022, after which they decreased until the end of the study.

4 | Discussion

While fentanyl and fentanyl-related drugs continue to drive overdose mortality in Canada, the prevalence of nitazenes suggests a continuing trend toward unexpected opioids with higher potency and serious implications for overdose prevention efforts [26]. The majority of nitazenes are highly potent, with some compounds, such as etonitazepyne, exhibiting potencies far greater than fentanyl [27, 28]. Evidence on the effectiveness of opioid receptor antagonists, such as naloxone, against high potency nitazene binding is preliminary, and therefore there is uncertainty around the specific dosage requirements in the case of nitazene overdoses [27], though Isoardi et al. found that standard naloxone dosage regimens were effective in most cases in Australian clinical settings [14]. One study found that patients required varying, often high doses of naloxone, with some responding to 2 mg, others to 8 mg, but some dying after 6 mg was administered (though in

TABLE 1 | Toronto's Drug Checking Service nitazenes detected from 12 February 2021 to 30 June 2024 ($n = 489$).

	Nitazene	Date first identified (year-mm-dd)	n (% of $n = 489$)	Sample type	Expected drugs	Reported overdoses
1	Metonitazene	2021-05-31	231 (47.24)	Substance (160) Equipment (71)	Carfentanil (3) Crack cocaine (1) 'Don't know' (7) Fentanyl (200) Hydrocodone (1) Hydromorphone (3) MDMA (2) Methadone (1) Metonitazene (1) Oxycodone (96) Polysubstance (3)	23
2	Isotonitazene/ protonitazene[a]	2021-02-12	198 (40.49)	Substance (104) Equipment (94)	Carfentanil (1) 'Don't know' (12) Down (1) Hydrocodone (1) Fentanyl (164) Heroin (4) MDMA (5) Nitazene (1) Oxycodone (7) Polysubstance (4)	32
3	Etonitazepyne (*N*-pyrrolidino etonitazene)	2021-07-13	81 (16.56)	Substance (45) Equipment (26)	'Don't know' (2) Oxycodone (4) Cocaine (1) Fentanyl (75)	28
4	*N*-desethyl isotonitazene/ *N*-desethyl protonitazene[a]	2022-02-03	21 (4.29)	Substance (14) Equipment (7)	Carfentanil (1) 'Don't know' (1) Fentanyl (18) MDMA (1)	< 6[b]
5	5-aminoisotonitazene	2021-05-17	17 (3.48)	Substance (7) Equipment (10)	'Don't know' (1) Down (1) Fentanyl (12) MDMA (2) Oxycodone (1)	< 6[b]
6	Etodesnitazene	2021-06-24	16 (3.27)	Substance (7) Equipment (9)	'Don't know' (1) Fentanyl (15)	< 6[b]
7	Etonitazene	2021-05-05	3 (0.61)	Substance (2) Equipment (1)	Fentanyl (4)	< 6[b]
8	*N*-desethyl etonitazene	2022-02-24	3 (0.61)	Substance (4)	Fentanyl (1) Oxycodone (1) Oxymorphone (1)	0
9	Isotonitazepyne (*N*-pyrrilidino isotonitazene) / Protonitazepyne (*N*-pyrrolidino protonitazene)[a]	2024-03-06	3 (0.61)	Substance (4)	Oxycodone (4)	0
10	4′-hydroxynitazene	2021-09-20	1 (0.2)	Substance (1)	MDMA (1)	0

Note: Counts are not mutually exclusive, as they represent the total number of different nitazenes detected across the 489 samples in which some samples contained more than 1 nitazene. MDMA = 3,4-Methylenedioxymethamphetamine.

[a]Toronto's Drug Checking Service reports these two drugs together because they have similar chemical structures which cannot currently be differentiated by the laboratory protocols.

[b]Nitazene overdose data are suppressed because of small cell size.

TABLE 2 | Health Canada's Drug Analysis Service nitazenes detected from November 2019 to June 2024 ($n = 3542$).

	Nitazene	Month first identified (year-mm)	Province first identified	*n* (% of *n* = 3542)	Provincial, *n*	
1	Metonitazene	2021–01	Ontario	1144 (32.3)	AL = 21 BC = 20 MB = 3 NB = 23 NL = 3	NS = 1 ON = 949 PEI = 2 QC = 122
2	Protonitazene	2021–03	Quebec	1042 (29.42)	AL = 18 BC = 4 MB = 1 NB = 125 NL = 2	NS = 5 ON = 326 PEI = 3 QC = 558
3	Isotonitazene	2019–11	Quebec	665 (18.77)	AL = 73 BC = 9 MB = 3 NB = 20 NL = 1	NS = 9 ON = 264 QC = 280 SK = 6
4	Etodesnitazene	2020–08	Quebec	527 (14.88)	AL = 5 BC = 56 NS = 3	ON = 427 QC = 30 SK = 6
5	Etonitazepyne (*N*-pyrrolidino etonitazene)	2021–09	Alberta	220 (6.21)	AL = 16 BC = 7 ON = 185	QC = 10 SK = 2
6	Protonitazepyne (*N*-pyrrolidino protonitazene)	2023–07	British Columbia	124 (3.5)	AL = 3 BC = 2 NB = 8	ON = 52 QC = 59
7	*N*-desethyl isotonitazene	2023–03	Ontario	99 (2.8)	AL = 2 BC = 1 NB = 2 NL = 1	NS = 1 ON = 62 PEI = 1 QC = 29
8	Butonitazene	2022–04	British Columbia	12 (0.34)	BC = 2 ON = 7	QC = 3
9	*N*-desethyl etonitazene	2024–03	Ontario	4 (0.11)	ON = 4	
10	Ethyleneoxynitazene	2023–08	Ontario	3 (0.08)	ON = 3	
11	Flunitazene	2021–03	Ontario	1 (0.03)	ON = 1	
12	5-aminoisotonitazene	2021–09	Ontario	1 (0.03)	ON = 1	

Note: Counts are not mutually exclusive, as they represent the total number of different nitazenes detected across the 3542 samples in which some samples contained more than one nitazene.
Abbreviations: AL, Alberta; BC, British Columbia; MB, Manitoba; NB, New Brunswick; NL, Newfoundland and Labrador; NS, Nova Scotia; ON, Ontario; PEI, Prince Edward Island; QC, Quebec; SK, Saskatchewan.

some cases these were intranasal doses, which are not equivalent to parenteral doses) [29]. Co-detection of nitazenes with benzodiazepine-related substances, common in the data presented herein, represents a significant danger to the central nervous system given that nitazenes alone are central nervous system depressants. When these drugs are detected together, the risk of respiratory depression or secondary cardiac arrest is further heightened [30]. Indeed, a systematic review of nitazene-related fatalities reported these events occurred almost always when other central nervous system depressants were present in combination [31].

Our findings from DCS in Toronto and British Columbia also highlight that nitazenes were almost always unexpected. While this lack of awareness is understandable given that nitazenes are relatively novel and not a drug of choice in the unregulated market [32], the discordance between what people are expecting their purchased drugs to contain and what they are found to contain has serious implications. Without awareness of the presence of nitazenes in the drug supply, people who use drugs are ill-equipped to make informed decisions or adopt behavioural changes that could mitigate the risks associated with such potent substances [30]. Hence, this discrepancy highlights the need for

TABLE 3 | BCCSU nitazenes detected from 2 January 2021 to 30 June 2024 ($n = 43$).

	Nitazene	Date first identified (year-mm-dd)	n (% of $n = 43$)	Expected drugs	Substance appearances
1	Metonitazene	2021-02-13	18 (41.86)	Diazepam (1) Down (5) Fentanyl (8) Unknown (3)	Brown powder (2) Dark yellow powder (1) Green powder (2) Green-tan granular powder (91) Light yellow granular powder (1) Off-white powder (1) Orange powder (1) Purple chunk (1) Tan granular powder (2) Tan powder (4) Tan solid (1) Yellow powder (2)
2	Isotonitazene	2021-01-29	13 (30.23)	Down (6) Fentanyl (4) Heroin (1) Unknown (4)	Black resinous material (2) Brown granular powder (4) Light brown powder (2) Orange-tan granular powder (1) Purple granular powder (1) Tan powder (1) White powder (4)
3	Protonitazepyne (*N*-pyrrolidino protonitazene)	2023-06-23	5 (11.63)	Down (4) Metonitazene (1) Unknown (1)	Blue powder (1) Brown powder (2) Beige powder (1) Orange powder (1)
4	Protonitazene	2021-12-16	4 (9.3)	Diazepam (2) Down (1) Unknown (1)	Pale yellow powered (1) Orange powder (1) Pink powder (1) White powder (1)
5	Etodesnitazene	2021-01-02	4 (9.3)	Down (1) Fentanyl (4)	Brown powder (1) Light brown paste (1) Yellow solid (1) Dark brown-green granular powder (1)
6	Etonitazepyne (*N*-pyrrolidino etonitazene)	2023-10-31	1 (2.33)	Unknown (1)	White powder (1)

Note: Counts are not mutually exclusive, as they represent the total number of different nitazenes detected across the 43 samples in which some samples contained more than one nitazene.

continued and expanded support of DCS to detect and disseminate real-time information about contents in the unregulated drug supply, not only to service users but also to the public.

International findings also highlight the emergence of nitazene in settings outside of North America. Similar to law enforcement seized drug samples analysed by HC-DAS laboratories, São Paulo State Police in Brazil seized 140 samples containing nitazenes from July 2022 to April 2023 [11]. The majority of seized nitazenes were metonitazene, and often co-detected with other compounds, aligning with our findings for Canada [11]. However, a contrasting pattern emerges in Brazil. Gonçalves de Araújo et al. detected a higher percentage of nitazenes (95%) compared to Canadian agencies, and rather than co-detections with benzodiazepine-related drugs, nitazenes were most often detected with synthetic cannabinoids [11]. Additionally, the unregulated drug market in the UK detected nitazenes in substances sold as other substances, such as other opioids, benzodiazepines and cannabis products [33], aligning with our findings on unexpected nitazene detections in Canada's unregulated opioid supply. Further emphasising the spread of nitazenes and associated risks, Bade et al. detected nitazenes in the US, specifically Washington State and Illinois, via the analysis of wastewater [34]. This research also supports the potential for expanded surveillance via wastewater [35] to overcome the limited population coverage of DCS and drug seizure analysis. Comparing nitazene trends in Brazil, the United Kingdom the United States and Canada reinforces the need for continuous drug monitoring and rapid dissemination of findings to mitigate risks for people who use drugs, including overdose.

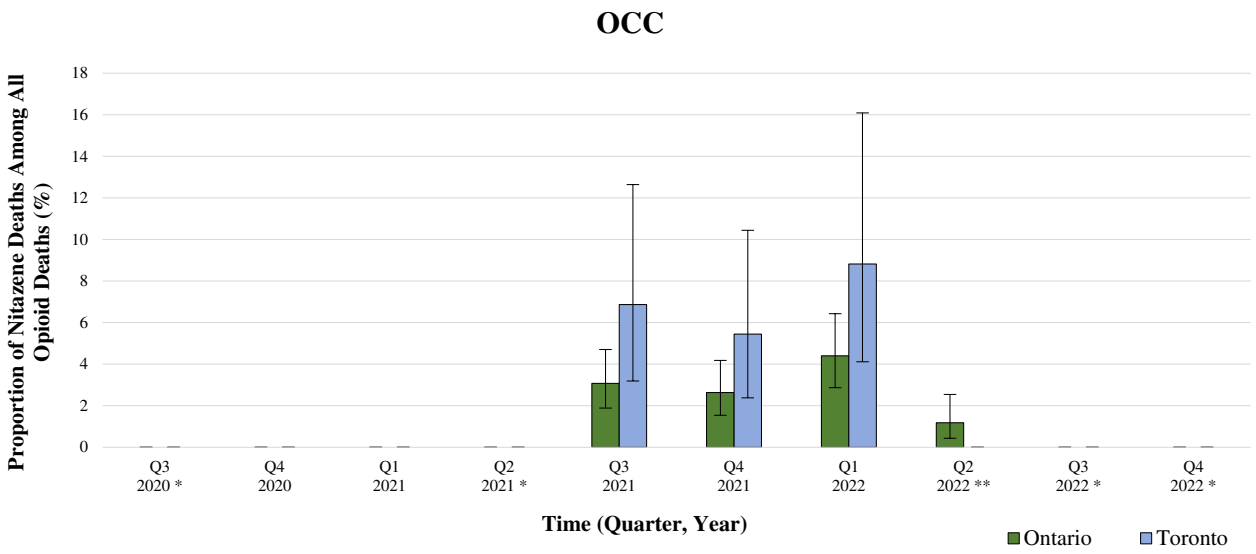


FIGURE 2 | Percentages and 95% confidence intervals of Ontario nitazene deaths in all Ontario opioid deaths, and Toronto nitazene deaths in all Toronto opioid deaths, over time from the date of first detection. 'All opioid deaths' refers to deaths in which Office of the Chief Coroner (OCC) toxicology reports identified any opioid as present at the time of death, including cases where opioids were and were not attributed to death, and 'nitazene deaths' refers to opioid deaths in which OCC toxicology reports identified any nitazene as present at the time of death, including cases where nitazenes were and were not attributed to death. Q1, quarter 1; Q2, quarter 2; Q3, quarter 3; Q4, quarter 4. *Ontario and Toronto's nitazene overdose data are suppressed because of small cell size. **Toronto's nitazene overdose data are suppressed because of small cell size.

4.1 | Limitations

The data presented rely on samples submitted to TDCS, BCCSU and HC-DAS for analysis, and do not fully represent the contents of the unregulated drug market in Canada. Samples submitted by law enforcement and analysed by HC-DAS have been seized at varying levels of the supply chain and may not reflect the full extent of adulteration in the unregulated drug market. Analysing synthetic opioids like nitazenes requires high-performing instruments, and instrument libraries must be continuously updated to include these various novel and emerging drugs. In targeted analyses, if no reference materials for specific nitazene compounds are available, they may not be reported. As HC-DAS' primary mandate is to analyse suspected illegal drug samples to identify whether they contain controlled substances under the *Controlled Drugs and Substances Act* [13], noncontrolled substances (e.g., xylazine) are not systematically reported when found in combination with a controlled substance. Therefore, results based on these data should be interpreted with caution when making conclusions regarding the type and nature of substances circulating in the unregulated market. Findings presented herein may differ from other data from study settings as these data are presented and analysed differently.[2] Previous research has also shown that some mail-in samples submitted to DCS participating in BCCSU-coordinated data collection originate from outside of Canada (e.g., Australia) [36]. As such, we caution against assuming that all BCCSU samples reflect substances circulating in BC unregulated drug markets.

Responses to survey questions on overdose and drug expectation from service users at DCS were self-reported by participants and thus have inherent limitations. Both opioid and nitazene death data from the OCC include cases where an opioid or nitazene, respectively, was present at the time of death, regardless of whether such substances were attributed to death. While data on the detection of opioids and nitazenes in deaths from the OCC therefore cannot be interpreted as such substances causing deaths, their presence in death data further highlights the widespread contamination of the unregulated drug supply. This phenomenon also applies to TDCS data on service user reported previous overdoses related to samples submitted that were found to contain nitazenes, as nitazenes cannot be interpreted as causing the self-reported overdose. Finally, with respect to analytic methods, the AME statistical analysis, which averaged detections and overdoses over time, potentially overlooked small effects. Additionally, the limited sample size and lack of coverage of the full study period for data from the OCC, as well as the nonrandom nature of BCCSU nitazene detections, restricted our analysis to descriptive statistics, preventing definitive conclusions about trends from these data sources.

5 | Conclusions

Nitazenes are circulating across Canada, suggesting enhanced harm reduction responses, health care provision and related overdose prevention given their high potency, unexpected detection and co-occurrence with other central nervous system depressants. Considering the increasingly toxic and unpredictable unregulated drug supply, there is a continued and growing need for sustained overdose prevention and harm reduction service provision, including DCS to monitor and disseminate information on drug supply contents.

Author Contributions

Each author certifies that their contribution to this work meets the standards of the International Committee of Medical Journal Editors.

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Conflicts of Interest

D.W. and D.R.B. are co-founders of DoseCheck, a commercial entity developing a mobile drug checking technology. In 2025, D.W. acted as an expert witness in a legal challenge in British Columbia involving drug checking services. Constraints on publishing: none. The other authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Endnotes

[1] Health Canada defines apparent opioid toxicity as death caused by intoxication or toxicity (poisoning) resulting from substance use, where one or more of the substances is an opioid, regardless of how it was obtained (i.e., illegally or prescription), and other substances may also be involved [3].

[2] For information about the most frequently identified substances in Canada and by province and drug notification, please refer to the following link: https://health-infobase.canada.ca/drug-analysis-service/analyzed-drug-report.html.

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