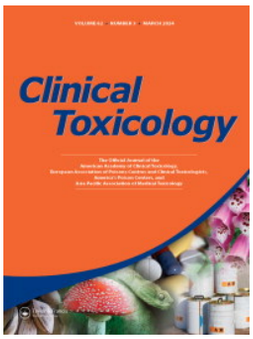

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POISON CENTRE RESEARCH

Intentional benzodiazepine poisoning in older adults reported to United States Poison Centers

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ABSTRACT

Introduction: Despite known contraindications, benzodiazepines are frequently prescribed for older adults. This study utilizes poison control center data on benzodiazepine-involved cases aged 50 and above to compare the characteristics of suspected suicide attempt with other intentional misuse cases. We also examined associations of major medical outcomes (major effect/death) with demographic characteristics and other co-used substances in each group.

Methods: The study employed data from the America's Poison Center National Poison Data System from 2015–2022. Descriptive statistics and binary logistic regression models were used.

Results: Of the benzodiazepine-poisoning cases of intentional misuse ($n = 93{,}245$), 85 percent were suicide attempts and 15 percent were other intentional misuses. Reports to poisons centers showed a decline from 2019–2022 when compared to 2015–2016. However, the likelihood of a reported suicide attempt, compared to other intentional misuse, was greater in 2019–2022 compared to 2015–2016 and among those who co-used antidepressants, anxiolytics, atypical antipsychotics, other benzodiazepines, other analgesics, anticonvulsants, and alcohol. The odds of major effect/death in both groups were also greater in 2019–2022, with suicide attempt cases in advanced ages showing higher odds. The co-use of antidepressants, prescription opioids, atypical antipsychotics, anticonvulsants, and other analgesics were associated with a higher likelihood of major effect/death in both exposure groups. For instance, adjusted odds ratios for co-used prescription opioids were 2.20 (95 percent confidence intervals: 2.09–2.31) among suicide attempt cases and 3.51 (95 percent confidence intervals: 3.10–3.97) among other intentional misuse cases.

Discussion: Healthcare providers need to screen for suicidal ideation among benzodiazepine users, with special attention to an increased risk of suicide attempt among those who co-use antidepressants and opioids and to decreasing adverse outcomes in all misuse cases. Assessments of underlying mental health and substance use problems and medication regimens to minimize polypharmacy and drug interactions are needed to reduce adverse outcomes.

Conclusions: Though the numbers of benzodiazepine-involved suicide attempt and other intentional misuse cases reported to United States poison centers decreased in recent years, the likelihood of major medical effect/death among these cases have increased.

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Older adults; benzodiazepines; suicide attempt; antidepressants; opioids; alcohol

Introduction

The American Geriatric Society's Beers Criteria for Potentially Inappropriate Medication Use in Older Adults recommends that benzodiazepines and non-benzodiazepine hypnotics (e.g., zolpidem) should be avoided in all older adults due to the risk of cognitive impairment, delirium, falls, fractures, motor vehicle crashes, and dependence [1–7]. Nevertheless, benzodiazepine use among individuals aged 50 and older in the United States (US), has been significantly greater than what the available evidence suggests is appropriate [8–13]. Between 2003 and 2015, benzodiazepine prescriptions at ambulatory care visits doubled for people aged 45–64 and those aged 65 and older, especially for anxiety and depression, back and chronic pain, neurologic conditions, and other unspecified conditions [14]. Although long-term benzodiazepine use is especially contraindicated for older adults, one study [15] also found that about a third of benzodiazepine prescriptions for the people aged 65 years and older were for longer than 120 days per year.

Research has shown that adults aged 50 and older are more likely than younger adults to misuse benzodiazepines (defined as using more often than prescribed), and that benzodiazepine misuse is strongly associated with comorbidity and polypharmacy, especially involving prescription opioids [10,16]. Co-use of benzodiazepines and opioids in older adults can be fatal when taken concurrently [17]. Despite the inherent danger of co-use, ambulatory care visit data have shown that the co-prescribing rates of benzodiazepines and opioids more than doubled between 2006/2007 and 2014/2015 for those people aged 65 and older, with female gender, a visit for chronic care, receipt of six or more

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concomitantly prescribed medications, and clinical diagnoses of anxiety and pain as the significant correlates of co-prescribing [18].

In the US, drug overdose deaths have increased sharply among late-middle-aged and older adults in recent years. Between 2020 and 2021 alone, the increases were 21% for the 55–64 age group and 28% for the 65 and older age groups, representing the largest increase of all age groups [19]. Benzodiazepines have become increasingly involved in overdose deaths. In 2021, prescription and/or illicit benzodiazepines were identified in nearly 12% of all drug overdose deaths and in 14% of all overdose deaths involving prescription and/or illicitly manufactured opioids [20]. State-level benzodiazepine prescribing rates have been significantly correlated with benzodiazepine co-involvement in all opioid overdose deaths [21].

The US Centers for Disease Control and Prevention data also indicate that, after a slight decline in 2018–2020, suicide rates have increased again in 2021 and 2022, with the largest increases among the 45–64 and the 65 and older age groups [22,23]. Benzodiazepine misuse among older adults has been identified as a contributing factor for suicidality [20,21,24,25]. A study based on the US National Survey of Drug Use and Health discovered that a quarter of adults aged 50 and older who misused both benzodiazepine and opioids reported past-year suicidal ideation, compared to 2% of those who did not misuse either medication class [25]. An analysis of 24-month live emergency department and inpatient discharges for drug poisoning suicidal acts that resulted in deaths in 11 states between 2011 and 2016 revealed that about one-fifth of the suicidal drug overdoses involved benzodiazepines, and one-sixth involved opioids, even though opioids were most commonly identified in fatal suicide poisonings [26].

These data show the importance of examining benzodiazepine misuse and its outcomes in late-middle-aged and older adults, especially among those who co-use benzodiazepine with other substances. While previous research has examined benzodiazepine use and misuse and adverse outcomes among older adults, benzodiazepine-involved cases reported to poison centers have not yet been explored. In the present study based on benzodiazepine exposure cases aged 50 and older in the 2015–2022 US National Poison Data System maintained by America's Poison Centers, we compared two groups of intentional misuse cases, suspected suicide attempts and other intentional misuses, with regard to demographic and exposure-related characteristics, other substance involvement, and medical outcomes. We then examined associations of major medical outcomes (major effects/deaths) with sociodemographic variables and co-used other substances in suicide attempts and other intentional misuses.

Methods

Study design and setting

This is an observational study based on the 8 years (1 January 2015 through 31 December 2022) of pooled National Poison Data System data originating from 55 Poison Centers in the US with locations in all 50 states, the District of Columbia, and Puerto Rico (see National Poison Data System website [https://aapcc.org/data-system] and Gummin et al. [27] for detailed descriptions). Based on the authors' institutional review board guidelines, an institutional review board exemption was granted for analysis of these de-identified data.

Participants

We identified closed cases aged 50 and older involving benzodiazepines using a combination of substances/product identification codes/generic category codes and including any number of other substances. The National Poison Data System lists all co-used substances in each case, allowing for an analysis of these substances. The National Poison Data System lists cases, not individuals; however, the likelihood of these cases including duplicate individuals is minimal as poison center specialists are trained to detect and correct any duplication as soon as it is discovered.

In this study, we focused on intentional exposure cases that included suspected suicide attempt, misuse, abuse, and other intentional exposures for unknown reasons, after excluding cases of confirmed non-exposure, cases with effects unrelated to the exposure (i.e., the exposure was not responsible for the reported effect), and indirectly reported death cases that were mostly from Arizona. The indirectly reported cases (in which poison centers received information from medical examiners or media but were not directly managed [27]) have been sporadic. The high number in Arizona was due to the inclusion of deaths from state vital statistics from 2017 through 2022. We also excluded cases where benzodiazepine exposures were unintentional (therapeutic error, unintentional misuse, inadvertent exposures through environmental/other routes, adverse reaction, or other unintentional reasons [contamination/tampering, malicious intent, withdrawal]).

Measures

Reason for exposure: suicide attempt or other intentional misuse: In this study, the intentional exposure cases were further categorized into: (1) suspected suicide attempt (suicide attempt hereafter) referring to intentional benzodiazepine poisoning for self-harm and suicidal intent, and (2) other intentional misuse or abuse without suicidal intent (intentional misuse hereafter). The majority (91.5% in this study) of suicide attempt cases were reported to poison centers from healthcare facilities.

Co-use of other substances: These included any of the National Poison Data System-coded prescription antidepressants (31 codes); prescription opioids (23 codes); alcoholic beverages; drugs for cardiovascular diseases (33 codes); atypical antipsychotics; anxiolytics other than benzodiazepines; muscle relaxants (eight codes); anticonvulsants (16 codes); other analgesics; second/third benzodiazepine; and antihistamines (12 codes).

Medical outcomes: The National Poison Data System has the following medical outcome categories for human exposure: no effect; minor effect; moderate effect; major effect; and death. As opposed to moderate effect referring to "signs

or symptoms that were not life-threatening or had no residual disability or disfigurement," major effect refers to "signs or symptoms that were life-threatening or resulted in significant residual disability or disfigurement" [27]. As aforementioned, we excluded indirectly reported deaths in this study. Then, we combined these outcomes into two categories: (1) major effect ($n = 11,648$) or death ($n = 786$), and (2) no major effect/death. Although the National Poison Data System also assigns expected outcomes (judged to be nontoxic, minimal/no more than minor clinical effects possible, or potentially toxic) for the cases that were not followed, we included these cases (8.3% of benzodiazepine-involved suicide attempt and other intentional abuse cases in this study) in the no major effect/death group to be conservative.

Other covariates in multivariable models included the following: exposure year (2015–2022), US census region, age group (50–59 years through 90 years and greater), gender, and chronicity (acute, acute-on-chronic, chronic, and unknown). We reported exposure location, call and management/care sites, and the National Poison Data System-provided number of all substances involved in each case for descriptive purpose only.

Analysis

All analyses were conducted using Stata 18/MP (Stata Corp, College Station, TX). First, we applied descriptive statistics (Pearson's χ^2 or independent-sample t tests) to compare all suicide attempt and all intentional misuse cases with respect to demographics, exposure-related characteristics, co-used substances, and medical outcomes. Second, we assessed changes in the numbers of suicide attempt and other intentional misuse cases over the eight years. Third, we fitted a binary logistic regression model to examine demographics and co-used substances that were associated with suicide attempt versus intentional misuse. Finally, we fitted two logistic regression models to explore demographics and co-used substances linked with major effect/death outcomes in cases of suicide attempt and intentional misuse, respectively. As a preliminary diagnostic measure, we checked for multicollinearity among covariates using the variance inflation factor, with a cut-off of 2.50 [28], as determined from linear regression models, which indicated no concerning multicollinearity. Binary logistic regression results are reported as adjusted odds ratios (aORs) with 95% confidence intervals (CI).

To investigate any variations in the adjusted predicted probabilities of major effect/death by exposure year, reason for exposure, and gender, we further utilize gender-specific logistic regression models (with major effect/death as the dependent variable) incorporating interaction terms between each exposure year and reason for exposure as covariates. The results of these logistic regression models are presented in graphs.

Results

Demographic and exposure-related characteristics by reason of exposure

The 2015–2022 National Poison Data System included a total of 123,322 benzodiazepine-involved cases aged 50 and older. Of these, we identified a total of 93,245 suicide attempt (79,033; 84.8%) or intentional misuse (14,212; 15.2%) cases, after excluding 98 confirmed nonexposed cases, 2,468 cases with effects unrelated to the exposure, 73 cases with unknown gender, 252 (230 from Arizona) indirectly reported death cases, and 27,186 cases of unintentional exposure.

Table 1 shows that nearly 60% of suicide attempt and intentional misuse cases over the eight years were in the age group 50-59 years, and 71% of suicide attempt and 60% of intentional misuse cases were women. About 95% of suicide attempt and 75% of intentional misuse cases were managed at a healthcare facility. More than a third of the suicide cases, compared to one fifth of intentional misuse cases, were admitted to a critical care unit. Of all suicide attempt and intentional misuse cases, 13% resulted in a major effect ($n = 11,115$) or death ($n = 1,319$), but the rate of major effect/death was higher in suicide attempt (14%) than in intentional misuse (9%) cases. Table 1 also shows the 12 most frequently co-used substances. Higher percentages of suicide attempt than intentional misuse cases used antidepressants, alcohol, cardiovascular drugs, atypical antipsychotics, other anxiolytics, gabapentin, other types of analgesics, anticonvulsants, additional benzodiazeines, and antihistamines, while a greater percentage of intentional misuse cases used prescription opioids.

Changes in the numbers of cases, 2015–2022

Figure 1 shows that the numbers of benzodiazepine-involved suicide attempt and intentional misuse cases reported to poisons centers decreased nearly 30% from 2015 to 2022 for both genders (Pearson's $\chi^2 = 26.63$, $df = 1$, $P < 0.001$), with the decrease being particularly noticeable in 2019–2022. Further analysis indicated that despite the decreasing numbers, the proportion of suicide attempt cases increased from 84% in 2015–2018 to 86% in 2019–2022 (Pearson's $\chi^2 = 36.50$, $df = 1$, $P < 0.001$).

Correlates of suicide attempt versus intentional misuse: Logistic regression results

The first column of Table 2 shows that compared to intentional misuse, the odds of reported suicide attempt were greater in 2017–2022 than in 2015–2016 and among cases in the Midwest, South, Midwest, and Puerto Rico than in the Northeast, and among women (adjusted odds ratio (aOR) = 1.59, 95% CI: 1.53–1.65). However, the odds were lower among cases aged 60-79 and in chronic exposure cases.

The odds of reported suicide attempt were also greater among cases that co-used antidepressants (aOR = 1.98, 95% CI: 1.86–2.10), alcohol, cardiovascular drugs, atypical antipsychotics, anxiolytics, other analgesics, anticonvulsants, and additional benzodiazepines; however, the odds were lower among cases who co-used prescription opioids.

Correlates of major effect/death in each exposure group: Logistic regression results

The second and third columns of Table 2 show that in both reported suicide attempt and intentional misuse cases, the

Table 1. Characteristics of benzodiazepine-involved suicide attempt and other intentional misuse cases age 50 and older.

	Suicide attempt $n = 79,033$ (84.8%)	Other intentional misuse $n = 14,212$ (15.2%)	*P*
Year (%)			<0.001
2015–2016	28.8	30.9	
2017–2018	27.2	30.9	
2019–2020	23.3	22.3	
2021–2022	20.7	18.9	
Census region (%)			<0.001
Northeast	15.8	19.1	
Midwest	23.0	22.4	
South	40.5	39.6	
West	19.7	18.6	
Puerto Rico	1.0	0.2	
Age group (%)			<0.001
50–59	59.7	56.3	
60–69	28.6	31.2	
70–79	8.9	9.4	
80–89	2.4	2.5	
90+	0.4	0.5	
Gender (%)			<0.001
Male	29.5	40.0	
Female	70.5	60.0	
Exposure site (%)			<0.001
Own residence	95.6	91.2	
Healthcare facility	1.1	2.4	
All other[a] or unknown	3.3	6.4	
Call site (%)			<0.001
Own residence	2.5	18.7	
Healthcare facility	91.5	73.1	
All other[a] or unknown	6.0	8.2	
Chronicity[b]			<0.001
Acute	47.4	43.9	
Acute on chronic	44.5	40.1	
Chronic	1.3	7.4	
Unknown	6.8	8.6	
Management/care site (%)			<0.001
On site (non-health care facility)	0.6	13.3	
Health care facility treated/evaluated & released	17.5	28.6	
Admitted to a psychiatric facility	25.6	8.5	
Admitted to a noncritical care unit	17.6	17.3	
Admitted to a critical care unit	34.1	20.8	
Refused referral/no show/lost to follow-up/left against medical advice/unknown	4.8	11.5	
Other medicine or substance co-used (%)			
Antidepressants	19.8	9.7	<0.001
Prescription opioids	16.5	22.9	<0.001
Alcohol	20.6	15.2	<0.001
Cardiovascular drugs	10.4	4.3	<0.001
Atypical antipsychotics	9.3	5.8	<0.001
Anxiolytics	8.8	5.8	<0.001
Muscle relaxants	6.8	6.7	0.784
Gabapentin	5.6	5.0	0.004
Other analgesics	5.2	4.0	<0.001
Anticonvulsants	5.1	3.1	<0.001
Additional benzodiazepines	5.0	4.1	<0.001
Antihistamines	4.6	3.6	<0.001
No. of products involved, mean (SD)	2.6 (1.8)	2.2 (1.6)	<0.001
Medical outcomes in two groups (%)			<0.001
No major effect or death	85.9	90.7	
Major effect/death	14.1	9.3	
Medical outcomes in detail (%)			<0.001
No effect	11.0	10.0	
Minor effect	32.4	28.7	
Moderate effect	36.5	31.7	
Major effect	13.2	8.6	
Death	0.9	0.7	
Not followed, judged to be a potentially toxic exposure	3.9	8.4	
Not followed, minimal clinical effects possible (no more than minor effect possible)	2.2	11.4	
Not followed, judged to be nontoxic exposure (clinical effects not expected)	0.1	0.5	

[a]Other people's residence, public area, workplace, or other location.
[b]Acute: single, repeated or continuous exposure occurring over 8 hours or less; acute-on-chronic: single exposure that was preceded by a continuous, repeated, or intermittent exposure occurring over a period greater than 8 hours; and chronic: continuous or repeated exposures occurring over more than 8 hours.
P-values were calculated based on Pearson's χ^2 tests for categorical variables and independent-sample *t* test for the number of products.

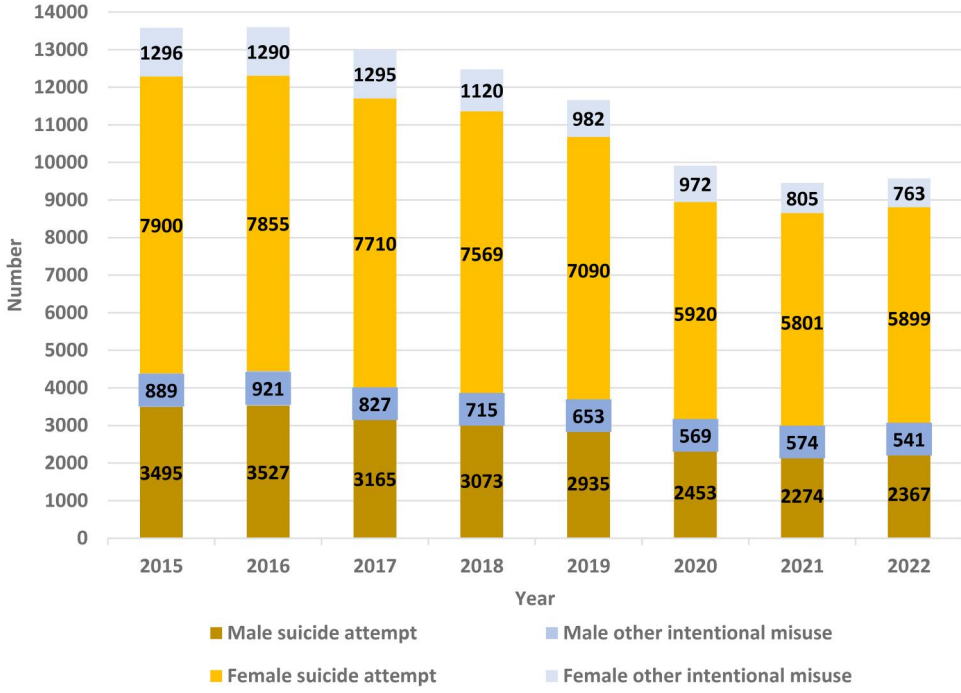

Figure 1. Number of benzodiazepine-involved suicide attempt and other intentional misuse cases reported to poison centers, 2015–2022.

Table 2. Correlates of suicide attempt versus other unintentional misuse and of major effect/death compared to no major effect/death in each exposure reason group: Logistic regression results.

	Correlates of suicide attempt	Correlates of major effect/death	
	Suicide attempt versus other intentional misuse aOR (95% confidence interval)	In suicide attempt: Major effect/death versus none aOR (95% confidence interval)	In other intentional misuse: major effect/death versus none aOR (95% confidence interval)
Year: versus 2015-2016			
2017-2018	1.05 (1.00–1.10)*	1.17 (1.10–1.25)***	1.45 (1.22–1.72)***
2019-2020	1.12 (1.067–1.18)***	1.73 (1.63–1.83)***	2.42 (2.04–2.87)***
2021-2022	1.18 (1.12–1.25)***	1.76 (1.66–1.87)***	2.59 (2.17–3.09)***
Census region: versus Northeast			
Midwest	1.26 (1.19–1.34)***	0.89 (0.83–0.95)***	0.54 (0.45–0.64)***
South	1.31 (1.24–1.38)***	0.89 (0.83–0.94)***	0.61 (0.53–0.70)***
West	1.35 (1.27–1.43)***	0.81 (0.76–0.87)***	0.38 (0.31–0.46)***
Puerto Rico	6.26 (4.25–9.24)***	0.39 (0.28–0.53)***	0.60 (0.14–2.60)
Age group: versus 50-59			
60-69	0.89 (0.85–0.93)***	1.24 (1.18–1.30)***	0.90 (0.79–1.03)
70-79	0.91 (0.85–0.97)**	1.54 (1.44–1.66)***	0.80 (0.65–1.00)
80-89	0.95 (0.85–1.07)	1.88 (1.66–2.12)***	1.22 (0.84–1.77)
90+	0.81 (0.62–1.05)	2.87 (2.21–3.74)***	0.84 (0.33–2.16)
Female versus male	1.59 (1.53–1.65)***	0.93 (0.89–0.97)	1.05 (0.93–1.18)
Chronicity versus acute			
Acute on chronic	0.97 (0.93–1.01)	1.05 (1.01–1.10)*	0.89 (0.78–1.02)
Chronic	0.17 (0.15–0.18)***	0.90 (0.74–1.09)	0.78 (0.60–1.01)
Unknown	0.74 (0.69–0.79)	1.76 (1.63–1.89)***	2.12 (1.77–2.53)***
Antidepressants	1.98 (1.86–2.10)***	1.55 (1.48–1.63)***	1.52 (1.27–1.83)***
Prescription opioids	0.71 (0.68–0.74)***	2.20 (2.09–2.31)***	3.51 (3.10–3.97)***
Alcohol	1.49 (1.41–1.56)***	1.02 (0.97–1.08)	1.02 (0.86–1.21)
Cardiovascular drugs	2.28 (2.09–2.49)***	1.67 (1.57–1.77)***	1.27 (0.98–1.65)
Atypical antipsychotics	1.35 (1.25–1.46)***	1.91 (1.79–2.03)***	1.40 (1.11–1.76)**
Anxiolytics	1.45 (1.35–1.57)***	1.12 (1.04-1.20)**	0.81 (0.62-1.05)
Muscle relaxants	0.96 (0.89–1.04)	1.83 (1.70–1.96)***	1.14 (0.92–1.41)
Gabapentin	0.96 (0.88–1.05)	1.14 (1.05–1.24)**	0.96 (0.75–1.23)
Other analgesics	1.21 (1.10–1.33)***	1.36 (1.25–1.48)***	1.73 (1.34–2.23)***
Anticonvulsants	1.24 (1.11–1.37)***	1.41 (1.30–1.54)***	1.52 (1.14–2.02)**
Additional benzodiazepines	1.20 (1.09-1.31)***	1.25 (1.14-1.36)***	0.92 (0.68–1.24)
Antihistamines	1.03 (0.93–1.14)	1.08 (0.99–1.18)	0.49 (0.34–0.72)***
Model statistics	$n = 93,245$; Log likelihood χ^2=4491.51, $P < 0.001$	$n = 79,033$; Log likelihood χ^2=4272.42, $P < 0.001$	$n = 14,212$; Log likelihood χ^2=882.39, $P < 0.001$

*$P < 0.05$;
**$P < 0.01$;
***$P < 0.001$

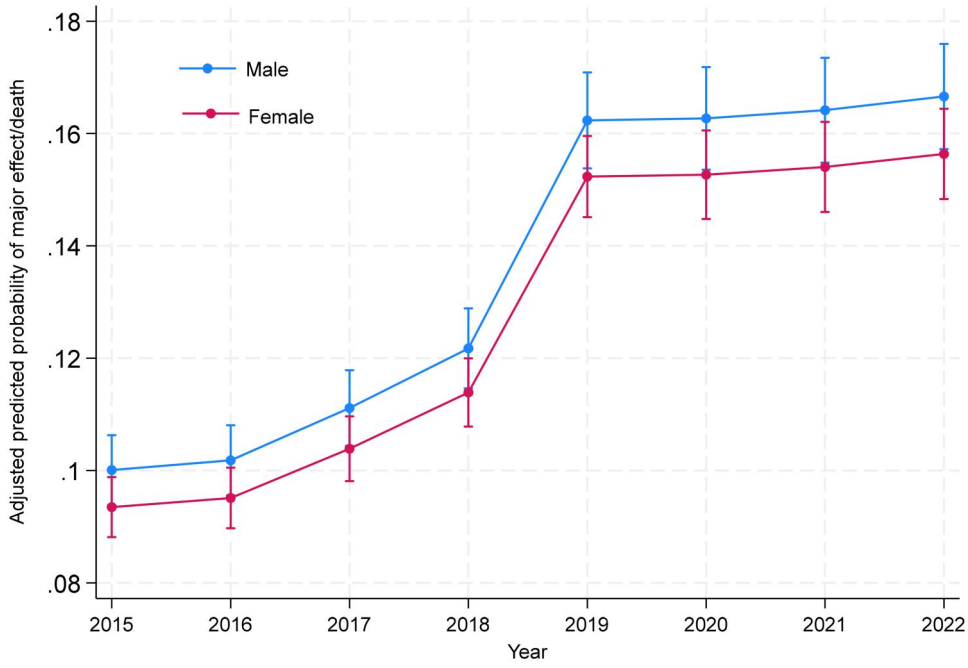

Figure 2. Adjusted predicted probability of major effect/death in benzodiazepine-involved suicide attempt cases by year. Error bars show 95% confidence intervals.

odds of major effect/death were greater in 2017–2022 compared to 2015–2016 and among those with unknown chronicity, but were lower in the Midwest, South, and the West. Age was a significant covariate in reported suicide attempts only, and the odds were significantly greater in the 60 and older age groups than in the 50–59 age group, with increasing odds in advanced age groups (e.g., aOR = 2.87, 95% CI: 2.21–3.74 in the 90 and older age group compared to the 50–59 age group). Acute-to-chronic use was also associated with greater odds of major effect/death in suicide attempt cases.

In both suicide attempt and intentional misuse cases, the odds of reported major effect/death were also greater among those who co-used antidepressants, prescription opioids, antipsychotics, anticonvulsants, and other analgesics (aORs = 1.55, 95% CI:1.48–1.63 for antidepressants for suicide attempt and aORs = 1.52, 95% CI: 1.27–1.83 for intentional misuse; aORs = 2.20, 95% CI: 2.09–2.31 and 3.51, 95% CI: 3.10–3.97 for prescription opioids; aORs = 1.91, 95% CI: 1.79–2.03 and 1.40, 95% CI: 1.11–1.76 for antipsychotics; aORs = 1.41, 95% CI: 1.30–1.54 and 1.52, 95% CI: 1.14–2.02 for anticonvulsants; and aORs = 1.36, 95% CI: 1.25–1.48 and 1.73, 95% CI: 1.34–2.23 for other analgesics). Additionally, in reported suicide attempts, co-use of cardiovascular drugs, anxiolytics, muscle relaxants, gabapentin, and additional benzodiazepines were associated with greater odds of major effect/death.

Figures 2 and 3 are graphic presentations of the gender-specific logistic regression results as the adjusted predicted probabilities of major effect/death in reported suicide attempt and intentional misuse cases. After increasing significantly in 2019 for both genders, the probabilities of major effect/death in suicide attempt cases appear to have plateaued in 2019–2022, but those in intentional misuse cases, while maintaining an overall increasing trend, had some fluctuations.

Discussion

The present study's findings provide important insights into benzodiazepine misuse in cases aged 50 years and older. The findings show that the numbers of benzodiazepine-involved suicide attempt and other intentional misuse cases aged 50 and older that were reported to US poison centers declined significantly from 2015 to 2022. However, compared to 2015–2016, the proportion of suicide attempt cases increased significantly starting in 2017 and especially in 2019–2022. The findings also show that the odds of major effect/death in both suicide attempt and other intentional misuse cases were significantly greater starting in 2017 and especially in 2019–2022 than in 2015–2016.

The increasing rates of suicide attempt cases warrant healthcare providers to reduce potentially inappropriate benzodiazepine prescribing and provide psychoeducation about the dangers of benzodiazepine misuse. The finding that close to 90% of reported suicide attempt and other intentional misuse cases were in the sixth and seventh decades also underscores the importance of monitoring benzodiazepine prescribing and misusing in individuals in these age groups. Although the odds of suicide attempt were higher in the younger age groups, those in advanced ages showed significantly greater odds of major effect/death, suggesting that the older the individuals attempting suicide, the more severe the outcome of the poisoning. Our findings also show that co-use of alcohol and all other prescription medications, antidepressants in particular, was associated with greater

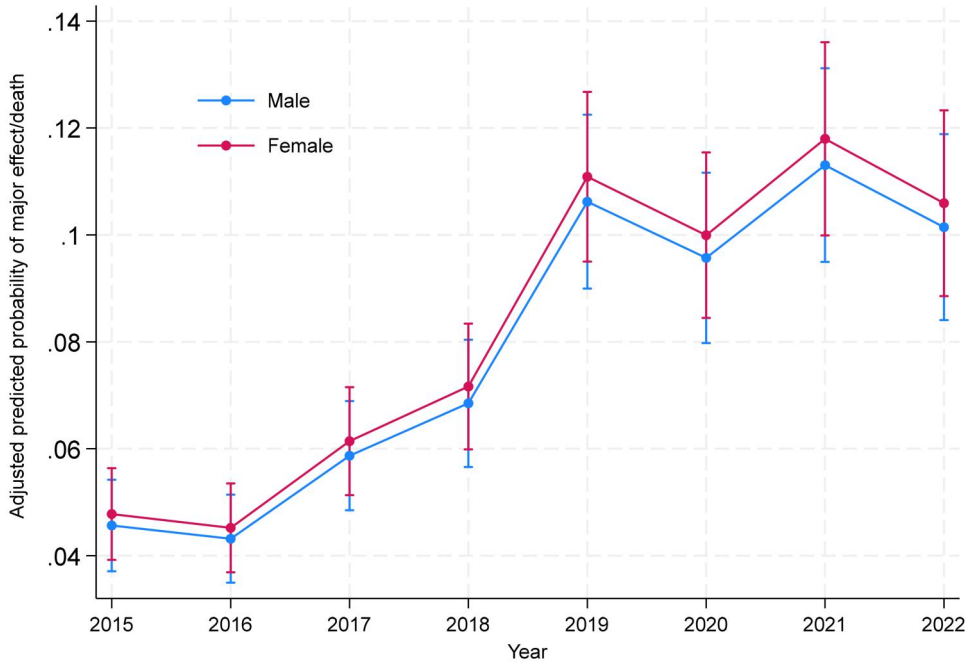

Figure 3. Adjusted predicted probability of major effect/death in benzodiazepine-involved other intentional misuse cases by year. Error bars show 95% confidence intervals.

odds of suicide attempt versus other intentional misuse. The co-use of other prescription medicine suggests co-morbid physical and mental health conditions in many cases and highlights the need for more concerted efforts to screen suicidal ideation among older adults who use benzodiazepine and may suffer from depression, anxiety, pain, and other physical health problems.

The outcome of major effect/death in both reported suicide attempt and other intentional misuse cases was also significantly associated with the co-use of other substances, including antidepressants and prescription opioids. The finding that antidepressants were a significant factor for major effect/death in both suicide attempt and other intentional misuse cases is concerning. Studies have shown that while benzodiazepines and antidepressants are often co-prescribed for older adults with depression, especially for those with higher depressive symptoms, anxiety disorder, and other psychiatric illnesses, benzodiazepine use concurrent with antidepressants does not significantly improve depressive outcomes and moderately increases mortality [29–31].

Co-used opioids may have been responsible for the sharply increased likelihood of major medical effect/death in 2019–2022. This corresponds to sharp increases in opioid and cocaine and other psychostimulant overdose deaths, with nonfatal and fatal drug overdose in the US starting to increase sharply in 2019 [19]. Data from 32 US states and the District of Columbia also showed that from 2019 to 2020, benzodiazepine overdose emergency department visits per 100,000 emergency department visits increased (24%), both with opioid involvement (34%) and without (21%) [32]. The same data showed that in April-June 2019 to April–June 2020 alone, prescription benzodiazepine deaths increased 22%, and illicit benzodiazepine deaths increased 520% [32].

The finding that cases in the Northeast region had greater risks of being reported suicide attempts and intentional misuses and having had major effect/death in both exposure groups also likely reflects greater poisoning (compared to firearm) suicide rates in the region [33]. Thorough assessments of underlying medical conditions, mental health issues, and substance use disorders, along with a review of the medication regimens to minimize polypharmacy and drug interactions, are needed to reduce adverse outcomes.

Although alcohol co-use was reported in one fifth of suicide attempt and one sixth of intentional misuse cases, it was not a significant factor for major effect/death. Benzodiazepine use and misuse are common in people with alcohol use disorder [34], and alcohol and benzodiazepine co-involvement in opioid-involved overdose deaths are common [35]. Thus, the finding that alcohol co-use was not associated with major effect/death among suicide attempt and intentional misuse cases calls for more research, as increased toxicity from alcohol (and other substances), especially among older adults, is likely to be a contributing factor for more severe adverse effects.

There are some limitations related to the National Poison Data System. First, since the study examined only exposures that were reported to poisons centers, the generalizability of these finding is limited. Second, deaths among cases are likely underestimates as not all cases were followed up, and it is not clear if all reported deaths were related to substance use or from other causes. Third, the National Poison Data System does not distinguish between prescription and illicit benzodiazepines and there was no way to separate them. Illicit fentanyl was not coded until 30 October 2019. The lack of data prevented examination of the major effect/death separately for prescription and illicit benzodiazepines or for

those possibly contaminated with illicit fentanyl. Fourth, data that are telephone-reported to poison centers without medical record validation and toxicological confirmation may compromise validity. Fifth, a large proportion of cases had missing data on drug quantity and exposure chronicity, preventing analysis of these variables. Sixth, the lack of data on characteristics such as race, pre-existing health conditions, and substance use history, and the source of benzodiazepines (e.g., own or others' prescription or illicitly produced) precluded more detailed analyses.

Conclusions

Despite the decreased numbers of benzodiazepine-involved cases reported to poison centers between 2015 and 2022, the proportion of suicide attempt cases as well as the likelihood of major effect/death among both suicide attempt and other intentional misuse cases increased during this period, especially since 2019. Co-use of antidepressants and prescription opioids were also associated with greater odds of major effect/death in both exposure groups.

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Authors' contributions

All authors contributed to conceptualization. SDB applied for and obtained the de-identified NPDS data and provided overall guidance on the data system and analysis. NGC conducted data analysis and drafted the paper. BYC provided consultation on pharmaceutical and medical contents. CNM provided statistical consultation. All authors contributed to final editing and agree to publication of the paper. Each author certifies that their contribution to this work meets the standards of the International Committee of Medical Journal Editors.

Disclosure statement

America's Poison Centers maintains the National Poison Data System (NPDS), which houses de-identified records of self-reported information from callers to the country's Poison Centers (PCs). The NPDS data do not reflect the entire universe of U.S. exposures and incidences related to any substance(s). Exposures do not necessarily represent a poisoning or overdose and America's Poison Centers is not able to completely verify the accuracy of every report. National Poison Data System data do not necessarily reflect the opinions of America's Poison Centers.

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Data availability statement

The America's Poison Centers (APC) releases the National Poison Data System (NPDS) to investigators following a review of data request. The authors do not have permission to make the NPDS data set use in this study available to other investigators.

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