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Prescribing Patterns, Substance Use Disorder Diagnoses, and Access to Treatment Prior to Substance-Related Toxicity Deaths in Ontario

Stimulant, Opioid, Benzodiazepine, and Alcohol-Related Toxicity Deaths

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A Report By
The Ontario Drug Policy Research Network
and Public Health Ontario

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Background

Over the past decade, the rate of substance-related toxicity deaths have dramatically increased[1], representing a major contributor to the rise in working age mortality; especially among people aged 25-44 years in Ontario, Canada.[2] In our previous report, we observed a total of 8,767 accidental substance-related toxicity deaths involving alcohol, stimulants, benzodiazepines, and/or opioids between 2018 and 2021 in Ontario, with annual substance-related toxicity deaths almost doubling from 1,586 in 2018 to 2,886 in 2021.[2] We found that the majority of these deaths, occurred among adults aged 25-44 years, males and people residing in lower income quintile neighbourhoods. Opioids (85.2%) and/or stimulants (60.2%) were the most common direct contributors to death, with alcohol (13.4%) or benzodiazepines (8.6%) less frequently involved.[2] Importantly, in recent years the majority of substance-related toxicity deaths are attributable to non-pharmaceutical/unregulated opioids (i.e., fentanyl), benzodiazepines (e.g., etizolam) and stimulants (i.e., cocaine and methamphetamines)[2]. Additionally, there is a rising trend in polysubstance use and related harms, with co-ingestion of multiple substances increasing the risk of overdose and further complicating treatment and harm reduction responses.[3]

A better understanding of healthcare encounters or "touchpoints" present opportunities to identify and engage with people at a high risk of a substance-related toxicity death. In these interactions, healthcare professionals could deliver harm reduction services and empower people who use substances to initiate new treatments or care.[4] Our previous findings focusing on opioids, highlighted that approximately two thirds of people who died from opioid-related toxicity had a prior opioid use disorder diagnosis.[5] Yet, only one-third had been treated with opioid agonist therapy (OAT) in the 5 years prior to death, highlighting gaps in access to OAT treatment.[5] During the pandemic period, 17.5% of deaths occurred among people who had visited an emergency department (ED) in the prior 30 days, with non-prescription opioids primarily contributing to death. With the availability of enhanced data on all substance-related toxicity deaths, there is an urgent need to better understand these interactions with the healthcare system for non-fatal substance-related toxicities, the diagnoses of substance use disorders, exposure to prescribed medicines and access to medical treatment prior to death.

This information will help inform future harm reduction interventions and improve access to healthcare and other supportive services for people who use substances, as more research is required to investigate the factors associated with substance-related toxicity deaths.[6] Therefore, in this report we sought to describe: prior prescribing patterns, previous substance use diagnoses, non-fatal substance-related toxicities and access to treatment(s) prior to accidental substance-related toxicity deaths involving opioids, benzodiazepines, stimulants and/or alcohol in Ontario between January 2018 and June 2022.

Methods

Setting

We conducted a descriptive cross-sectional study to describe prior prescribing patterns, substance use disorder diagnoses and healthcare encounters for previous non-fatal substance-related toxicities among people who died from accidental alcohol, stimulant, benzodiazepine and/or opioid-related toxicity in Ontario, Canada between January 1, 2018 and June 30, 2022. An accidental substance-related toxicity death was defined as an acute toxicity death that was confirmed as accidental/unintentional (i.e. an injury where death was not intended, foreseen or expected) and resulted from the direct contribution of the consumed substance (alcohol, stimulant, benzodiazepine, and/or opioid), regardless of how the substance was obtained.

Data Sources

We obtained all data from ICES (formerly the Institute for Clinical Evaluative Sciences), an independent, non-profit research institute who as a prescribed entity under Ontario's Personal Health Information Act (PHIPA) and the Coroners Act are permitted to use healthcare and demographic data, without individual consent, for evaluating, planning and/or monitoring the health system.[7] To capture substance-related toxicity deaths, we combined the Drug and Drug/Alcohol Related Death Database (DDARD), which contains records from coronial investigations completed by the Office of the Chief Coroner/Ontario Forensic Pathology Service on probable and confirmed cases of opioid-related toxicity deaths, with the Alcohol, Stimulant, and Benzodiazepine Related Mortality Database. The combination of both datasets allowed for the broad assessment of all alcohol, stimulant, benzodiazepine, and opioid-related toxicity deaths in Ontario. More details on how these databases were combined can be found in our previous report.[2] Substance-related toxicity deaths reflect those where the above described substances were determined to be direct contributors of death.

To examine medications dispensed prior to death, we used the Narcotics Monitoring System (NMS), which captures all controlled substances that are dispensed from community pharmacies (i.e. opioids [we excluded cough and anti-diarrheal preparations], benzodiazepines, and stimulants) in Ontario, regardless of means of payment. We used the Registered Persons Database (RPDB) to capture basic descriptive demographic information including age and sex, with people without an Ontario health card excluded from our analysis. For information on emergency department (ED) visits, acute hospital admissions, and mental health related hospital admissions we used the Canadian Institute for Health Information's National Ambulatory Care Reporting System (NACRS), Discharge Abstract Database (DAD) and Ontario Mental Health Reporting System (OHMRS). We used the Ontario Health Insurance Plan (OHIP) to capture outpatient visits for substance use disorders. As treatments for alcohol and benzodiazepine use disorders (e.g. naltrexone, acamprosate) are not captured in the NMS, we used the Ontario Drug Benefit (ODB) claims database to determine exposure to these treatment options among a restricted cohort of people eligible for the ODB Program (Note: disulfiram is not covered by ODB and was not captured in this analysis). The ODB database captures all prescriptions for medications reimbursed by the public drug program in Ontario.

These datasets were linked using unique encoded identifiers and analyzed at ICES. As a prescribed entity under section 45 of PHIPA, the use of this data does not require review or approval by a Research Ethics Board.

Analysis

For each specific substance-related toxicity death, we stratified results according to the number of substances involved (mono or poly substance use), age (<25, 25-44, 45-64, and ≥ 65 years), sex (female, male) and whether non-pharmaceutical substances were involved in death. To evaluate changes in patterns of substance-related toxicity deaths over the four-and-a-half year study period we also compared (i) the first 12 months (defined as January 1, 2018-December 31, 2018) and (ii) the last 12 months of the study (defined as July 1, 2021-June 30, 2022). We used descriptive statistics to summarize trends, demographic characteristics, medication prescribing, previous substance use disorder diagnoses and prior non-fatal hospital treated substance-related toxicities. We used chi-square/Fisher's exact tests to assess whether differences were statistically significant, using a significance level of $p<0.05$.

Measures

We described our findings among overall substance-related deaths and further classified according to deaths directly attributable to alcohol, stimulants, benzodiazepines and opioids, separately. Please note that these groups are not mutually exclusive, as polysubstance use directly contributing to death was common. In these circumstances, individuals whose death involves polysubstance use are represented in each relevant substance specific analysis as well as in the overall analysis.

We reported prior dispensing of related substance(s) (any opioids, opioid analgesics, stimulants, and benzodiazepines) in the last 30 days, 1 year, and 5 years before death. Dispensed substances were reported among deaths directly attributable to that specific substance type (i.e. benzodiazepines dispensed among benzodiazepine-related toxicity deaths, any opioids and opioid analgesics among opioid-related toxicity deaths and stimulants among stimulant-related toxicity deaths). However, it is important to note that these medications were not necessarily a direct contributor to subsequent substance-related toxicity deaths. For benzodiazepine-related, opioid-related and stimulant-related toxicity deaths, we also reported the proportion of deaths where drugs from non-pharmaceutical supply contributed to death. Using ED visits or in-patient hospitalizations using ICD-10 codes (See Appendix B, Table B1), we captured non-fatal substance-related toxicity events occurring in the year prior to death that resulted in people presenting to hospital for treatment.

For prior substance use disorder diagnoses, we identified any previous ED visits, in-patient or mental health hospitalizations with a substance use disorder diagnosis in the previous 5 years, using ICD-9 and ICD-10 codes (See Appendix B, Table B2) and any previous outpatient visits with a substance use disorder diagnosis in the 1 year prior to death. We classified a substance use disorder for each substance category using the following definitions, summarized below. We also conducted a sensitivity analysis to expand the definitions more broadly (See Appendix B, Table B2).

Table 1: Definitions used to define substance use disorders in the report

	Definition
Any substance use disorder	Any substance use disorder hospital based diagnosis in the past 5 years or any substance use disorder outpatient visit in the past year (excluding alcohol outpatient visits)
Opioid use disorder	Any opioid use disorder hospital based diagnosis or OAT dispensing or OHIP OAT related outpatient claim in the past 5 years
Stimulant use disorder	Any stimulant use disorder hospital based diagnosis in the past 5 years
Benzodiazepine use disorder	Any benzodiazepine use disorder hospital based diagnosis in the past 5 years
Alcohol use disorder	Any alcohol use disorder hospital based diagnosis in the past 5 years or any alcohol use disorder outpatient visit in the past year

NOTE

To align with the DSM-5 criteria, clinical criteria, and recommended terminology to help reduce stigma,[8, 9] in this report we use the term 'substance use disorder'. It is important to note however, that people with a substance use disorder diagnoses, may not consider themselves to have 'disordered' use.

We identified prior pharmacological treatment for opioid use disorder, alcohol use disorder and benzodiazepine use disorder in the following time periods: same day of death (i.e. prior dispensing that overlaps or is dispensed on the date of death), in the previous 30 days and 1 year and we also looked at the past 5 years for OAT treatment. We reported opioid agonist treatment (OAT) using the NMS database, to capture previous dispensing of methadone, buprenorphine containing products and/or slow release oral morphine (SROM). We identified prior pharmacological treatment for alcohol use disorder in two ways: (i) receipt of first line licensed treatments, naltrexone or acamprosate and (ii) medications sometimes used 'off label' to treat alcohol use disorder: topiramate or gabapentin. We defined treatment for benzodiazepine use disorders by capturing prior dispensing of "off label" use of (i) gabapentin and/or pregabalin and (ii) carbamazepine. All treatment options for alcohol use disorder and benzodiazepine use disorder were only available through the ODB database and therefore these analyses were restricted to a subset of the cohort who were eligible for public drug benefits.

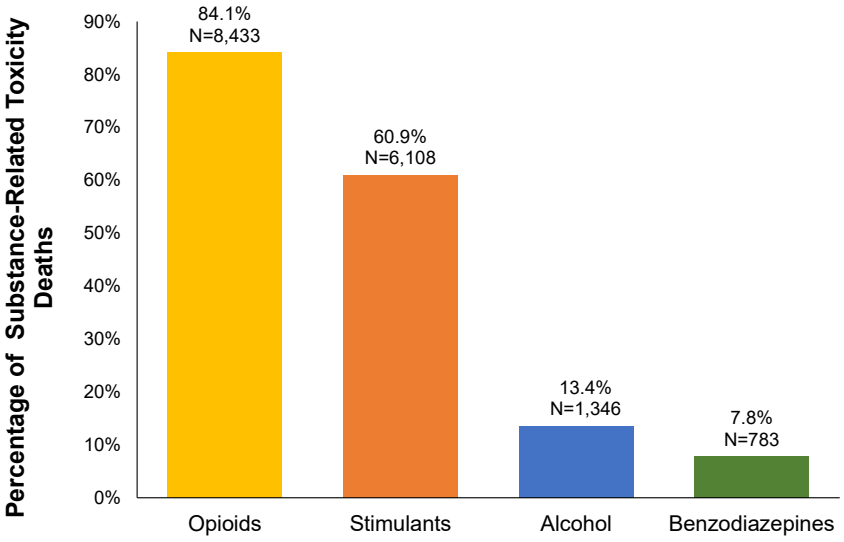
Key Findings

NOTES FOR ALL ANALYSES

- Substance-related toxicity deaths may overlap (i.e., belong to more than one substance grouping), unless explicitly stated as a mono-substance death.
- Number of substances directly contributing to death represent broad groupings (i.e., alcohol, stimulant, benzodiazepine, or opioid).

Overall Substance-Related Toxicity Deaths

Figure 1: Proportion of substance-related toxicity deaths directly attributable to specific substances



Overall, there were 10,024 accidental substance-related toxicity deaths in Ontario from January 1, 2018 to June 30, 2022 that involved alcohol, stimulants, benzodiazepines, and/or opioids directly contributing to death. We observed a 72.2% increase in the number of deaths from the first 12 months of the study period (N=1,570) compared to those that occurred in the last 12 months of the study period (N=2,704). Among the 10,024 overall substance-related toxicity deaths, 84.1% involved opioids, 60.9% involved stimulants, 13.4% involved alcohol, and 7.8% involved benzodiazepines.

Table 2: Hospital treated non-fatal substance-related toxicities in the year prior to death, among people who died from substance-related toxicity

Hospital treated non-fatal substance-related toxicities (prior 1 year)	Substance-related toxicity deaths
Substance-related toxicity (involving any 4 substances)†	1,995 (19.9%)
Opioid-related toxicity†	1,749 (17.4%)
Stimulant-related toxicity†	499 (5.0%)
Benzodiazepine-related toxicity†	204 (2.0%)
Alcohol-related toxicity†	103 (1.0%)

NOTE

† See Appendix B, Table B1 for definitions.

Approximately one-fifth (19.9%, N=1,995) of people who died from substance-related toxicity, were treated in a hospital setting for a non-fatal substance-related toxicity involving opioids, stimulants, benzodiazepines, and/or alcohol in the year before death. Specifically, in the year prior to death, 17.4% (N=1,749) of individuals were treated in hospital for opioid-related toxicities, 5.0% (N=499) for stimulant-related toxicities, 2.0% (N=204) for benzodiazepine-related toxicities and 1.0% (N=103) for alcohol-related toxicities.

Table 3: Prior healthcare encounters for substance use disorder diagnoses† among individuals who died from substance-related toxicity

	Substance-related toxicity deaths (N=10,024)
Any healthcare encounter for substance use disorder	6,149 (61.3%)
Hospital based encounters with substance use disorder diagnoses (prior 5 years)	4,671 (46.6%)
Opioid use disorder§	2,324 (23.2%)
Stimulant use disorder§	2,220 (22.2%)
Benzodiazepine use disorder§	252 (2.5%)
Alcohol use disorder§	2,429 (24.2%)
Number of hospital based encounters with substance use disorder diagnoses (prior 5 years)	
0	5,353 (53.4%)
1	2,724 (27.2%)
2	1,391 (13.9%)
≥3	556 (5.5%)
Any substance use related diagnoses outpatient visits (prior 1 year)*	3,919 (39.1%)
Alcohol use disorder outpatient diagnoses (prior 1 year)	537 (5.4%)
0	9,487 (94.6%)
1	288 (2.9%)
2	98 (1.0%)
≥3	151 (1.5%)
Any other substance use disorder outpatient diagnoses (prior 1 year)	3,673 (36.6%)
0	6,351 (63.4%)
1	679 (6.8%)
2	318 (3.2%)
≥3	2,676 (26.7%)

NOTE

- † See Appendix B, Table B2 for definitions.
- § These categories are not mutually exclusive (i.e. an individual could have multiple diagnoses for different substance use disorders)
- * Both alcohol use disorder and other substance use disorder outpatient diagnoses.

Overall, among all people who died from substance-related toxicity, almost two-thirds (61.3%) had a healthcare encounter where a substance use disorder diagnosis was indicated, with 46.6% having a diagnosis in a hospital setting and 39.1% having a diagnosis in an outpatient setting.

When considering hospital based encounters, approximately one-quarter of people who died from substance-related toxicity, had a diagnosis of opioid use disorder (23.2%), stimulant use disorder (22.2%) and/or alcohol use disorder (24.2%) in the 5 years prior to death. In contrast, hospital based diagnoses of benzodiazepine use disorder were much less common (2.5%). Although substance-related toxicity deaths most often occurred among individuals with no previous hospital diagnoses of substance use disorder involving any of the 4 substances (53.4%, N= 5,353), 19.4% of people had 2 or more hospital visits where a substance use disorder diagnosis was indicated in the past 5 years (13.9% with 2 hospital visits, 5.5% with 3+ visits with a substance use disorder).

Over one-third of people who died from substance-related toxicity had an outpatient physician visit related

to a substance use disorder (not including alcohol use disorder) in the year prior to death (36.6%, N=3,673), with only 5.4% (N=537) having an alcohol use disorder related outpatient visit. Despite almost two-thirds of people (63.4%, N=6,351) who died from substance-related toxicity deaths not having an outpatient healthcare visit related to a substance use disorder diagnosis (excluding alcohol use disorder) in the year prior to death, the prevalence of 3 or more outpatient visits was still relatively high (26.7%). This suggests that when people are engaged with an outpatient physician related to their substance use disorder, there are typically many physician visits in the year before death and possibly represents frequent visits if people are receiving OAT treatment.

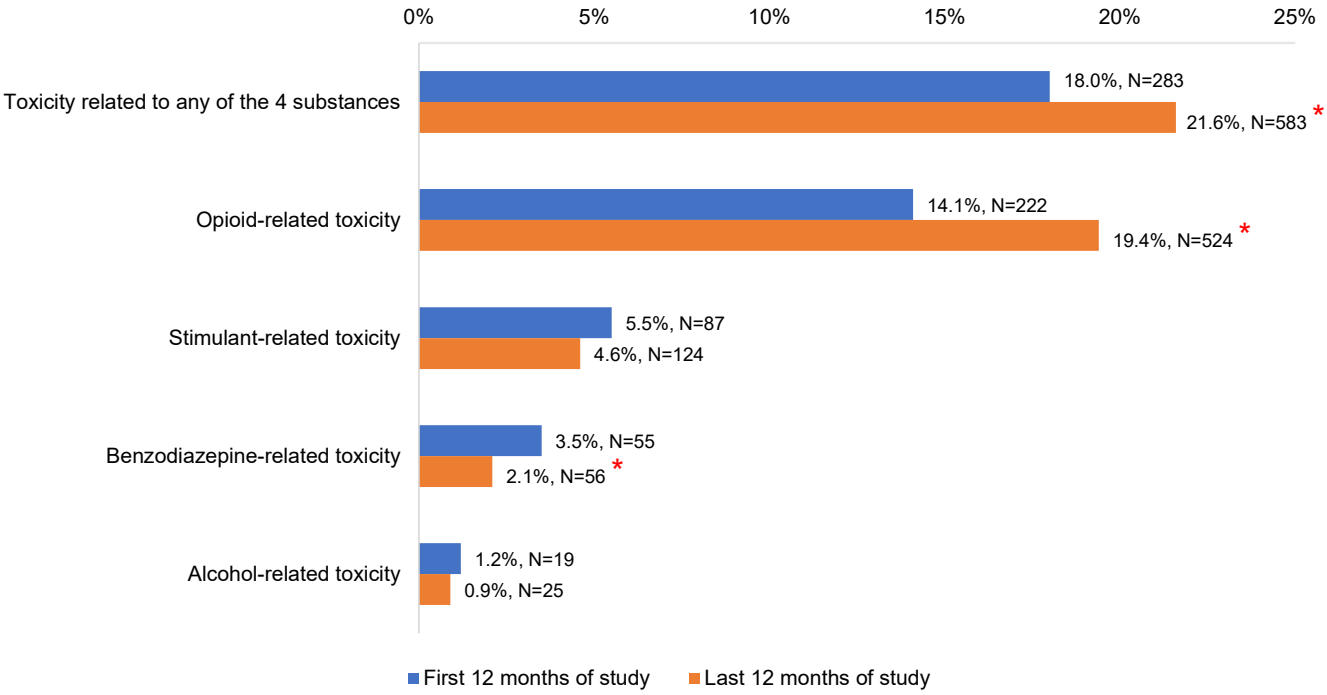
Comparisons in Substance-Related Toxicity Deaths over Time

Number of Substance-Related Toxicity Deaths

First 12 Months
January 1, 2018 – December 31, 2018
N = 1,570

Last 12 Months
July 1, 2021– June 30, 2022
N = 2,704

Figure 2: Hospital treated non-fatal substance-related toxicities† in the year prior to death among individuals who died from substance-related toxicity in the first 12 months of study period (N=1,570) versus the last 12 months of the study period (N=2,704)

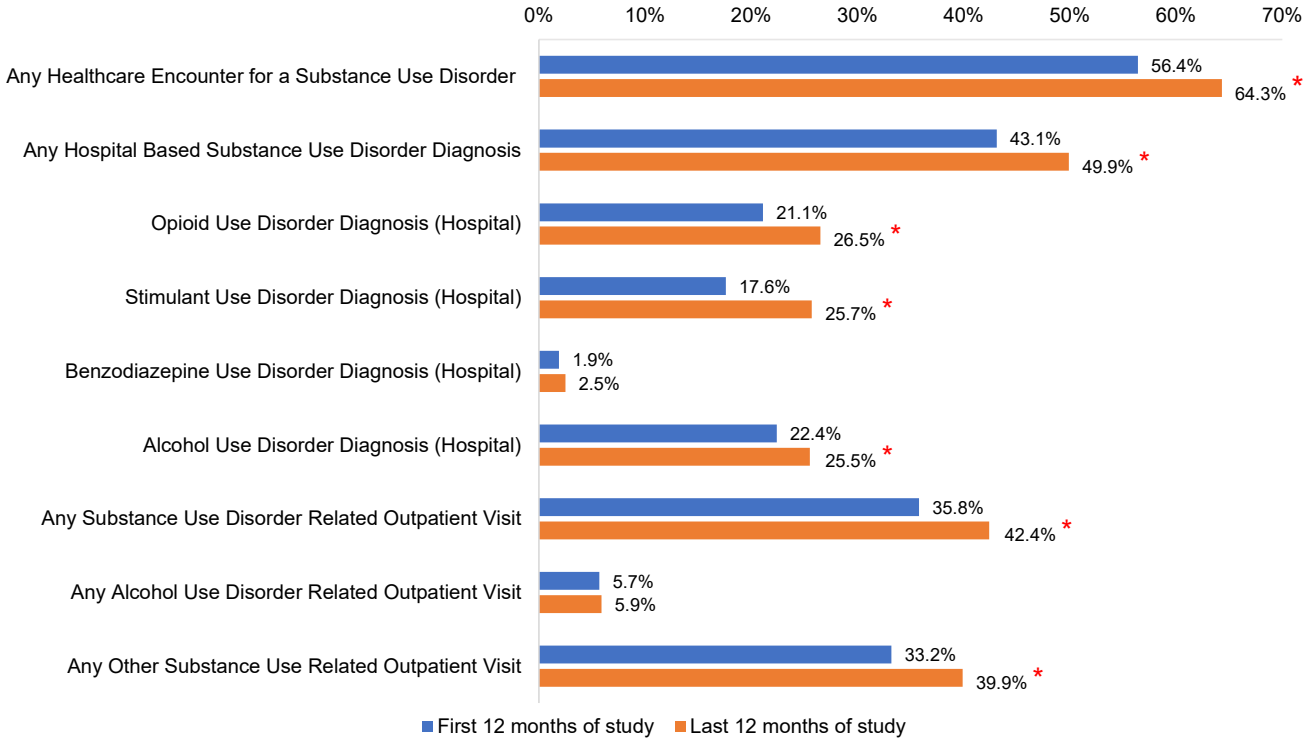


NOTE

- † See Appendix B, Table B1 for definitions.
- * indicates statistically significant difference between first 12 months and last 12 months ($p<0.05$).

When comparing the first year and final year of the study period, the proportion of people with a prior non-fatal substance-related toxicity that resulted in a hospital visit increased from 18.0% (N=283) to 21.6% (N=583). This was driven by an increase in prior opioid-related toxicities that resulted in a hospital visit (from 14.1%, N=222 to 19.4%, N=524) with small declines in the prevalence of hospital treated toxicities related to other substances.

Figure 3: Prior healthcare contact for substance use disorder diagnoses† (including hospital and outpatient visits) among people who died from substance-related toxicity in the first 12 months (N=1570) versus the last 12 months of the study period (N=2704)



NOTE

- † See Appendix B, Table B2 for definitions.
- * indicates statistically significant difference between first 12 months and last 12 months ($p<0.05$).

Overall, the prevalence of any healthcare contact related to any substance use disorder prior to a substance-related toxicity death rose over our study period, increasing from 56.4% to 64.3% ($p<.001$). In general, hospital visits where substance use disorder diagnoses were indicated increased over the study period, with the largest increase occurring in hospital visits with stimulant use disorders, which rose from 17.6% to 25.7%. Lastly, outpatient visits related to any substance use disorder (excluding alcohol use disorder) rose slightly over the study period (33.2% vs. 39.9%), while outpatient visits related to alcohol use disorder were similar between the two periods (5.7% vs. 5.9%).

Substance-Specific Findings

Opioid-Related Toxicity Deaths

NOTE

- Opioid use disorder diagnosis and substance use disorder diagnosis are defined in Appendix B, Table B2.
- Hospital treated substance-related toxicities are defined in Appendix B, Table B1.

Table 4: Descriptive characteristics for opioid-related toxicity deaths

	Opioid-related toxicity deaths (N=8,433)
Age category	
<25	661 (7.8%)
25 to 44	4,539 (53.8%)
45 to 64	3,016 (35.8%)
≥65	217 (2.6%)
Sex	
Female	2,152 (25.5%)
Male	6,281 (74.5%)
Number of substances directly contributing to death	
1 (opioids only)	2,863 (33.9%)
2+ (polysubstance use)	5,570 (66.1%)

Overall, out of the 10,024 substance-related toxicity deaths, we identified 8,433 people who died from opioid-related toxicity over the study period (84.1%). Over half of opioid-related toxicity deaths, (53.8%, N=4,539) occurred among people between 25-44 years old, with a small proportion among those <25 years old (7.8%, N=661) and ≥ 65 years (2.6%, N=217). Almost three-quarters of deaths occurred among males (74.5%, N=6,281). In two-thirds of opioid-related toxicity deaths (66.1%, N=5,570), opioids in combination with another substance (i.e. stimulant, benzodiazepine or alcohol) contributed to the death (polysubstance use).

Table 5: Involvement of non-pharmaceutical opioids and prior prescribing patterns of prescription opioids, among opioid-related toxicity deaths

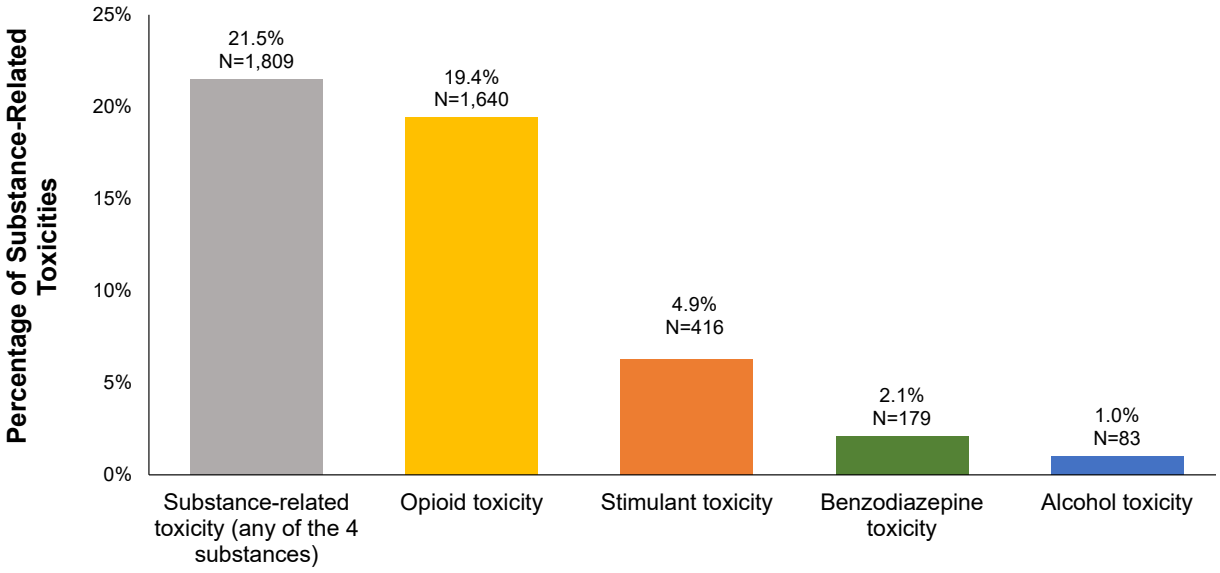
	Opioid-related toxicity deaths (N=8,433)
Non-pharmaceutical opioid(s) directly contributing to death	7,242 (85.9%)
Any prescription opioids dispensed†	
30 days	2,364 (28.0%)
1 year	4,250 (50.4%)
5 years	6,271 (74.4%)
Prescription opioids analgesics dispensed (excludes OAT)†	
30 days	1,296 (15.4%)
1 year	2,520 (29.9%)
5 years	4,990 (59.2%)

The vast majority of opioid-related toxicity deaths (85.9%, N=7,242) involved non-pharmaceutical opioids (i.e., fentanyl sourced from unregulated sources). In the five-years prior to death, an opioid was dispensed (for any indication) to almost three-quarters of people who died from opioid-related toxicity (74.4%, N=6,271). However when restricted to opioid analgesics to treat pain (i.e., excluding opioids for OAT), the proportion decreased to 59.2% (N=4,990). Only 15.4% of people had been dispensed an opioid analgesic to treat pain in the month before death.

NOTE

- † For individuals who were recently dispensed a prescription opioid prior to death, it is important to note that these medications were not necessarily a direct contributor to subsequent opioid-related toxicity deaths.
- Prior OAT use among individuals with opioid use disorder is reported later in Figure 5.

Figure 4: Hospital treated substance-related toxicities in the year prior to death among people who died from opioid-related toxicity (N=8,433)



Approximately 1 in 5 people who died from opioid-related toxicity had a hospital treated toxicity event involving opioids, stimulants, benzodiazepines and/or alcohol in the year prior to death (21.5%, N=1,809). Prior non-fatal opioid-related toxicities were the most common (19.4%, N=1640), followed by stimulant-related toxicities (4.9%, N=416), benzodiazepine-related toxicities (2.1%, N=179) and alcohol-related toxicities (1.0%, N=83).

Table 6: Prior substance use disorder diagnoses among people who died from opioid-related toxicity

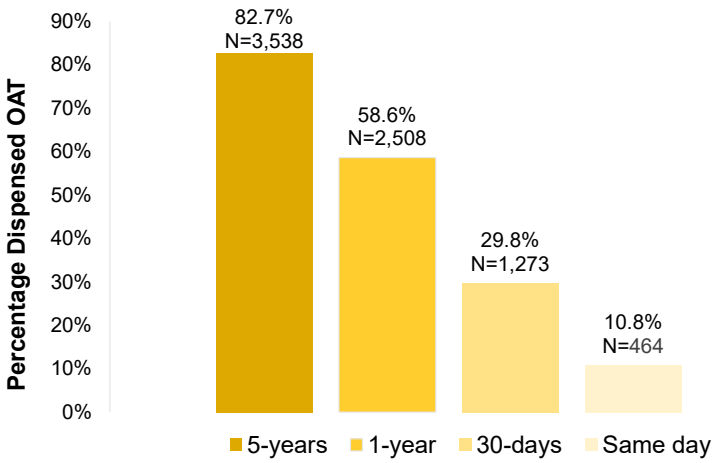
	Opioid-related toxicity deaths (N=8,433)
Any substance use disorder diagnosis†	5,277 (62.6%)
Opioid use disorder diagnosis (prior 5 years)†	4,278 (50.7%)
Hospital based encounters with opioid use disorder diagnosis (prior 5 years)†	2,168 (25.7%)
Any outpatient diagnoses related to substance use (prior 1 year) †	3,370 (40.0%)

NOTE

† See Appendix B, Table B2 for definitions.

Overall, approximately two-thirds of people who died from opioid-related toxicity had a diagnosis of a substance use disorder in a hospital or outpatient setting prior to death (62.6%). When restricted to diagnoses of opioid use disorder (based on hospital records, OAT dispensing and physician services related to OAT provision), approximately half of people had a confirmed opioid use disorder diagnosis (50.7%) prior to death, with one-quarter having a diagnosis that was indicated on a hospital record (25.7%). Finally, although outpatient visits are not specific to substance type (i.e. unable to differentiate between stimulant, opioid or benzodiazepine use disorder), approximately 2 in 5 people had an outpatient physician visit where a substance use disorder (excluding alcohol use disorder) was listed by the treating physician in the year before death.

Figure 5: Prior receipt of OAT among people with an opioid use disorder who died from opioid-related toxicity (N=4,278)



Among people with an opioid use disorder diagnosis, we found that the majority had received OAT (methadone, buprenorphine containing products and/or slow release oral morphine (SROM)) in the five years prior to death (82.7%, N=3,538); although this decreased to only 29.8% having received treatment in the month before death and 1 in 10 (10.8%) receiving OAT on the same day of death.

Table 7: Prevalence of opioid use disorder diagnosis and prior hospital treated opioid-related toxicity among opioid-related toxicity deaths, stratified by descriptive characteristics

	Opioid-related toxicity deaths (Overall)	Opioid use disorder diagnosis† (prior 5 years)	Hospital treated opioid-related toxicity* (prior 1 year)
Total deaths	8,433	4,278 (50.7%)	1,640 (19.4%)
Age			
<25	661	269 (40.7%)	156 (23.6%)
25-44	4,539	2,549 (56.2%)	990 (21.8%)
45-64	3,016	1,382 (45.8%)	466 (15.5%)
≥65	217	78 (35.9%)	28 (12.9%)
Sex			
Female	2,152	1,168 (54.3%)	390 (18.1%)
Male	6,281	3,110 (49.5%)	1,250 (19.9%)
Number of substances directly contributing to death			
1 (opioids only)	2,863	1,617 (56.5%)	557 (19.5%)
2+ (polysubstance use)	5,570	2,661 (47.8%)	1,083 (19.4%)
Hospital treated opioid-related toxicity (prior 1 year)			
Opioid-related toxicity	1,640	1,185 (72.3%)	1,640 (100%)
No opioid-related toxicity	6,793	3,093 (45.5%)	0 (0%)

NOTE

†See Appendix B, Table B2 for definitions.
*See Appendix B, Table B1 for definitions.
All % reported are row percentages using the number of opioid-related toxicity deaths categories as the denominator.

While approximately half (50.7%) of people who died from opioid-related toxicity had a confirmed opioid use disorder diagnosis prior to death, this differed across demographic characteristics and circumstances

surrounding death. When stratified by age, opioid use disorder diagnoses varied significantly across age groups (p<.001). People aged 25 to 44 years were most likely to have an opioid use disorder diagnosis at time of death (56.2%), with just under half of people (45.8%) aged 45 to 64 years having an opioid use disorder diagnosis. In contrast, 40.7% of people aged <25 years and one-third (35.9%) of those aged ≥ 65 years who died from opioid-related toxicity had an opioid use disorder diagnosis at time of death. Additionally, we found that females who died from opioid-related toxicity more commonly had an opioid use disorder diagnosis (54.3%) than males (49.5%; p<.001). When considering the number of substances involved in these deaths, fatal toxicities involving only opioids (without contributions of stimulants, alcohol or benzodiazepines) were more significantly likely to occur among people with opioid use disorder (56.5%), compared to those involving opioids plus one or more other substances (47.8%; p<.001); although the prevalence of opioid use disorder was high in both of these groups. Finally, nearly three-quarters (72.3%) of those with previous hospital-treated opioid-related toxicities had an opioid use disorder diagnosis at time of death, which was significantly higher than among people with an opioid use disorder diagnosis without a recent opioid-related toxicity event (45.5%; p<.001).

Just under 1 in 5 people (19.4%) who died from opioid-related toxicity had a recent hospital visit related to a non-fatal opioid-related toxicity in the year prior to death. When stratified according to age, there was significant variation across age groups (p<.001). Young people aged less than 25 years of age were most likely to have a hospital treated non-fatal opioid-related toxicity in the year prior to death (23.6%, N=156), with just over 1 in 5 people aged 25-44 years (21.8%, N=990) receiving hospital care. Rates were lower among older age groups with 15.5% (N=466) of those aged 45-64 years and 12.9% (N=28) of adults aged 65 years and older having a prior non-fatal toxicity event treated in hospital. There were no significant differences in the prevalence of prior non-fatal hospital treated opioid toxicities by sex or the number of substances directly contributing to death.

Stimulant-Related Toxicity Deaths

NOTE

- Stimulant use disorder is defined in Appendix B, Table B2.
- Hospital treated substance-related toxicities are described in Appendix B, Table B1.

Table 8: Descriptive characteristics for stimulant-related toxicity deaths

	Stimulant-related toxicity deaths (N=6,108)
Age category	
<25	399 (6.5%)
25 to 44	3,226 (52.8%)
45 to 64	2,312 (37.9%)
≥65	171 (2.8%)
Sex	
Female	1,509 (24.7%)
Male	4,599 (75.3%)
Stimulant type	
Cocaine	4,288 (70.2%)
Methamphetamines	2,740 (44.9%)
Number of substances directly contributing to death	
1 (stimulants only)	1,230 (20.1%)
2+ (polysubstance use)	4,878 (79.9%)

Overall, 6,108 deaths were directly attributable to stimulants in Ontario during the study period. The distributions of fatal stimulant toxicities across age groups and sex are similar to those observed in opioid-related toxicity deaths. Specifically, over half of these deaths occurred among people aged 25-44 years, with less than 10% occurring among those aged <25 and ≥65 years. We also reported that stimulant–related toxicity deaths were concentrated among males (75.3%). It is important to note that the majority (79.9%) of stimulant-related deaths involved polysubstance use (i.e., stimulants with alcohol, opioids and/or benzodiazepines), while only 20.1% of deaths involved a stimulant only. Cocaine was the stimulant most commonly directly contributing to death (70.2%). However, methamphetamines were also commonly involved in death, directly contributing to nearly half of stimulant-related toxicity deaths (44.9%).

Table 9: Involvement of non-pharmaceutical stimulants and prior prescribing patterns of prescription stimulants, among stimulant-related toxicity deaths

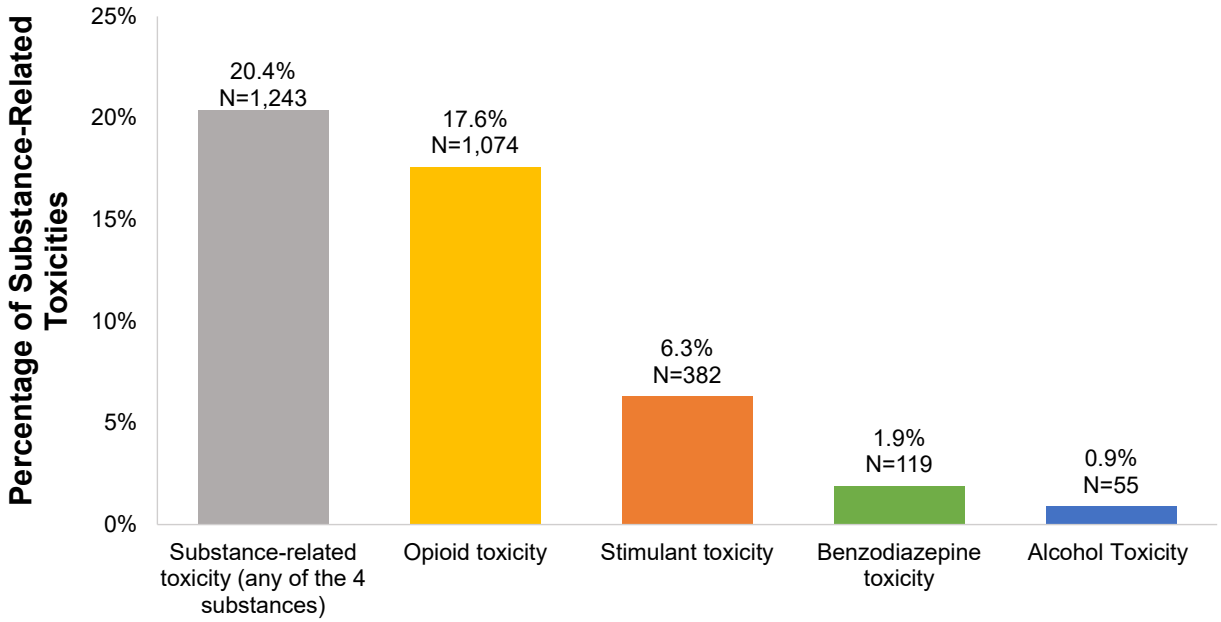
	Stimulant-related toxicity deaths (N=6,108)
Cocaine and/or methamphetamines directly contributing to death	6,055 (99.1%)
Prescription stimulants dispensed	
30 days	285 (4.7%)
1 year	461 (7.5%)
5 years	736 (12.0%)

NOTE

For individuals who were recently dispensed a prescription stimulant prior to death, these medications were not necessarily a direct contributor to subsequent stimulant toxicity deaths.

Among the 6,108 individuals who died from stimulant-related toxicity, recent receipt of stimulant prescriptions was uncommon. Only 1 in 20 (4.7%, N = 285) people were dispensed any stimulant prescription (used in the treatment of attention-deficit/hyperactivity disorder (ADHD) or other medical conditions such as narcolepsy) in the prior month increasing to only 12.0% (N=736) having any stimulant dispensed in the previous 5 years. This aligns with the finding that the vast majority (99.1%) of stimulant-related toxicity deaths involved cocaine and/or methamphetamines and therefore involvement of pharmaceutical stimulants in toxicity deaths is exceedingly rare.

Figure 6: Hospital treated substance-related toxicities in the year prior to death, among people who died from stimulant-related toxicity (N=6,108)



One-fifth of stimulant-related toxicity deaths occurred among people who had experienced at least one hospital treated substance-related toxicity involving any opioids, stimulants, benzodiazepines and/or alcohol in the past year (20.4%, N=1,243). Hospital treated substance-related toxicities in the year prior to death most often involved opioids (17.6%, N=1,074), with only 6.3% being related to stimulant-related toxicity events (N=382).

Table 10: Prior substance use disorder diagnoses among people who died from stimulant-related toxicity

	Stimulant-related toxicity deaths (N=6,108)
Any substance use disorder diagnosis†	3,656 (59.9%)
Stimulant use disorder diagnosis (hospital based encounters in prior 5 years)†	1,630 (26.7%)
Any outpatient diagnoses related to substance use (prior 1 year)†	2,134 (34.9%)

NOTE

† See Appendix B, Table B2 for definitions.

Nearly 60% of people who died from stimulant-related toxicity had a healthcare encounter for a substance use disorder diagnosis (not including alcohol) at time of death (59.9%) which, is similar to what was observed among opioid-related toxicity deaths. When considering hospital visits where a stimulant use disorder was specifically indicated, this prevalence fell to just over one-quarter of individuals (26.7%, N=1,630). Finally, approximately one-third of people who died from stimulant-related toxicity had an outpatient visit for a substance use disorder (excluding alcohol use disorder) in the year prior to death (34.9%, N=2,134).

Table 11: Prevalence of stimulant use disorder and prior hospital treated stimulant-related toxicities among stimulant-related toxicity deaths, stratified by descriptive characteristics

	Stimulant-related toxicity deaths (overall)	Stimulant use disorder diagnoses† (prior 5 years)	Hospital treated stimulant-related toxicity* (prior 1 year)
Total deaths	6,108	1,630 (26.7%)	382 (6.3%)
Age			
<25	399	132 (33.1%)	46 (11.5%)
25-44	3,226	974 (30.2%)	233 (7.2%)
45-64	2,312	497 (21.5%)	97 (4.2%)
≥ 65	171	27 (15.8%)	6 (3.5%)
Sex			
Female	1,509	484 (32.1%)	117 (7.8%)
Male	4,599	1,146 (24.9%)	265 (5.8%)
Stimulant type			
Cocaine	4,288	1,018 (23.7%)	255 (5.9%)
Methamphetamines	2,740	913 (33.3%)	201 (7.3%)
Number of substances directly contributing to death			
1 (stimulants only)	1,230	309 (25.1%)	73 (5.9%)
2+ (polysubstance use)	4,878	1,321 (27.1%)	309 (6.3%)
Hospital treated stimulant-related toxicity (prior 1 year)			
Stimulant-related toxicity	382	190 (49.7%)	382 (100%)
No stimulant-related toxicity	5,726	1,440 (25.1%)	0 (0%)

NOTE

- †See Appendix B, Table B2 for definitions.
- *See Appendix B, Table B1 for definitions.
- % are reported as row percentages using the number of stimulant-related toxicity deaths categories as the denominator.

While over one quarter (26.7%) of stimulant-related toxicity deaths occurred among people with a stimulant use disorder diagnosis (based on prior hospital encounters) this prevalence varied across demographics, substances involved in death and previous toxicity events. Across age groups, prior diagnosis of stimulant use disorder varied significantly (p<.001). Just under one-third of those aged <25 and 25 to 44 years who died from stimulant-related toxicity had a stimulant use disorder, this was lower in older age groups reducing to 21.5% among those aged 45 to 64 years and 15.8% among those aged ≥ 65 years. Similar to what we observed among opioid toxicities, females who died from stimulant-related toxicity were significantly more likely to have a stimulant use disorder diagnosis compared to males (32.1% vs 24.9%; p<.001), as were those with a prior hospital treated stimulant-related toxicity (49.7% vs 25.1%; p<.001). Finally, there were differences in prior stimulant use disorder diagnoses according to the stimulant directly contributing to death, with people who had methamphetamines directly contributing to death, having a higher prevalence of stimulant use disorder (33.3%) compared to those with cocaine directly contributing to death (23.7%, p<.001).

In total, 6.3% of people (N=382) who died from stimulant-related toxicity had a hospital visit related to

stimulant-related toxicity in the year prior. This varied significantly across age groups (p<.001). Just over 1 in 10 people aged less than 25 years received hospital care in the previous year; while 7.2% of people aged 25-44 years, 4.2% aged 45-64 years and 3.5% of adults aged ≥ 65 years, received hospital care for a stimulant-related toxicity. A slightly higher proportion of women who died from stimulant-related toxicity received prior hospital care for a stimulant-related toxicity compared to men (7.8% compared to 5.8%; p=0.01). There was no significant difference in the number of substances directly contributing to death.

Benzodiazepine-Related Toxicity Deaths

NOTE

- Benzodiazepine use disorder is defined in Appendix B, Table B2.
- Hospital treated substance-related toxicities are described in Appendix B, Table B1.

Table 12: Descriptive characteristics for benzodiazepine-related toxicity deaths

	Benzodiazepine-related toxicity deaths (N=783)
Age category	
<25	89 (11.4%)
25 to 44	374 (47.8%)
45 to 64	291 (37.2%)
≥ 65	29 (3.7%)
Sex	
Female	231 (29.5%)
Male	552 (70.5%)
Number of substances directly contributing to death	
1 (benzodiazepine only)	15 (1.9%)
2+ (polysubstance use)	768 (98.1%)

In total, we observed 783 benzodiazepine-related toxicity deaths over the study period; the smallest number across the four substance-specific categories. Consistent with other substance-related toxicity deaths, nearly half of benzodiazepine-related toxicity deaths (47.8%, N=374) occurred among people aged 25-44 years old and over one-third were aged 45-64 years (37.2%, N=291). The prevalence of deaths in the youngest (<25 years) and oldest (≥ 65 years) age categories, were slightly higher among benzodiazepine-related toxicity deaths compared to opioid-related and stimulant-related toxicity deaths. As observed in other substance-related toxicity deaths, the majority of deaths occurred among males (70.5%, N=552), although this was slightly less pronounced than the sex distributions observed for the other substance-related toxicity deaths. The vast majority of benzodiazepine-related toxicity deaths involved polysubstance use (98.1%, N=768), with a very small proportion of deaths involving benzodiazepines alone (1.9%, N=15). It is important to note that this was the highest proportion observed across the four substance specific categories, highlighting the important role of polysubstance use in benzodiazepine-related toxicity deaths.

Table 13: Prior dispensing of prescription benzodiazepines, among benzodiazepine-related toxicity deaths

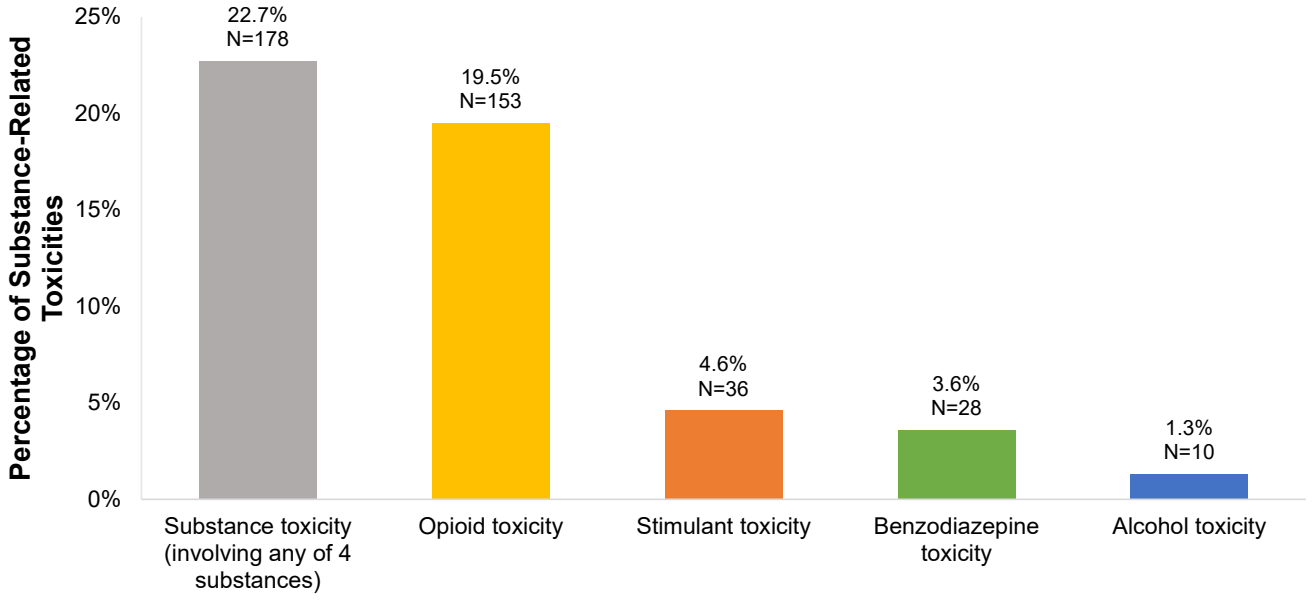
	30 days	1 year	5 years
Benzodiazepine-related toxicity deaths (N=783)	280 (35.8%)	358 (45.7%)	459 (58.6%)
Toxicity deaths directly attributable to pharmaceutical benzodiazepines (N=441)	245 (59.6%)	288 (70.1%)	331 (80.5%)
Toxicity deaths directly attributable to non-pharmaceutical benzodiazepines (N=390)	42 (10.8%)	81 (20.8%)	144 (36.9%)

NOTE

It is important to note that for individuals who were recently dispensed a prescription benzodiazepine prior to death, these medications were not necessarily a direct contributor to subsequent benzodiazepine-related toxicity deaths.

Nearly half of benzodiazepine-related toxicity deaths (49.8%, N=390) occurred among people who had a non-pharmaceutical benzodiazepine (such as: bromazolam, etizolam, flualprazolam, and flubromazolam) directly contributing to death. These unregulated benzodiazepines are not available for prescription in Canada, and are increasingly being found in the unregulated fentanyl supply. Therefore, people are generally not intending to use these substances, but are inadvertently exposed to them through the unregulated opioid supply. In the 5 years prior to death, a benzodiazepine was dispensed to 58.6% of people who died from benzodiazepine-related toxicity, which decreased to just over one-third (35.8%) in the 30 days prior to death. However, this differed considerably based on whether the deaths had pharmaceutical benzodiazepines directly contributing to death. Specifically, prior benzodiazepine dispensing was much more common (59.6% in the previous 30 days) among people whose death involved pharmaceutical benzodiazepines compared to those with non-pharmaceutical benzodiazepine directly contributing to death (10.8% in the previous 30 days).

Figure 7: Hospital treated substance-related toxicities in the year prior to death, among people who died from benzodiazepine-related toxicity (N=783)



Consistent with the findings for opioid-related and stimulant-related toxicity deaths, almost one quarter of benzodiazepine-related toxicity deaths (22.7%, N=178) occurred among people with at least one previous hospital treated substance-related toxicity involving opioids, stimulants, benzodiazepines and/or alcohol in the year before death. The most common substance involved in these toxicities was opioids (19.5%, N=153). Although prior hospital treated benzodiazepine-related toxicities were uncommon (3.6%, N=28), they were more common among those experiencing a benzodiazepine-related toxicity death than was observed among opioid-related toxicity deaths (2.1%) and stimulant-related toxicity deaths (1.9%).

Table 14: Prior substance use disorder diagnoses among people who died from benzodiazepine-related toxicity

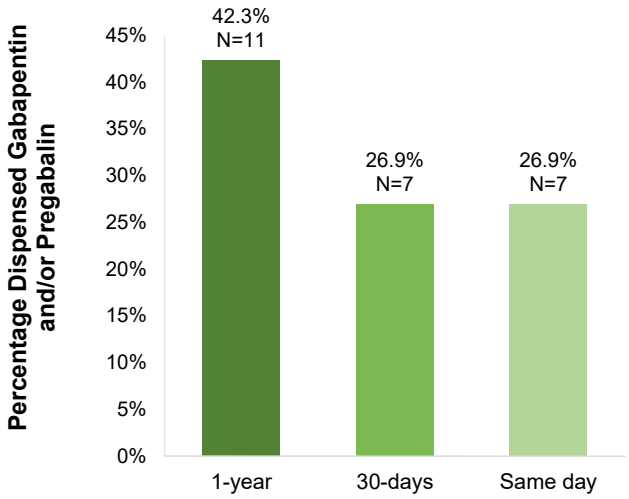
	Benzodiazepine-related toxicity deaths (N=783)
Any substance use disorder diagnoses†	502 (64.1%)
Benzodiazepine use disorder diagnoses (hospital based encounters in prior 5 years)†	34 (4.3%)
Any outpatient diagnoses related to substance use (prior 1 year)†	325 (41.5%)

NOTE

† See Appendix B, Table B2 for definitions.

Although nearly two-thirds of people who had a benzodiazepine directly contribute to death had a substance use disorder diagnosis at time of death (64.1%, N=502), a much smaller proportion had a hospital visit for reasons related to a benzodiazepine use disorder diagnosis in the previous 5 years (4.3%, N=34). We found that in the year prior to death, 41.5% (N=325) of people who had a benzodiazepine-related toxicity death had at least one outpatient healthcare visit related to a substance use disorder (excluding visits related to alcohol use disorders), although we were unable to determine if these were related to benzodiazepine use or other substance use disorders. When interpreting these results, it is important to note the high polysubstance use recorded among benzodiazepine-related toxicity deaths, where 98.1% involved other substances (based on our previous report findings, most commonly opioids).[2] Therefore, these prior diagnoses of substance use disorders are most likely tied to an individual's use of other substances, and not the benzodiazepines directly.

Figure 8: Prior receipt of gabapentin and/or pregabalin among those with benzodiazepine use disorder diagnoses who died from benzodiazepine-related toxicity and were eligible for public drug benefits (N=26)



A total of 26 people who died with a benzodiazepine directly contributing to death had a confirmed benzodiazepine use disorder and were eligible for the public drug program (meaning that we can capture exposure to gabapentinoids). In this group, 42.3% (N=11) were dispensed a gabapentinoid (i.e. gabapentin and/or pregabalin) in the past year and approximately one-quarter (26.9%, N=7) were actively being treated with these medicines at their time of death. Carbamazepine was also included in our analysis; however no individuals were dispensed this potential treatment option in the past year.

Table 15: Benzodiazepine use disorder diagnoses and prior hospital treated benzodiazepine-related toxicity among benzodiazepine-related toxicity deaths, stratified by descriptive characteristics

	Benzodiazepine-related toxicity deaths (overall)	Benzodiazepine use disorder diagnoses† (prior 5 years)	Hospital treated benzodiazepine-related toxicity* (prior 1 year)
Total deaths	783	34 (4.3%)	28 (3.6%)
Age			
<25	89	7 (7.9%)	7-11 (8-12%)
25 to 44	374	18 (4.8%)	16 (4.3%)
45 to 64	291	9 (3.1%)	1-5 (0.3%-1.7%)
≥65	29	0 (0%)	0 (0.0%)
Sex			
Female	231	7 (3.0%)	1-5 (0.4%-2.2%)
Male	552	27 (4.9%)	23-27 (4.2%-4.9%)
Hospital treated benzodiazepine-related toxicity (prior 1 year)			
Benzodiazepine-related toxicity	28	6 (21.4%)	28 (100%)
No benzodiazepine-related toxicity	755	28 (3.7%)	0 (%)

NOTE

- † See Appendix B, Table B2 for definitions.
- *See Appendix B, Table B1 for definitions.
- % reported are row percentages using the number of benzodiazepine-related toxicity deaths categories as the denominator.
- Reporting of number of substances directly contributing to deaths was not included due to small cells.

Overall, only 4.3% of benzodiazepine-related toxicity deaths had a confirmed diagnosis of a benzodiazepine use disorder, although there are no outpatient physician visit codes specific to benzodiazepine use disorder and so this definition relies only on diagnoses found in hospital records. Across age groups, the highest prevalence of a benzodiazepine use disorder was observed among those aged <25 years (7.9%), with less than 5% of benzodiazepine-related toxicity deaths in other age groups occurring among people with a hospital confirmed benzodiazepine use disorder diagnosis (p=0.15). In contrast to the other substance groups, a higher proportion of men were diagnosed with a benzodiazepine use disorder prior to death compared to women (4.9% vs. 3.0%; p=0.24).

Alcohol-Related Toxicity Deaths

NOTE

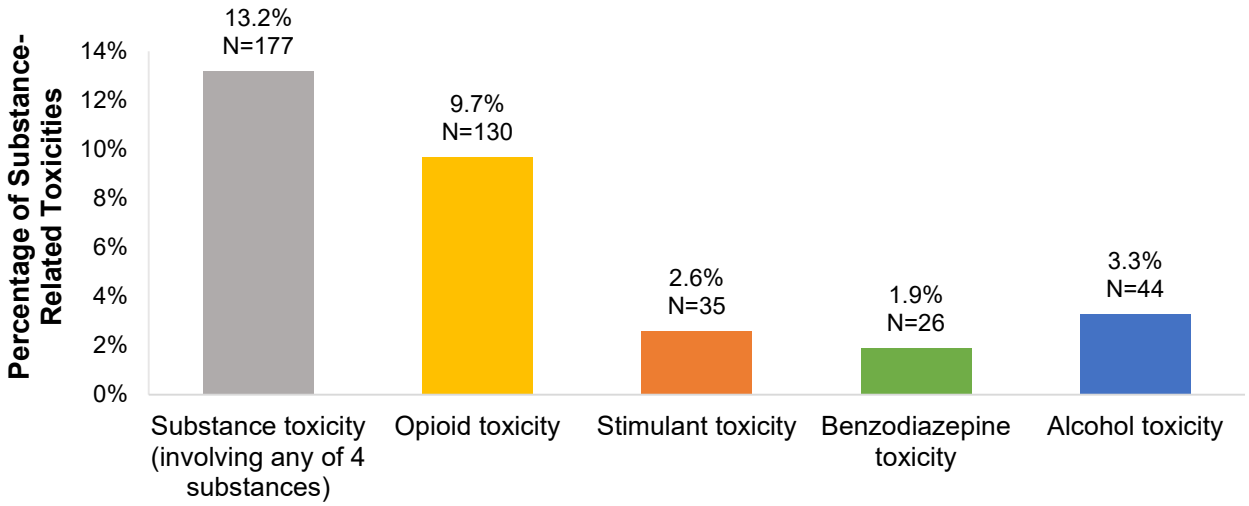
- Alcohol use disorder is defined in Appendix B, Table B2.
- Hospital treated substance-related toxicities are defined in Appendix B, Table B1.
- Age categories <25 and 25-44 years were combined for this analysis due to small numbers.

Table 16: Descriptive characteristics for alcohol-related toxicity deaths

	Alcohol-related toxicity deaths (N=1,346)
Age category	
≤ 44	761 (56.5%)
45 to 64	534 (39.7%)
≥ 65	51 (3.8%)
Sex	
Female	352 (26.2%)
Male	994 (73.8%)
Number of substances directly contributing to death	
1 (alcohol alone)	217 (16.1%)
2+ (polysubstance use)	1,129 (83.9%)

Over the study period, a total of 1,346 deaths were directly attributable to alcohol. Over half of alcohol-related toxicity deaths occurred among people aged less than 45 years (56.5%) and nearly three-quarters were males (73.8%). The majority of these deaths involved polysubstance use (83.9%), with 217 deaths (16.1%) directly attributed to alcohol alone.

Figure 9: Hospital treated substance-related toxicities in the year prior to death, among people who died from alcohol-related toxicity (N=1,346)



In contrast to other substance-related toxicity deaths, prior hospital treated toxicity events were more uncommon in this population, occurring among only 13.2% (N=177) of people with an alcohol-related toxicity death. Although opioid-related toxicity events remained the most common type of prior toxicity event (9.7%, N=130), the prevalence remained lower than observed for other substance-related deaths. Prior alcohol toxicity events – while remaining uncommon, were more likely to have occurred among people experiencing an alcohol-related toxicity death (3.3%, N=44), compared to other substance-related deaths (ranges from 0.9% to 1.3%).

Table 17: Prior substance use disorder diagnoses among people who died from alcohol-related toxicity

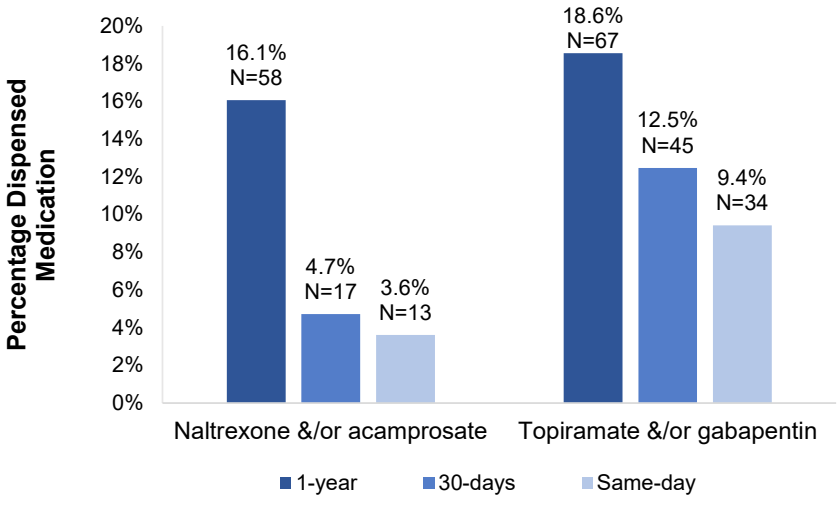
	Alcohol-related toxicity deaths (N=1,346)
Any substance use disorder diagnosis†	803 (59.7%)
Any alcohol use disorder diagnosis†	679 (50.4%)
Hospital based encounters with alcohol use disorder diagnosis (prior 5 years)†	654 (48.6%)
Outpatient visits related to alcohol use disorder†	
Any	216 (16.0%)
0	1,130 (84.0%)
1	103 (7.7%)
2	45 (3.3%)
≥3	68 (5.1%)

Overall, approximately 60% of people who had alcohol directly contribute to their death had a substance use disorder diagnosis (59.7%, N=803), with the majority of these individuals having an alcohol use disorder diagnosis in a hospital or outpatient setting (50.4%, N=679). Engagement with the hospital healthcare system for reasons related to alcohol use disorder in the 5 years prior to death was most common, occurring in nearly half of all alcohol-related toxicity deaths (48.6%, N=654), with outpatient visits related to alcohol use disorder occurring among only 16.0% of individuals, suggesting poor access to outpatient alcohol treatment services for this group.

NOTE

† See Appendix B, Table B2 for definitions.

Figure 10: Prior receipt of pharmacological treatment for alcohol use disorders for people with an alcohol use disorder diagnosis and who were eligible for public drug benefits, among alcohol-related toxicity deaths (N=361)



We constructed a sub-cohort of all alcohol-related toxicity deaths that occurred among people with an alcohol use disorder diagnosis (confirmed in hospital or an outpatient setting) who were eligible for public drug benefits to capture the prevalence of recent receipt of pharmacological treatment. In this analysis, among the 361 alcohol-related toxicity deaths meeting these criteria, 16.1% had received naltrexone and/or acamprosate in the past year, which decreased to 4.7% (N=17) and 3.6% (N=13) at 30 days and same day of death, respectively. We also reported exposure to other "off label" treatments sometimes used to manage alcohol use disorder, including topiramate and/or gabapentin. In this analysis, exposure to treatment was similarly low in the past year (18.6%, N=67), although exposure in the past month and at time of death was slightly higher (12.5% and 9.4%, respectively).

Table 18: Prevalence of alcohol use disorder diagnoses and prior hospital treated alcohol-related toxicity among alcohol-related toxicity deaths, stratified by descriptive characteristics

	Alcohol-related toxicity deaths (overall)	Alcohol use disorder diagnoses† (prior 5 years)	Hospital treated alcohol-related toxicity* (prior 1 year)
Total deaths	1,346	679 (50.4%)	44 (3.3%)
Age			
≤ 44	761	395 (51.9%)	32 (4.2%)
45 to 64	534	256 (47.9%)	7-11 (1.3%-2.1%)
≥65	51	28 (54.9%)	1-5 (2.0%-9.8%)
Sex			
Female	352	185 (52.6%)	14 (4.0%)
Male	994	494 (49.7%)	30 (3.0%)
Number of substances directly contributing to death			
1 (alcohol alone)	217	147 (67.7%)	9 (4.1%)
2+ (polysubstance use)	1,129	532 (47.1%)	35 (3.1%)
Hospital treated alcohol-related toxicity (prior 1 year)			
Alcohol-related toxicity	44	37 (84.1%)	44 (100%)
No alcohol-related toxicity	1,302	642 (49.3%	0 (0%)

NOTE

- † See Appendix B, Table B2 for definitions.
- *See Appendix B, Table B1 for definitions.
- All % reported are row percentages reported using the number of alcohol-related toxicity deaths categories as the denominator.

Overall, approximately half (50.4%) of people who had alcohol directly contribute to their death had an alcohol use disorder diagnosis. In contrast to other substance-related toxicity deaths, there was less variation across age groups and sex, with the prevalence of alcohol use disorder remaining close to 50% in each demographic subgroup. As expected, a higher proportion of people with only alcohol directly contributing to death (i.e. with no contribution of opioids, stimulants or benzodiazepines) had an alcohol use disorder diagnosis (67.7%) compared to alcohol-related toxicity deaths involving polysubstance use (47.1%; p<.001). Finally, people with a prior hospital treated alcohol-related toxicity were much more likely to have an alcohol use disorder (84.1%) compared to those with no prior hospital treated alcohol-related toxicity (49.3%; p<.001). When looking at prior hospital treatment for alcohol-related toxicities in the previous year, no significant differences across demographic characteristics and circumstances surrounding death were observed.

Limitations

1. Our analysis, is limited to acute substance-related toxicity deaths, with individuals who did not have a valid Ontario health card excluded from our analysis (7% in total). Furthermore, our analysis does not contain outcomes which occur in the long-term due to substance use (e.g., chronic conditions such as cirrhosis) or other acute injuries related to the substance (e.g., vehicle collision resulting from impaired driving). Thus, our report does not fully capture all substance-related toxicity deaths, which extend beyond acute substance-related toxicities.

2. When looking at prior dispensing of substances, the strength of the dose dispensed and frequency were not captured in this analysis. The risk of fatal overdose may follow a dose response, with fatality more likely with opioid doses above 50 MME/day.[10] Furthermore, we did not capture inpatient pharmacological treatment and non-pharmacological treatments (such as counselling) individuals may have received prior to a substance-related toxicity death.

3. For pharmacological treatment, for alcohol, and benzodiazepine use disorders, our analysis was restricted to dispensing of medications recorded in the Ontario Drugs Benefit database and as a result, does not capture everyone dispensed these medicines in Ontario. Furthermore, disulfiram is not covered by the ODB and as a result, we were unable to capture prescribing or dispensing of this treatment for alcohol use disorder.

4. In our analysis, we could not differentiate stimulant and/or benzodiazepine dispensing to help manage a substance use disorder versus those prescribed for other indications. Therefore, some of the prior dispensing of these medications among people with benzodiazepine and stimulant-related toxicity deaths could be reflective of attempts to help provide treatment and/or harm reduction to people exposed to these substances from the unregulated drug supply. However, it is important to note that prescribing substances such as stimulants through safer supply programs is reported to be relatively uncommon.[11]

5. Finally, it is important to note that definitions used to define a prior diagnoses of substance use disorders are not validated. Consistent with the literature, there is no validated definitions and heterogeneity in screening for substance use disorders, therefore there is potential for misclassification of people with or without substance use disorders in our analysis.[12] In particular, our definition is only able to capture people who had a healthcare encounter for a substance use disorder, and many people may not engage with the healthcare system or may not have their diagnosis indicated appropriately on their records. Where possible, we have reported any substance use disorder diagnosis and substance specific diagnosis; however outpatient codes for substance-related disorders only differentiate between alcohol use disorder and other substance use disorders (they are not substance specific). For opioid use disorder diagnoses, prior OAT and fee codes specific to the provision of this treatment were used to supplement the definition of opioid use disorder in this study. However, we were unable to include outpatient diagnoses for stimulant and benzodiazepine use disorders. After sensitivity analysis, we chose not to use general outpatient definitions due to the high degree of combined opioid use and our inability to differentiate opioid use disorder from other substance use disorders using these outpatient codes.

Discussion

In our previous report, we highlighted that substance-related toxicity deaths in Ontario had grown considerably over the COVID-19 pandemic.[2] In this current report, we further investigate the frequency of previous healthcare encounters for non-fatal substance-related toxicities, previous diagnoses of multiple substance use disorders and prescribing patterns of medicines among people who died from substance-related toxicity. In total, we report on 10,024 accidental substance toxicity deaths in Ontario over the four and a half year study period. Similar to our previous report, the majority of substance-related toxicity deaths we report involved polysubstance use[2], with opioids the most common substance directly attributed to deaths. We also highlight the role of non-pharmaceutical/unregulated substance use, with 85.9% of opioid-related toxicity deaths involving unregulated opioids, 99.1% of stimulant-related toxicity deaths involved stimulants originating from the unregulated drug supply and 49.8% of benzodiazepine-related toxicity deaths involving non-pharmaceutical benzodiazepines.

Our findings relating to healthcare encounters for non-fatal substance-related toxicities prior to death, highlighted that just over 1 in 5 people who died from opioid, stimulant or benzodiazepine-related toxicities received hospital care for substance-related toxicity in the year prior to death. This proportion was much smaller among people who died from alcohol-related toxicity, with 13.2% presenting to a hospital for any substance-related toxicities in the year prior to death. These prior critical care encounters provide vital windows of opportunity for healthcare professionals to engage with people who use substances.[13] The high frequency of these interactions identified in this report suggest that there may be missed opportunities to provide better support to people treated for substance-related toxicities within hospital settings, including initiating treatment when appropriate and coordinating connections with community based programs.[14] However, strategies to support transitions in care from an acute hospital setting to community based care still vary greatly. For example, a recent publication from Ontario reported that only 1 in 18 patients were dispensed OAT within a week of discharge for a hospital encounter for opioid-related toxicity.[15] Accordingly, a more streamlined approach could help people who have experienced substance-related harms to access care and treatment during transitions between settings (e.g. after hospital discharge to a family physician or community pharmacy). It is also important to note that people who use substances face many barriers in accessing primary care services and are less likely to find a new physician, making it more difficult to receive appropriate treatment in a timely manner.[16] This reinforces the need for expanded access to primary care in this population and streamlined efforts to coordinate connection to these services upon hospital discharge.

We found important differences in the prevalence of hospital and outpatient visits related to substance use disorder diagnoses among people experiencing substance-related toxicity deaths, suggesting that there are important opportunities to intervene and support people at risk of substance-related harms in both inpatient and outpatient settings. For example, nearly half of people who died from alcohol-related toxicity (48.6%) engaged with the hospital system in the 5 years prior to death for an alcohol use disorder, while only 1 in 4 people who died from opioid-related toxicity (25.7%) or stimulant-related toxicity (26.7%) engaged with the hospital system for reasons associated to an opioid or stimulant use disorder diagnoses over a similar timeframe. In contrast, prior outpatient physician visits related to alcohol use disorder were less common (16% of people who died from alcohol-related toxicity), whereas over one-third of people who died from opioid or stimulant-related toxicity had an outpatient physician visit for a substance use disorder in the past year. These findings may be reflective of people with an alcohol use disorder being more likely to initially present to hospital due to alcohol intoxication related trauma, injuries or symptoms of withdrawal[17, 18] compared to people with other substance use disorders who may more frequently engage with primary care and other outpatient physician services to access care. A notably small number of people who died from benzodiazepine-related toxicity deaths (4.3%) engaged with the hospital healthcare system for reasons related to benzodiazepine use disorder diagnoses. This is likely explained by the fact that the vast majority of people who died from benzodiazepine-related toxicity deaths (98.1%), had

polysubstance use contributing to death (primarily opioids and stimulants) and with the growing presence of benzodiazepines in the unregulated drug supply and polysubstance use, exposure to benzodiazepines (and resulting benzodiazepine use disorder) may be underappreciated or underdiagnosed.

Our above findings have shown that, while substance use disorder prevalence was relatively high among all substance-related toxicity deaths, a large proportion of substance-related toxicity deaths are occurring among people without any recent healthcare encounter for an indicated substance use disorder. For example, approximately 2 in 5 people who died from opioid or stimulant-related toxicity did not have a substance use disorder diagnosis in the 5 years prior. This may be due to an under-diagnosis of substance use disorders for some people who are disconnected with the healthcare system, people possibly avoiding accessing healthcare due to the fear of stigma, or a substance use diagnosis not recorded when people receive treatment for a condition related to substance use such as injuries. Additionally, it also likely reflects the underlying toxicity of the unregulated drug supply. The volatility of the unregulated drug supply holds particular risks for associated substance use that exist among people who occasionally use substances. As our findings have shown, exposure to fentanyl and stimulants from the unregulated drug supply are directly responsible for the vast majority of substance-related toxicity deaths in Ontario. This is an important finding as it reinforces the need for responses to substance-related toxicity deaths which include both access to treatment for those who desire it alongside other comprehensive health, harm reduction and social interventions that will meet the needs of people with and without substance use disorders.

Over half of the people who died from opioid-related toxicity with a prior opioid use disorder diagnosis, had accessed OAT in the year before death (58.6%); yet this declined to just over 1 in 10 people (10.8%) actively receiving treatment at the time of death. Given the well-established benefits of OAT in reducing both mortality and morbidity among people with opioid use disorder,[19] future investments focused on providing tailored patient-centered treatment that supports OAT retention could be beneficial in reducing this treatment gap. For example, expanded access to longer acting OAT formulations, higher doses, and combination therapy (i.e. methadone and slow release oral morphine),[20, 21] supporting patient autonomy in selecting preferred treatment types, and reducing requirements for frequent interactions (such as providing options for virtual care, particularly for people in rural areas) could help mitigate barriers to treatment that have been established in the literature[22-24] and improve quality of life.[25]

We found that half of people who died from alcohol-related toxicity had a previous healthcare encounter related to an alcohol use disorder diagnosis; however pharmacological treatment among this population was very low. Although medications to treat alcohol use disorder exists, evidence suggests that they are often underutilized in many healthcare settings.[26, 27] Interestingly, in this report, a similar proportion of people were prescribed the recommended first line treatments naltrexone and/or acamprosate (16.1%) as were prescribed “off label” treatment options such as topiramate and gabapentin (18.6%), in the past year.[26] An important consideration in this is that the majority of alcohol-related toxicity deaths (84%) in this study involved polysubstance use, which highlights the need for a comprehensive approach to address polysubstance use instead of addressing particular substances in isolation. Polysubstance use can also introduce barriers for prescribing suitable treatment options. For example, naltrexone (an opioid antagonist) is contraindicated for use among people taking opioids (including OAT). Furthermore, before the initiation of acamprosate treatment prior abstinence from alcohol consumption is typically required, which may result in a hesitancy in initiating treatment courses among people who may not be in a position to fully abstain from alcohol use.[28] Finally, there have also been several shortages of acamprosate supplies across Canada in recent years which have likely imparted difficulties in accessing this treatment for alcohol use disorder over this time.[29]

For this report, we also investigated previous dispensing of medications prior to substance-related toxicity deaths. Among people who died from benzodiazepine-related toxicity deaths, 35.8% were dispensed benzodiazepines

in the month before death, however this declined to just over 10% among people whose deaths involved a non-pharmaceutical benzodiazepine. It is also important to note that benzodiazepine dispensing is common at a population level, and therefore this prior dispensing may not be related to the toxicity itself.[30] This is evident by the fact that over 98% of benzodiazepine-related toxicity deaths involved other substances, which aligns with the growing presence of this drug in the unregulated fentanyl supply. Among opioid and stimulant-related toxicity deaths, only 15.4% and 4.7% of people had been prescribed a pharmaceutical opioid analgesic or pharmaceutical stimulant in the month before death, respectively. This likely reflects the differential role of pharmaceutical and non-pharmaceutical drugs in the current landscape of substance-related harms in Ontario. Specifically, the majority of opioid-related toxicity deaths (85.9%) involved unregulated opioids and similarly 99.1% of stimulant-related toxicity deaths involved stimulants originating from the unregulated drug supply. In contrast, only half of benzodiazepine-related toxicity deaths (49.8%) involved non-pharmaceutical benzodiazepines. This should inform responses to these harms, where a focus on maximizing the safety of people accessing the unregulated opioid and stimulant drug supply is needed, including optimal care for mental health symptoms. Importantly, there is also clear evidence of the high prevalence of non-pharmaceutical benzodiazepines in the unregulated fentanyl supply which has led to concerns about the contribution of non-pharmaceutical benzodiazepines to fentanyl-related toxicity deaths, and rising benzodiazepine dependence and withdrawal among people who use opioids. With approximately half of benzodiazepine-related toxicity deaths having non-pharmaceutical benzodiazepines directly contributing to death, there is a need to also consider how to integrate benzodiazepine-related treatment and withdrawal supports for people who use opioids who are increasingly being exposed to high potency benzodiazepines in the fentanyl supply. As in our previous report, we found that just under 1 in 10 opioid-related toxicity deaths involved concurrent use with a benzodiazepine.[2]

Despite three-quarters of substance-related toxicity deaths occurring among men, we observed that a higher proportion of women who died from opioid, stimulant or alcohol-related toxicities previously had a healthcare encounter for a diagnosed substance use disorders. Women may be more likely to seek medical help when experiencing mental health challenges[31] and could possibly explain why they are more likely to seek medical help compared to men for substance use disorders. These findings reflect the need for responses to substance-related toxicities to be responsive to the needs of both men and women and to recognize the high prevalence of substance use disorders among women at risk of harms. To help inform future interventions for women, it is vital that any barriers to treatment and harm reduction are identified. In particular, while stigma experienced by people who use substances presents many barriers to accessing care, these can be even greater among parents and may manifest as delays in accessing health and social care, including maternal health services.[32, 33]

Providing more integrated treatment and social care services are vital to help connect people with substance use disorders to additional supports. However, it is important to note that treatment can encompass a variety of modalities, and our results do not capture non-pharmaceutical treatment such as psychosocial and community based treatments. Psychosocial substance use interventions including face-to-face interventions such as cognitive behavioral therapy (CBT), counselling, motivational and social support, may also be important parts of treatment regimens for substance use disorders.[34] Therefore, ensuring that people who use substances have multiple accessible support networks and enhanced awareness of the different treatment and harm reduction options available to them may also enable them to make informed decisions about their care. Finally, although treatment can play an important role in supporting people with substance use disorders, our results highlight the high rates of people dying of substance-related toxicities who do not have diagnosed substance use disorders who would therefore not be eligible for treatment. This finding reinforces the need for investment in treatment, harm reduction and social care programs that are informed by evidence and structured to meet the identified needs of people who use substances. This includes novel OAT formulations and modalities, safer alternatives to the unregulated drug supply[35] and supervised consumption sites.

Conclusion

Over the past 4.5 years, more than ten thousand Ontarians have lost their lives to substance-related toxicities, primarily driven by the unregulated drug supply. This report demonstrates that a large number of these people have recently interacted with hospital care to treat non-fatal substance-related toxicity events (most commonly opioid-related toxicities) or a substance use disorder. Despite this, recent medical treatment among people with substance use disorders is generally low, identifying potential missed opportunities for connection of people who use substances to community based treatment. It is also important to note that not everyone at risk of substance-related harms will be interested in, or eligible for, treatment. Accordingly, it's important that broad access to harm reduction, health, and social care programs are also available. Finally, these findings suggest the need for improved co-ordination of care throughout the healthcare system and other sectors, which can support rapid identification of individuals' health and social needs related to their substance use and a more comprehensive approach to the complex needs of people who use multiple substances. The final report in this series will further investigate broader healthcare utilization for both physical and mental health co-morbidities within this cohort, with the goal of identifying broad healthcare needs among people who use substances and opportunities for expanded support and upstream interventions.

Contributors

Ontario Drug Policy Research Network

The Ontario Drug Policy Research Network (ODPRN) is a province wide network of researchers who provide timely, high quality, drug policy relevant research to decision makers. The ODPRN houses the Ontario Opioid Drug Observatory (OODO) which is funded through a grant from the Canadian Institutes of Health Research (CIHR). This observatory aims to measure, assess and evaluate the use of prescription opioids, opioid-related overdoses, and opioid-related drug policy by leveraging large, population-level data sources. For more information, visit **odprn.ca**.

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- health promotion, chronic disease and injury prevention
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Office of the Chief Coroner – Privacy Statement

Personal information used in developing this report was collected under the authority of the Coroners Act, R.S.O. 1990, C. C.37, as amended. Questions about this collection should be directed to the Chief Coroner, 25 Morton Shulman Avenue, Toronto ON M3M 0B2, Tel.: 416 314-4000 or Toll Free: 1 877 991- 9959.

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Appendix A: Glossary

Substance involvement in toxicity deaths:

- **Directly contributing to death:** Substances determined by the pathologist and/or coroner to have directly contributed to the death based on the complete investigative findings, i.e., toxicology findings and the information obtained during the death investigation.

Opioids:

A family of substances that include opioids available through regulated and pharmaceutical sources for the treatment of pain and opioid use disorder (e.g., oxycodone, hydromorphone, morphine, methadone) and opioids available primarily through unregulated or non-pharmaceutical markets or sources (e.g., heroin, fentanyl, carfentanil).

Origin of opioids:

- Opioids with **primarily unregulated and non-pharmaceutical origins** include:
  - Heroin, heroin metabolites (morphine where monoacetylmorphine (6-MAM) was also detected), U-47700
  - Fentanyl, fentanyl analogues (including carfentanil)
- Opioids with **primarily regulated and pharmaceutical origins** include:
  - Buprenorphine, codeine, hydrocodone, hydromorphone, methadone, morphine where 6-MAM was not detected, oxycodone, oxymorphone or tramadol. This category may include opioids that were prescribed to the deceased person or that were prescribed to someone else (i.e., diverted).

Benzodiazepines:

A class of sedative and anti-anxiety drugs that are widely prescribed for the treatment of anxiety, sleep disorders (e.g., insomnia), certain forms of epilepsy, and alcohol withdrawal. Currently, 14 different benzodiazepines are approved for use in Canada. Benzodiazepines that are not approved for medical use in Canada, such as etizolam, are increasingly being found in the unregulated drug supply.

Origin of benzodiazepines:

- Benzodiazepines with **primarily unregulated and non-pharmaceutical origins**:
  - Indicates the presence of benzodiazepines (non-prescription only; exclusively bromazolam, etizolam, flualprazolam, and flubromazolam)
- Benzodiazepines with **primarily regulated and pharmaceutical origins**:
  - Indicates the presence of benzodiazepines (prescription only; i.e., excluding bromazolam, etizolam, flualprazolam, and flubromazolam)

Stimulants:

A class of drugs used for the treatment of attention-deficit/hyperactivity disorder and sleeping disorders (e.g., narcolepsy). These drugs act on the central nervous system to increase alertness, attention and energy. This category also includes stimulants that are used occasionally and primarily available from the unregulated market, such as cocaine and methamphetamine.

Appendix B: Definitions of prior substance-related toxicities and substance use disorders and alcohol use disorders

Table B1: Definitions of prior substance-related toxicities in the 1 year prior to death, using emergency department (ED) visits or in-patient hospitalizations

We identified any emergency department visits (NACRS) or in-patient hospitalizations (DAD) for a non-fatal substance-related toxicity in the 1-year before death (excluding date of death), defined using the following ICD-10 codes separately for:
Opioid-related toxicity • **ICD-10 codes: T400, T401, T402, T403, T404, T406**
Stimulant-related toxicity • **ICD-10 codes: T436, T405**
Benzodiazepine-related toxicity • **ICD-10 code: T424**
Alcohol-related toxicity • ICD-10 code: T510
Substance-related toxicity • Using the definitions for the above substance-specific toxicity events, determine if a person had ≥1 hospital treated substance-related toxicity in the year prior to death

Table B2: Definitions of substance use disorders and alcohol use disorders used in the report

Substance	Classification	Defined as:
Alcohol	Alcohol use disorder hospital diagnoses only (using data from DAD, NACRS & OMHRS databases)	ICD-10 (DAD/NACRS/OMHRS): • F10 • K70 • G312 • G621 • G721 • I426 • K292 • K860 • Z502 • Z714 • Z8640 • E244 • K852 ICD-9 (OMHRS): 291.x [excl. 291.82], 303.x, 305.0
	Alcohol use disorder (definition used in this report)	In the past 5 years for any alcohol use disorder hospital diagnosis (summarized above) or prior 1 year for alcohol use disorder outpatient visits (OHIP DXCODE: 303, 291)
Opioids	Opioid Use Disorder hospital diagnoses only (using data from DAD, NACRS & OMHRS databases)	In the past 5 years, any hospital opioid use disorder diagnosis using: **ICD-10 (DAD/NACRS/OMHRS):** F11: Opioid-related disorders **ICD-9 (OMHRS):** 304.0, 305.5
	Opioid use disorder (definition used in the report)	In the past 5 years, any hospital opioid use disorder diagnosis (summarized above) or OAT dispensing or OHIP claims* *Any previous opioid-agonist related outpatient visits (OHIP) in the 5 years prior to death were identified using fee codes: K682, K683 & K684
	Opioid use disorder (broadest definition, used in sensitivity analysis)	In the past 5 years, any hospital opioid use disorder diagnosis or OAT dispensing or OHIP claims (with feecode only) or 1 year of substance use disorder outpatient visit (OHIP DXCODE: 304, OHIP Location: O, L, P, H)
Stimulants	**Stimulant use disorder (hospital diagnoses; using data from DAD, NACRS & OMHRS databases). Note: this is the definition used in the report**	**In the past 5 years any hospital diagnosis using:** **ICD-10 (DAD/NACRS/OMHRS): F14, F15** **ICD-9 (OMHRS): 304.4**
	Stimulant use disorder (more broad; used in sensitivity analysis)	In the past 5 years, any hospital substance use disorder diagnosis of stimulant use disorder (summarized above for specific stimulant diagnosis) or 1 year of substance use disorder outpatient visit (OHIP DXCODE: 304, OHIP Location: O, L, P, H)
Benzodiazepines	**Benzodiazepine (hospital diagnoses; using data from DAD, NACRS & OMHRS databases) Note: this is the definition used in this report**	**In the past 5 years any hospital diagnosis of:** **ICD-10 (DAD/NACRS/OMHRS): F13** **ICD-9 (OMHRS): 304.1**
	Benzodiazepine (more broad classification used in sensitivity analysis)	In the past 5 years, any hospital substance use disorder diagnosis of benzodiazepine use disorder (summarized above) or 1 year of substance use disorder outpatient visit (OHIP DXCODE: 304, OHIP Location: O, L, P, H)
Any substance use	**Any substance use disorder diagnosis**	Defined as hospital-based encounters with substance use disorder diagnoses in the prior 5 years or substance use disorder outpatient diagnoses in the prior 1 year (not including alcohol use disorder outpatient diagnoses)
	Any other substance use disorder outpatient diagnosis (overall substance reporting)/any outpatient diagnoses related to substance use (substance-specific findings)	Any outpatient visit for a substance use disorder (with the exception of alcohol use disorder outpatient diagnoses, they are not included in this definition)
	Any healthcare encounter for substance use disorder	Any healthcare encounter for a substance use disorder, is any hospital diagnosis in the last 5 years for substance use disorders/ alcohol use disorders and any outpatient visits in the past year for alcohol use disorders/substance use disorders