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Characteristics of poisonings involving ketamine in the United States, 2019–2021

Joseph J. Palamar[1], **Nicole D. Fitzgerald**[2], **David J. Grundy**[3], **Joshua C. Black**[3], **Jennifer S. Jewell**[3], **Linda B. Cottler**[2]

[1]Department of Population Health, New York University Grossman School of Medicine, New York, NY, USA

[2]Department of Epidemiology, College of Public Health and Health Professions, College of Medicine, University of Florida, Gainesville, FL, USA

[3]A Division of Denver Health, Rocky Mountain Poison & Drug Safety (RMPDS), Denver, CO, USA

Abstract

Background: The use of ketamine, a controlled dissociative anesthetic, has become more widespread in recent years with recreational/nonmedical use increasing and ketamine becoming more widely available in clinics to treat depression.

Aims: We examined recent trends in adverse effects related to ketamine use.

Methods: US National Poison Control data were examined, focusing on ketamine exposures among those aged ⩾13 between 2019 and 2021 ($n = 758$). We examined quarterly trends in exposure and delineated correlates of patients experiencing a major adverse effect or death.

Results: The number of reported exposures increased 81.1% from 2019 Quarter 1 through 2021 Quarter 4, from 37 to 67 ($p = 0.018$). The majority of patients were male (57.1%), and the plurality of cases involved intentional misuse or "abuse" (39.5%), followed by suspected suicide attempt (19.7%) and unintentional exposure (18.9%). A fifth (19.6%) experienced a major adverse effect or death. A third (33.4%) co-used other drugs; the drugs most commonly co-used were benzodiazepines (14.6%), alcohol (10.3%), and opioids (8.7%). Co-use of *gamma*-hydroxybutyrate (GHB; adjusted prevalence ratio (aPR) = 3.43, 95% confidence interval (CI): 1.57–7.46) and opioids (aPR = 2.44, 95% CI: 1.46–4.08) was associated with increased risk for a major adverse effect or death, as was injection-only administration (aPR = 2.68, 95% CI: 1.21–5.92).

Conclusions: Although still rare, poisonings involving ketamine have increased in recent years. Polydrug use—particularly with opioids or GHB—appears to be a particular risk factor for more

Corresponding author: Joseph J. Palamar, Department of Population Health, New York University Grossman School of Medicine, 180 Madison Avenue, Room 1752, New York, NY 10016, USA, joseph.palamar@nyulangone.org.

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serious adverse effects. As prevalence of use increases, it is important to monitor adverse effects and co-occurring behaviors to inform timely prevention and harm reduction as needed.

Keywords

Ketamine; poisonings; polydrug use

Introduction

Ketamine, a dissociative drug with anesthetic, analgesic, and hallucinogenic properties, has an established history of both medical and nonmedical use. In addition to this NMDA receptor antagonist's use as an anesthetic in human and veterinary medicine for half a century (Kohtala, 2021), ketamine has also been prevalent as a recreational drug in nightclub settings for decades (Halkitis et al., 2007; Palamar & Keyes, 2020). In recent years, ketamine use has become more widespread in the United States, which can be attributed, in part, to increasing availability of ketamine in both clinical and non-clinical settings and shifting prevalence of nonmedical use. Decades of research into ketamine's rapid antidepressant properties led to the US Food and Drug Administration's (US FDA, 2019) approval of the use of esketamine nasal spray for treatment-resistant depression in 2019, which has subsequently led to increased availability of ketamine in psychiatric treatment settings. Rates of ketamine seizures by US law enforcement also increased significantly from 2012 to 2019, suggesting increased availability outside clinical settings (Palamar et al., 2021). Along with indicators of availability, epidemiological research has shown that, while prevalence of non-medical use in the general US population has remained low, there was a quarterly increase in estimated past-year ketamine use from 2006 to 2019, which reached a peak of 0.9% in late 2019 (Palamar et al., 2021). Of note is the increasing prevalence of ketamine use among nightclub and dance festival attendees, which rose from 5.9% in 2016 to 15.3% in 2019 in a New York City sample (Palamar & Keyes, 2020).

While ketamine has a wide safety margin and is generally considered a less risky drug than various other types of drugs commonly used recreationally (Gable, 2004; Morgan et al., 2010; Nutt et al., 2010), both acute and chronic adverse effects associated with use have been described (Corkery et al., 2021; Fitzgerald et al., 2021), which appear to vary depending on dosage and frequency of use, co-use of ketamine with other substances, and interactions between the person using ketamine and the setting of use (Dillon et al., 2003). A recent systematic review found that most serious adverse effects, such as cognitive impairment, urinary cystitis, other urinary tract issues, and upper gastrointestinal problems ("K cramps"), were associated with chronic and "heavy" ketamine use, with several studies reporting a dose-effect relationship between duration of ketamine use and severity of adverse events (Van Amsterdam & Van Den Brink, 2022). Other studies have suggested that ketamine polysubstance use may be associated with adverse effects. For example, in a study of nightclub and festival attendees which found that nearly one-fifth (19.3%) of those who used ketamine in the past year experienced a harmful or very unpleasant effect, over half (56.3%) of those instances reportedly involved the use of other drugs—a quarter (25.0%) co-using ketamine with alcohol, 18.8% co-using with cocaine, and 18.8% co-using with ecstasy (Palamar et al., 2019). Impaired awareness or perception due to ketamine

intoxication as well as the drug's effects on coordination can also lead to a higher risk of acute physical harm and fatal accidents (Morgan et al., 2012).

Given the recent increases in both medical and nonmedical ketamine use and the potential for associated adverse effects, it is important for research to examine trends and co-occurring behaviors related to ketamine use and outcomes to inform prevention, intervention, and harm reduction efforts. Although ketamine-related deaths have been found to be relatively rare (Corkery et al., 2021; Darke et al., 2021; Dillon et al., 2003), the Centers for Disease Control and Prevention National Vital Statistics System (NVSS), which is the primary source of information on drug-related mortality in the United States, does not report on ketamine. One source of information which allows us to monitor trends in adverse effects related to ketamine use in the United States is the National Poison Control database. Unlike other national data sources such as NVSS, Poison Control data are uploaded in almost real time, including circumstances of exposure, and nonfatal overdose events, which may more effectively capture ketamine-related events. Previous studies have used US Poison Control data to examine national trends in ketamine poisonings ("exposures") from 2000 to 2015 (Ni et al., 2018) and from 1991 to 2019 (Palamar et al., 2021); however, trends in exposures related to ketamine in more recent years following its FDA approval are unknown. In this analysis, we first examine trends in ketamine exposures (quarterly) from 2019 to 2021 and we then examine correlates of experiencing major (severe) adverse effects or death.

Methods

Procedure

Poison Control data were obtained through a collaboration between the National Institute on Drug Abuse National Drug Early Warning System (Cottler et al., 2020), and the Researched Abuse Diversion and Addiction-Related Surveillance (RADARS) System Poison Center Program. Participating Poison Control Centers (PCCs) provided cases involving pre-identified Micromedex codes to RADARS System staff who then reviewed the cases for accuracy by examining the case notes. PCCs provide treatment advice to the public and to healthcare staff treating individuals with suspected poisonings involving drugs, chemicals, and plants. Information about the patient and circumstances of the exposure are recorded by individual PCCs as per standards set by America's Poison Center (APC) and stored in a database overseen by the National Poison Data System. Information is provided by the patient, healthcare provider, or other contact. RADARS System obtained data on ketamine poisonings reported between January 2019 and December 2021. Data were available from PCCs in all US states other than North Carolina (with coverage from 51 of the 55 US PCCs). The inclusion criteria of this analysis were that (1) cases reportedly involved a ketamine exposure (cases involving generic code 13800) and (2) cases were 13 years of age or older. As such, we identified 758 cases age ⩾13 (out of 799).

Variables

PCC staff collected data provided by the caller to the poison center on patient age and sex. With respect to characteristics of exposures, information was obtained regarding the reason or intention for exposure, whether other drugs were co-used, the route(s)

of administration, and severity of the outcome. Reasons for use included intentional "abuse," misuse, unintentional exposure (i.e., occupational, therapeutic error, unintentional unknown), suspected suicide (which may or may not have resulted in death), intentional use but unknown reason, adverse reaction, and other categories of exposure that were collapsed into other reason. "Abuse" is defined by APC as exposure resulting from intentional improper or incorrect use of a drug in which the patient was attempting to acquire a high, euphoric effect, or another psychotropic effect (Zosel et al., 2013). Misuse is defined as intentional improper or incorrect, or otherwise nonmedical use but for reasons *other* than acquiring a psychotropic effect. We combined "abuse" and misuse into a single category (Calcaterra et al., 2018). Information on reasons for use was collected by specialists in poison information (SPIs) from PCC contacts, who are instructed to determine whether exposures were due to intentional or unintentional actions based on coding guidelines provided by the APC. SPIs record the rationale for the selection of reason for use in cases notes.

Routes of administration included reported ingestion, injection, dermal administration, inhalation, and other method. Patients were able to report multiple routes. Based on past research (Palamar et al., 2016; Warrick et al., 2013), we recoded a variable indicating inhalation only, injection only, and ingestion only versus other routes or combinations of routes. Polydrug use was also queried, and we focused on co-use of alcohol, cannabis, cocaine, benzodiazepines, opioids (prescription opioids as well as heroin and fentanyl), *gamma*-hydroxybutyrate (GHB), methamphetamine, amphetamine, and other phenethylamines (e.g., ecstasy/ 3,4-methylenedioxymethamphetamine [MDMA], newer stimulant psychoactive drugs). Of note, benzodiazepines are drugs commonly used to treat anxiety, and methamphetamine, amphetamine, and other phenethylamines are stimulants. Drug use was based on self-report, although toxicology test results were considered when available.

Medical outcome was coded by PCC staff as none, mild, moderate, major, or death (Gummin et al., 2020). Exposure cases are followed by PCCs as appropriate to obtain the most precise medical outcome possible; while most cases are "closed" shortly after the initial contact, more medically complicated cases or cases involving death can remain open for months, in which data are continually collected (Gummin et al., 2020). Mild effects are defined as minimally bothersome effects, moderate effects are more pronounced or prolonged effects, and major effects are life threatening or permanently disabling effects. Deaths indicate that the patient was confirmed to have died in relation to use of the drug, which was either determined directly by PCC staff who were involved with case management or from death reports were obtained from a medical examiner or another source without the involvement of PCC staff. In cases which involved death reports obtained from another source, an APC faculty review team then judged whether the reported exposure was likely responsible or at least contributory to the death (Gummin et al., 2020).

Analyses

We first examined trends in the number of reported ketamine exposures by year/quarter using Joinpoint Regression version 4.8.0.1 (National Cancer Institute, 2020). Also known

as piecewise, multi-phase, broken line, or segmented regression, Joinpoint fits weighted least-square regression models to counts on a log-transformed scale (Ingram et al., 2018; Kim et al., 2000). It also uses Monte Carlo permutation tests with a Bonferroni correction for multiple testing and further identifies models with the best fit set of joinpoints (we specified for a maximum of three). We specified Poisson models under the assumption of non-constant variance or heterogeneity over time. We then examined aggregate data to describe the prevalence of characteristics of exposures. This was done in a univariable manner, and then we examined bivariable and multivariable correlates of exposures resulting in a major effect or death. Chi-square and Fisher's exact test were used to determine bivariable differences between each independent variable and whether the exposure resulted in a major effect or death or a less severe effect. Covariates were then fit into a multivariable generalized linear model using Poisson distribution and log link. This model allowed us to estimate adjusted prevalence ratios (aPRs) for each covariate. We imputed missing data for independent variables in the multivariable model. Multiple imputation was implemented using chained equations to handle missingness; predictors included variables in the case-complete model. In all, 10 datasets were imputed for the multivariable model and combined results (Rubin, 1987). All analyses other than trend analyses were conducted using Stata SE 17 (StataCorp, College Station, TX). This secondary analysis was exempt from review by New York University Langone Medical Center's institutional review board.

Results

As shown in Figure 1, the number of reported ketamine exposures increased 81.1% from 2019 Quarter 1 through 2021 Quarter 4, from 37 to 67 ($\beta = 0.05$, standard error = 0.02, $p = .018$). This was an overall linear increase with no detected joinpoints. Table 1 presents the characteristics of the sample. The majority of patients with ketamine exposure were male (57.1%), and the plurality of cases involved intentional "abuse" or misuse (39.5%). This was followed by suspected suicide (19.7%), unintentional exposure (18.9%), adverse drug reaction (10.6%), unknown intentional exposure (4.5%), and 7.0% noted other reasons. A third (33.4%) reported co-use of other drugs. Among those reporting polydrug use, 60.5% reported use of one additional drug; 24.1%, 11.5%, 3.6%, and 0.4% reported the use of an additional two, three, four, and five drugs, respectively. The drugs most commonly co-used were benzodiazepines (14.6%), alcohol (10.3%), and opioids (8.7%). With respect to route of administration, 44.3% only ingested ketamine, 18.8% only injected, 17.6% only inhaled, and 19.3% used via another route or a combination of routes. The majority (85.3%) used via one route, and 14.7% used via multiple routes. Regarding medical outcome, of cases followed with a final determination of effect, 11.8% reported no effect, 25.8% reported a minor effect, 42.8% reported a moderate effect, 18.4% reported a major effect, and 1.2% had a reported death. As such, a fifth (19.6%) of cases followed experienced a major adverse effect or death.

Table 2 presents the correlates of patients experiencing a major adverse effect or death. Bivariable test results suggest that prevalence of experiencing a major adverse effect or death was higher among those reporting co-use of GHB (7.0% vs. 0.6%, $p < 0.001$) or opioids (20.0% vs. 7.6%, $p < 0.001$). There was also a detected significant difference regarding reason for use ($p = 0.046$) and route of administration ($p = 0.002$). In the multivariable

model, co-use of GHB (aPR = 3.43, 95% confidence interval (CI: 1.57–7.46) and opioids (aPR = 2.44, 95% CI: 1.46–4.08) was associated with increased risk for experiencing a major adverse effect or death, as was injection-only route of administration (aPR = 2.68, 95% CI: 1.21–5.92).

Discussion

In this analysis of fatal and nonfatal ketamine-related exposures reported to US PCCs, we found that, although ketamine exposures are still rare, there were significant increases in reported exposures from early 2019 through late 2021. Previous epidemiological research has estimated that rates of ketamine exposures in the United States increased in a cubic manner from 1991 through 2019, with an increase from 1991 through 2000, followed by a dip through 2008, and an increase through 2014, with use remaining stable through 2019 (Palamar et al., 2021). Our timelier quarterly analysis of trends from 2019 through 2021 indicates that exposures increased between early 2019 and late 2021, suggesting another uptick in ketamine use.

This study also delineated correlates of ketamine exposures involving major adverse effects or death. The co-use of ketamine with GHB or opioids was found to be a risk factor for more severe adverse outcomes. The use of ketamine with central nervous system depressants such as opioids increases the risk of complications like respiratory depression (Corkery et al., 2021; Wolff & Winstock, 2006), and opioids have been one of the most prevalently detected other drugs in ketamine-involved deaths (Corkery et al., 2021; Darke et al., 2021). GHB, like ketamine, is a popular club drug or party drug, and is also commonly used in nightclub settings (Halkitis et al., 2007; Palamar & Keyes, 2020). Importantly, both GHB and ketamine can be considered as central nervous system-sedating drugs, and inhibition of respiratory rates resulting from co-use could result in hippocampal hypoxia (Van Amsterdam et al., 2012). One study found that the risk of hospital treatment for GHB was almost three times higher when GHB was co-ingested with ketamine (Kim et al., 2007). Thus, though ketamine alone may be a less risky drug, these findings indicate that ketamine use becomes riskier when used concomitantly with other substances, specifically those which also increase the risk for respiratory depression.

Although co-use of other drugs with ketamine was not linked to increased risk of more severe effects in this study, combining other drugs with ketamine can still place individuals who use at risk. For example, a recent study found that a quarter (25.0%) of adverse effects experienced after using ketamine were tied to alcohol co-use (Palamar et al., 2019). Adverse effects were more common with alcohol co-use as compared to co-use of cocaine (18.8%) and ecstasy (18.8%). In nightclub scenes, amphetamines have been commonly combined with ketamine to balance out the effects of each drug (Degenhardt & Topp, 2003). While it is not fully known whether use of stimulants can ameliorate adverse effects from ketamine, we need to keep in mind that while drugs such as opioids, cocaine, amphetamines, and GHB have a higher risk for acute toxicity and addiction than ketamine (Gable, 1993; Morgan et al., 2010; Nutt et al., 2007), co-use with ketamine may have potential to increase such risk.

While prevalence of nasal and injection use was comparable in this sample, administration of ketamine through injection was associated with increased risk for experiencing a major adverse effect or death. Ketamine is typically obtained in a powder form and administered through snorting or inhalation when used nonmedically, while intravenous use has been found to be relatively rare (Morgan et al., 2012), even among persons who inject other drugs (Lankenau et al., 2010). Nonmedical use involving injection could thus be seen as an indicator of higher severity of use, and thus, this might have been why injection use was more prevalent in this sample of people reporting poisonings. Given that intravenous administration involves a more rapid duration and onset of ketamine (Corkery et al., 2021), and rapid administration can result in complications such as impairment of pharyngeal and laryngeal reflex, diaphragm rigidity, and/or transient respiratory depression (Darke et al., 2021), it is possible that injection may act as a risk factor primarily though the user's lessened ability to titrate ketamine use. One study of ketamine-related deaths in Australia found that over 40% of decedents had a history of injection drug use, with over a third of deaths involving intravenous self-administration of ketamine (Darke et al., 2021).

While injection ketamine use was found to be a risk factor for more severe adverse effects, other routes of administration are not without risk. All routes can be safe given the correct dose and context of use (Kronenberg, 2002), but injection has the fastest drug effect with 100% bioavailability (Li & Vlisides, 2016), which can make use (e.g., recreational use) of large doses particularly dangerous. Intramuscular effects are slower (with 93% bioavailability), followed by intranasal (with 8–45% bioavailability) and oral effects (with 17–29% availability) (Li & Vlisides, 2016). Ketamine inhaled in powder form has a good safety profile in clinical settings (Matłoka et al., 2022), but given that most recreational use (e.g., in nightclubs) appears to be use in powder form, such nasal use can increase the risk of adverse effects given the contexts of use and higher likelihood of people using a less pure product (He et al., 2020; Palamar et al., 2019). The US FDA has also reported concerns about some nasal sprays (which can be obtained now in clinics), particularly take-home nasal sprays, as these appear to increase risk for misuse, "abuse," and adverse effects (US FDA, 2022). Oral doses can be even safer than other products as effects are delayed, but when a full dose (e.g., pill) is administered, little can be done to prevent drug effect, as opposed to other routes in which doses can be more easily titrated (Andrade, 2019). Injection, though, appears to be the riskier mode of administration with regard to severity of adverse effects so prevention and harm reduction efforts should target this route of use in particular.

There are limitations to this study. Since calls to PCCs are based on a patient, medical professional, or other party calling to report an exposure or to ask for medical advice for treatment, these data are not generalizable to all ketamine poisonings. Likewise, these data are also not generalizable to ketamine use in the general population, as cases mostly involve adverse effects and reporting to PCCs is voluntary. However, these data can be useful in complementing other sources of national data on prevalence of ketamine use and ketamine-related mortality to monitor trends in adverse effects associated with use. Poison Control data are based on the caller or other contact's reporting, which may or may not include the patient and could depend on second-hand information in some cases. In addition, toxicology testing was not always conducted to confirm ketamine exposures. Other

studies, for example, have found that unintentional or underreported exposure to ketamine is common among nightclub attendees (Palamar et al., 2021).

In conclusion, this analysis of RADARS System Poison Center data suggests that, although still rare, poisonings involving ketamine have increased in recent years, with polysubstance use—particularly co-use with opioids or GHB—and injection acting as significant risk factors for more serious adverse effects. As prevalence of both medical and nonmedical use of ketamine increases in the United States, we believe these findings can be used to help monitor adverse effects associated with ketamine exposures and to inform more timely prevention and harm reduction efforts.

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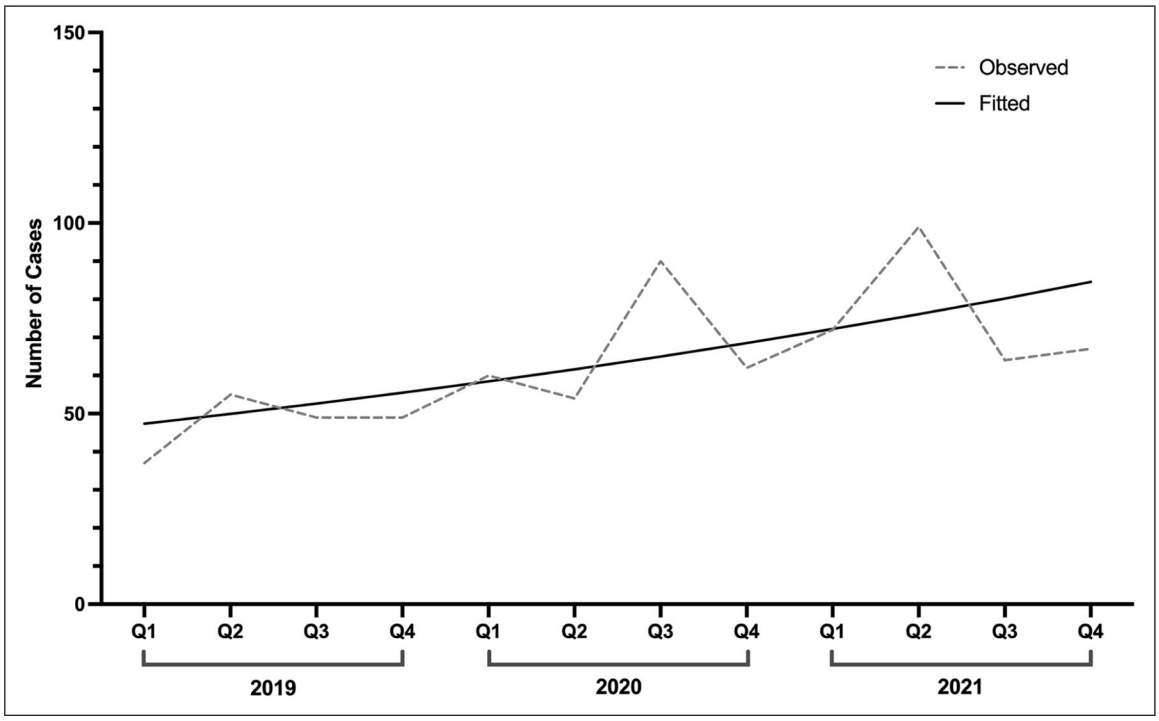

Figure 1.
Quarterly trend in ketamine exposures in the United States, 2019–2021.

Table 1.

Characteristics of cases involving ketamine exposure (n = 758).

	n **(%)**
Age	
13–19	104 (14.8)
20–29	247 (35.2)
30–39	186 (26.5)
⩾40	165 (23.5)
Sex	
Male	420 (57.1)
Female	
Reason	
Intentional misuse or abuse	299 (39.5)
Suspected suicide attempt	149 (19.7)
Unintentional exposure	143 (18.9)
Adverse reaction	80 (10.6)
Intentional unknown	34 (4.5)
Other reason	53 (7.0)
Co-drug use	
Any polydrug use	253 (33.4)
Benzodiazepines	111 (14.6)
Alcohol	78 (10.3)
Opioids	66 (8.7)
Cocaine	43 (5.7)
Cannabis	37 (4.9)
Amphetamine	18 (2.4)
Methamphetamine	12 (1.6)
Other phenethylamines	26 (3.4)
GHB	12 (1.6)
Route of administration	
Ingestion only	290 (44.3)
Injection only	123 (18.8)
Inhalation only	115 (17.6)
Other	126 (19.3)
Medical outcome	
No effect	69 (11.8)
Minor effect	151 (25.8)
Moderate effect	251 (42.8)
Major effect	108 (18.4)
Death	7 (1.2)

Note. Percentages reflect case-complete data. Other route of administration consists of dermal or other route or routes in combination with inhalation, injection, or ingestion.

GHB: *gamma*-hydroxybutyrate.

Table 2.

Bivariable and multivariable correlates of major adverse effect or death.

	Less than major effect *n* (%)	Major effect or death *n* (%)	aPR (95% CI)
Age			
13–19	71 (16.1)	12 (10.4)	Ref
20–29	149 (33.7)	40 (34.8)	1.30 (0.68–2.48)
30–39	118 (26.7)	29 (25.2)	1.21 (0.62–2.38)
⩾40	104 (23.5)	34 (29.6)	1.49 (0.75–2.99)
Sex			
Male	260 (57.5)	77 (67.0)	Ref
Female	192 (42.5)	38 (33.0)	0.72 (0.47–1.11)
Reason			
Intentional misuse or abuse	193 (41.0)	50 (43.5)[a]	Ref
Suspected suicide attempt	106 (22.5)	30 (26.1)	1.01 (0.63–1.63)
Unintentional exposure	89 (18.9)	11 (9.6)	0.58 (0.29–1.16)
Adverse reaction	40 (8.5)	8 (7.0)	0.67 (0.31–1.46)
Intentional unknown	19 (4.0)	11 (9.6)	1.73 (0.92–3.25)
Other reason	24 (5.1)	5 (4.4)	0.96 (0.38–2.39)
Co-drug use			
Benzodiazepines	81 (17.2)	19 (16.5)	0.70 (0.41–1.19)
Alcohol	49 (10.4)	16 (13.9)	1.12 (0.62–2.03)
Opioids	36 (7.6)	23 (20.0)[c]	2.44 (1.46–4.08)[b]
Cocaine	24 (5.1)	11 (9.6)	1.43 (0.69–2.96)
Cannabis	25 (5.3)	7 (6.1)	1.20 (0.53–2.69)
Amphetamine	11 (2.3)	4 (3.5)	1.18 (0.43–3.20)
Methamphetamine	9 (1.9)	3 (2.6)	1.88 (0.55–6.50)
Other phenethylamines	18 (3.8)	3 (2.6)	0.59 (0.16–2.08)
GHB	3 (0.6)	8 (7.0)[c]	3.43 (1.57–7.46)[b]
Route of administration			
Other	84 (20.2)	12 (11.5)[b]	Ref
Ingestion only	186 (44.7)	59 (56.7)	1.67 (0.83–3.35)

	Less than major effect *n* (%)	Major effect or death *n* (%)	aPR (95% CI)
Injection only	64 (15.4)	24 (23.1)	2.68 (1.21–5.92)[a]
Inhalation only	82 (19.7)	9 (8.7)	0.87 (0.30–2.48)

Note. Other route of administration consists of dermal or other route or routes in combination with inhalation, injection, or ingestion. Bivariable tests are based on case-complete data and the multivariable model is based on imputed data. The multivariable model controlled for year.

aPR: adjusted prevalence ratio; CI: confidence interval; GHB: *gamma*-hydroxybutyrate.

[a] $p < 0.05$,

[b] $p < 0.01$,

[c] $p < 0.001$.