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ORIGINAL RESEARCH ARTICLE

Fatal Intoxications with Zopiclone—A Cause for Concern?

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Abstract

Introduction Zopiclone, a controlled substance prescribed for insomnia, has become a common toxicological finding in forensic autopsy cases. This study investigated the role and extent of zopiclone use in fatal intoxications in Sweden.

Methods All forensic autopsy cases positive for zopiclone in femoral blood during 2012–2020 were selected. Among these cases, fatalities caused by intoxication according to the cause of death certificates issued by the forensic pathologist were identified. Intoxications where zopiclone contributed to the cause of death were included in the study. The Swedish Prescribed Drug Register was utilized to examine whether the included cases were prescribed zopiclone or not.

Results In total 7320 fatal intoxications underwent a forensic autopsy during the study period, 573 of them were caused by zopiclone. Among the zopiclone fatalities, 87% ($n = 494$) had a prescription for zopiclone, and 8% ($n = 43$) were monointoxications. Most fatalities, 62% ($n = 354$) were suicides, and zopiclone was involved in about 17% ($n = 354$) of all intoxication suicides in Sweden. Women were significantly ($p < 0.01$) overrepresented in suicides with zopiclone, comprising 56% ($n = 291$) of fatalities. The median age was 55 years among zopiclone intoxications compared with 44 years amongst all fatal intoxications.

Conclusion This study demonstrates that the toxicity of zopiclone can be lethal both in combination with other substances and on its own. Most individuals dying in fatal zopiclone intoxications were prescribed zopiclone, which potentially indicates that a more restrictive prescribing rate could prevent future intoxication deaths, especially when caring for patients with an increased suicide risk.

Key Points

Fatal intoxications with zopiclone are quite common in Sweden, constituting 8% of all fatal intoxications and 17% of all intoxication suicides. Most suicides with zopiclone were committed by older women.

The large majority (87%) of individuals dying in a fatal zopiclone intoxication had a dispensed prescription for zopiclone, which potentially indicates that a more restrictive prescribing rate could prevent future intoxication deaths.

Most deaths occurred in combination with other substances, but zopiclone can be lethal on its own.

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1 Introduction

Zopiclone is a controlled substance used in the treatment of insomnia [1]. It was introduced in Europe in 1987 and is considered the third generation of hypnotics after barbiturates and benzodiazepines [2]. Zopiclone is often grouped with zaleplon and zolpidem, all commonly referred to as Z-drugs [1, 3].

The use of zopiclone (as well as other sedatives) is widespread in Sweden. According to data published by the Swedish National Board of Health and Welfare, approximately 5% of the population over 19 years of age received a prescription for zopiclone in 2020 [4]. The popularity of zopiclone can be attributed to its effectiveness in inducing sleep, and that the safety profile is considered superior compared with benzodiazepines [1, 3, 5, 6]. Early clinical trials of zopiclone failed to show major morbidity or mortality in connection to the drug [1, 3, 7–10]. However, more recent data show that zopiclone has the potential to cause dependence and withdrawal [11, 12] and is involved in cases of driving under the influence [13, 14], motor vehicle crashes [3], and overdoses [3, 12, 15]. Sedative and hypnotic drugs have previously been shown to be

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commonly detected in intoxication suicides and suicide attempts [16–22].

Recent observational studies on intoxications with zopiclone are scarce [19]. When studying Z-drugs and their role in intoxications they are often grouped together with benzodiazepines, which complicates the understanding of their role in causing morbidity and mortality [19]. The Swedish National Board of Health and Welfare has published a report concluding that zopiclone was the most frequent drug found in suicides by intoxication between 2012 and 2018 in Sweden [23]. With these findings in mind, further research exploring potential hazards of zopiclone use are needed.

The overall aim of this study was to explore the role of zopiclone in fatal intoxications in a Swedish forensic autopsy material during a 9-year period from 2012 to 2020. More specifically, we aimed to identify cases of monointoxications and to compare the demographics and toxicological results between suicides and other manners of death.

2 Materials and Methods

2.1 Forensic Autopsies in Sweden

A forensic autopsy is requested by the police authorities when a suspected unnatural death occurs in Sweden. Unnatural deaths comprise fatalities where an external cause of death cannot be ruled out, for example, when there is suspicion of a crime, substance abuse, suicide, or medical malpractice or when the body is of unknown identity. Every year, about 5500 forensic autopsies are performed at the National Board of Forensic Medicine with the purpose of establishing the cause and manner of death. In this process, multiple factors, such as findings from the autopsy, histological samples, and toxicological analyses as well as information from the police are considered. Toxicological analysis of blood and other biological specimens, collected in standardized procedures during the autopsy, is performed at one centralized forensic toxicology laboratory located in Linköping, Sweden. The result of the investigation is reported on the cause of death certificate and in a database held by the National Board of Forensic Medicine.

2.2 Toxicological Analysis of Postmortem Samples

At the forensic toxicology laboratory an extensive toxicological screening for xenobiotics and ethanol is performed routinely. Ethanol in femoral blood and other specimens is analyzed by a headspace gas chromatography flame ionization detector (HS-GC-FID) method [24]. The drug screening procedure is performed in femoral blood using a liquid chromatography/time-of-flight mass spectrometry (LC-TOF-MS) method [25]. Positive findings are verified with different, more specific analytical methods. Zopiclone was quantified by liquid chromatography with tandem mass spectrometry (LC-MS/MS). In brief, the femoral blood samples were buffered with borate buffer at pH 9.0 followed by liquid–liquid extraction with ethyl acetate. Sample analysis was performed using a Waters Acquity UPLC I-Class system coupled to a Waters XEVO TQD (Milford, MA, USA). The calibration curve was linear over zopiclone concentrations ranging from 0.01 to 1.0 µg/g. The limit of quantification (LOQ) for zopiclone was 0.01 µg/g. This study utilized preexisting toxicological data collected in connection to the autopsies, no reanalysis of postmortem samples was performed.

2.3 Data Sources and Study Population

This is a register-based study in which the population was identified using the National Board of Forensic Medicine database. Among fatalities undergoing a forensic autopsy between 2012 and 2020, deaths caused by intoxication were identified on the basis of the information on the cause of death certificates issued by the forensic pathologist (Fig. 1). The inclusion of cases and the presentation of data were based on the autopsy date. The manner of death and sex of each case were retrieved in the database. Cases positive for zopiclone in femoral blood were selected for further investigation.

The first author (LT) reviewed the cause of death certificates to include cases where the forensic pathologist considered zopiclone as a causal drug (solely or in combination with other substances). Information of toxicological findings for all zopiclone intoxications was retrieved. A second assessment of all potential monointoxications with zopiclone was performed by the first author (LT) and a forensic pathologist (CS) to determine whether zopiclone caused the death alone, or if other substances were potential contributors to the lethality of the intoxication.

The Swedish Prescribed Drug Register contains information of prescribed and dispensed drugs at Swedish pharmacies [26]. The register was utilized to determine whether the individuals included in the study were prescribed zopiclone or not. A prescription was defined as valid if it was dispensed within 1 year before the death date. The linkage of the registers was performed utilizing the personal identification number assigned to every Swedish citizen [27].

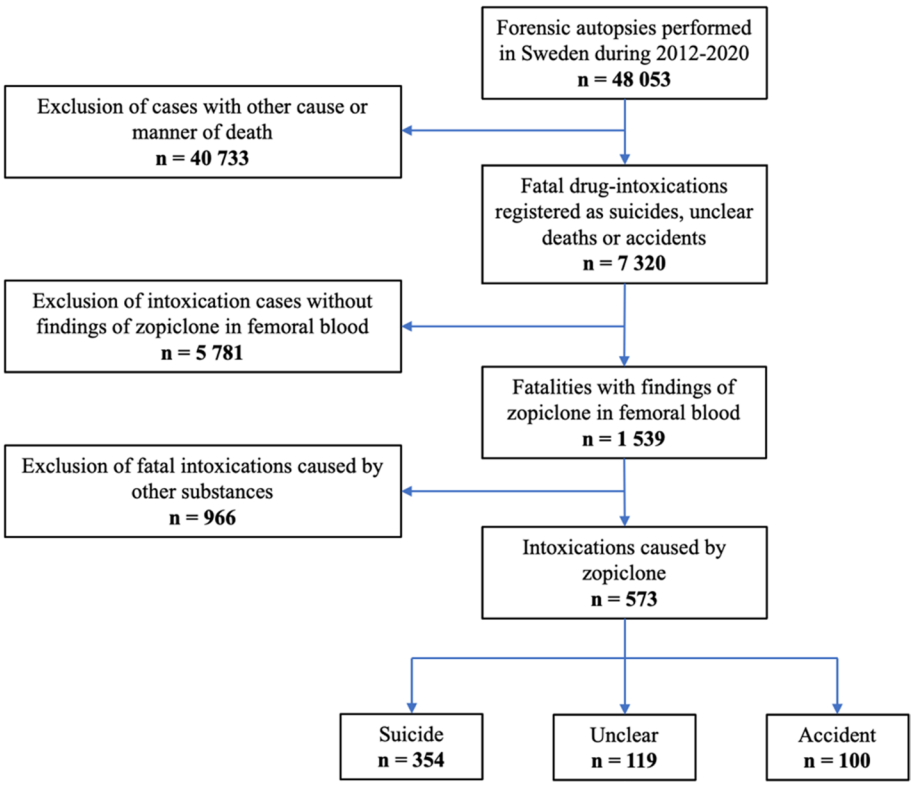


Fig. 1 A flow chart displaying the process of including fatal zopiclone intoxications among forensic autopsy cases between 2012 and 2020. The inclusion of cases was based on the cause of death certificate and the autopsy date

2.4 Definitions

2.4.1 Zopiclone Intoxications

Zopiclone intoxications were defined as intoxication fatalities in which the forensic pathologist registered zopiclone as a causal substance on the cause of death certificate or in the autopsy report. Monointoxications were defined as lethal intoxications caused by a single substance. Substances additional to zopiclone may have been present but were assessed as secondary findings, meaning that they were not potential contributors to the toxicity of the intoxication. Fatalities where zopiclone was the only substance found were classified as "monointoxication with no other findings". This study included cases classified as intentional intoxications (suicides), accidental intoxications, and intoxications of undetermined intent (unclear).

2.4.2 Other Findings

Toxicological findings additional to zopiclone in all types of blood were categorized into substance groups on the basis of their pharmacological effects. The Anatomic Therapeutic Chemical (ATC) classification system [28] was used in cases where pharmaceutical drugs were detected. Some exceptions to the ATC-classification system were made. Hypnotics were defined as the following ATC codes: N05BB, N05BE, N05CM, N05CH, R06AD, and R06AA02 (hydroxyzine, promethazine, propiomazine, alimemazine, buspirone, clomethiazole, melatonin, and diphenhydramine). Benzodiazepines were defined as ATC codes N05CD and N05BA (alprazolam, diazepam, flunitrazepam, lorazepam, nitrazepam, temazepam, oxazepam, and bromazepam) and Z-drugs as ATC code N05CF (zolpidem and zaleplon). Substances with ATC codes N02A, N07BC02, and R05DA01 (fentanyl, codeine, morphine, oxycodone, tramadol, methadone, buprenorphine, hydrocodone, tapentadol, dextropropoxyphene, and ethylmorphine) were categorized as opioids. Findings of ethanol were included if the femoral blood ethanol concentration was $\geq 0.2\%$.

2.4.3 Fatal Toxicity Index (FTI)

Fatal toxicity index (FTI) is a measure that can be applied when investigating relative drug toxicity [29]. In this study, the FTI for zopiclone was calculated by relating the number of autopsied zopiclone fatalities to the sales of zopiclone measured in defined daily dose (DDD) dispensed during a set time period. DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults (7.5 mg for zopiclone) [28, 30]. The Swedish eHealth agency compiled data on the dispensed DDD for zopiclone during 2012–2020 in Sweden, which was utilized in this study.

2.5 Statistical Analysis

Descriptive statistics, including frequencies, median, and percentiles, were used to describe the demographics of the study material and the concentrations of zopiclone. Chi-squared tests were used to compare the distribution of categorical variables between groups. For group comparisons of the median value, Mood's median test was used, and Bonferroni corrections of the *p*-values were applied to counteract the multiple-testing problem. Possible time trends were investigated using linear regression with bootstrap-based confidence intervals. The analysis was weighted against the yearly number of performed forensic autopsies. The significance level was set to 5%, with corresponding 95% confidence intervals (CI). All data were analyzed in IBM SPSS® (IBM, Armonk, NY, USA) versions 27.0 and 28.0.

3 Results

Out of the 1539 cases of intoxication where zopiclone was detected in femoral blood, 573 zopiclone-caused fatalities were identified among forensic autopsy cases in Sweden between 2012 and 2020 (Fig. 1). During the study period, zopiclone contributed to approximately 8% of fatal drug intoxications (573 out of 7320 cases) and about 17% of all intoxication suicides (354 out of 2118 cases; Table 1).

The yearly number of autopsied intoxications with zopiclone decreased during the study period (Fig. 2) after a plateau between 2012 and 2016. The lowest number was seen in 2020 with 42 deaths. The total sales of zopiclone (measured in dispensed DDD) increased between 2012 and 2016 and decreased between 2016 and 2020. The decrease of the number of fatalities was 0.76 cases per 1000 forensic autopsies and year (95% CI − 0.42 to − 1.14).

3.1 Population Demographics

Women constituted 51% (291 cases) of zopiclone intoxications (Table 1). Cases of suicide made up approximately 62% of the fatalities, and unclear and accidental intoxications constituted 21% and 17% of cases, respectively. As shown in Table 1, the median age among intoxications with zopiclone (55 years) was higher compared with the median age of all intoxication fatalities in Sweden (44 years). Among zopiclone suicides, the median age (58 years) was significantly higher ($p < 0.01$) compared with intoxications where the manner of death was unclear (51 years) or accidental (49 years). There was no significant difference in median age between accidents and unclear cases.

As presented in Table 1, women were significantly overrepresented in suicides with zopiclone, comprising 56% of cases ($p < 0.01$). Men were significantly overrepresented in both unclear and accidental intoxications, constituting 57% and 58% of fatalities, respectively ($p < 0.01$). Among the total number of intoxication fatalities in Sweden, men constituted 65% of deaths (Table 1). They comprised 79% of accidental and 63% of unclear fatalities, although women accounted for 55% of intoxication suicides (Table 1).

The largest number of zopiclone fatalities for both men and women occurred between the ages of 46 and 65 years (Fig. 3). In the age category 18–30 years, 71% of cases were men. Women were slightly overrepresented in the remaining age categories, most prominently among individuals aged > 80, where they constituted 55% of deaths (Fig. 3). Men were overrepresented among accidental fatalities in all age categories except 66–80 years, where women were implicated in more cases. Suicide was the most common manner of death in all age categories for women.

Almost 30% ($n = 156$) of all fatal zopiclone intoxications and 34% of all suicides with zopiclone ($n = 119$) afflicted

Table 1 Descriptive statistics of age and sex for all fatal drug intoxications as well as fatal zopiclone intoxications undergoing a forensic autopsy between 2012 and 2020 in Sweden

	Manner of death			
	Suicide	Unclear	Accident	Total
All intoxications				
Age (years), median (10th–90th percentile)	53 (28–76)	46 (25–67)	36 (23–59)	44 (25–67)
Male, *n* (%)[b]	955 (45)	1215 (63)	2582 (79)	4752 (65)
Female, *n* (%)[b]	1163 (55)	708 (37)	697 (21)	2568 (35)
All cases, *n* (%)[a]	2118 (29)	1923 (26)	3279 (45)	7320 (100)
Zopiclone intoxications				
Age (years), median (10th–90th percentile)	58 (34–84)	51 (31–71)	49 (27–70)	55 (31–78)
Male, *n* (%)[b]	156 (44)	68 (57)	58 (58)	282 (49)
Female, *n* (%)[b]	198 (56)	51 (43)	42 (42)	291 (51)
All cases, *n* (%)[a]	354 (62)	119 (21)	100 (17)	573 (100)

The information is displayed for each manner of death

[a]% within total

[b]% within manner of death and sex

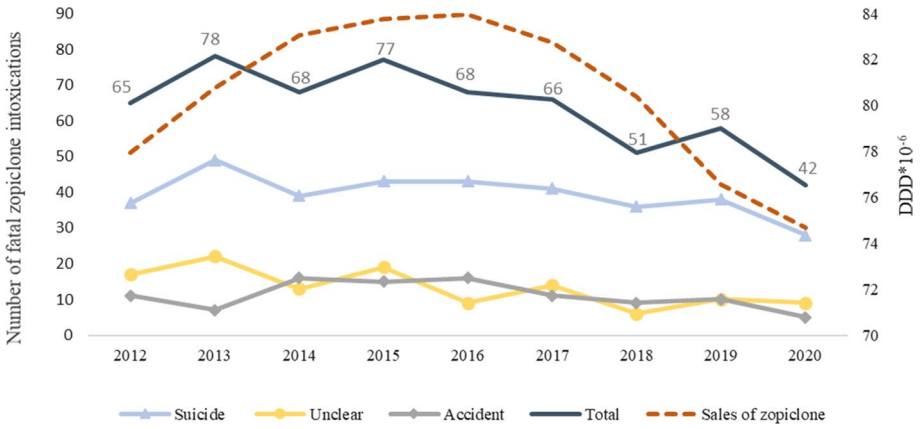


Fig. 2 The total number of fatal zopiclone intoxications during 2012–2020 in Sweden; the data are presented using the autopsy date. The number of deaths classified as suicides, accidents, and unclear for each year of the study period are displayed, as well as the yearly sales of zopiclone in Sweden measured as dispensed defined daily dose (DDD), DDD $\times 10^{-6}$

individuals > 65 years of age. Among zopiclone intoxications in the elderly (> 65 years), 77% (120 out of 156 cases) committed suicide.

3.2 Intoxications with Zopiclone

In total, 8% ($n = 43$) of all zopiclone fatalities were monointoxications, among which 86% were suicides. Out of the 43 monointoxications, 35% (15 cases) were monointoxications with no other findings in blood (Table 2). Individuals aged > 65 years comprised 65% of all monointoxications, and the eldest (> 80 years) constituted 34% of them. Out of the 15 monointoxications with no other findings, 80% (12 cases) involved individuals aged > 65 years.

The intoxications with zopiclone related to sales measured in DDD $\times 10^{-6}$ during 2012–2020 resulted in an FTI of 0.79 in total (Table 3), and 0.06 for monointoxications. No obvious time trends in FTI for zopiclone could be observed during the study period. Data were available for 571 of the 573 cases in the Swedish prescribed drug register; among them 87% ($n = 494$) were prescribed users of zopiclone. Only small variations of the proportion of prescriptions could be seen during the study period (Table 3).

The single substance most often detected along with zopiclone was ethanol (with a femoral blood concentration ≥ 0.2%). Ethanol was present in 213 cases, and it was the most common additional finding in both accidental and unclear zopiclone intoxications (found in 41% and 44% of the cases, respectively). For suicides, the most frequent additional substance in blood (from all sites) was propiomazine, found in 35% of the fatalities.

Among the additional findings of all zopiclone intoxications, the most common substance group was hypnotics, found in 50% of fatalities, followed by antidepressants (48%) and opioids (43%). Other Z-drugs (zolpidem and zaleplon) were found in 7% (42 cases) of cases.

As presented in Table 4, hypnotics were the most common substance group found in suicides and unclear deaths, detected in 51% and 55% of the cases, respectively. In the suicide category, antidepressant drugs ranked second and were found in 47% of the fatalities. Amongst the accidental

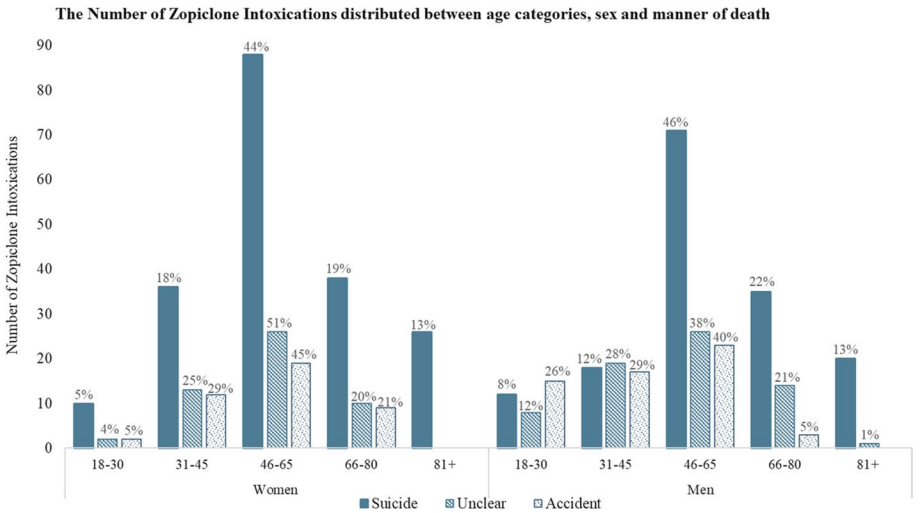


Fig. 3 The distribution of zopiclone intoxications (number of fatalities) separated based on manners of death between age categories. The data are presented for men and women, respectively. On top of the bars, the distribution is displayed as a percentage within manner of death and sex

Table 2 Total number of monointoxications with zopiclone (all cases) separated on the basis of manner of death as well as the number of monointoxications with and without other findings, and the postmortem concentrations of zopiclone between manners of death for all monointoxications

	Monointoxications with zopiclone			
	No other findings, *n* (%)	With other findings, *n* (%)	All, *n* (%)	Median concentration, µg/g (minimum–maximum)
Suicide	14 (93)	23 (82)	37 (86)	0.80 (0.04–3.70)
Unclear	1 (7)	4 (14)	5 (12)	0.45 (0.37–0.69)
Accident	0 (0)	1 (4)	1 (2)	–
All cases	15 (100)	28 (100)	43 (100)	0.79 (0.04–3.70)

Monointoxications are intoxications where zopiclone alone caused the death. No other findings, meaning that zopiclone was the only substance detected in blood in the toxicological analysis

Table 3 The fatal toxicity index (FTI) for zopiclone for each year (based on autopsy date) of the study period

Year	Zopiclone deaths	DDD[b]	FTI[a] Deaths/(DDD × 10^{-6})	Prescribed users of zopiclone[c] (%)
2012	65	77,944,465	0.83	83
2013	78	80,760,360	0.97	91
2014	68	83,071,233	0.82	82
2015	77	83,756,637	0.92	86
2016	68	83,959,362	0.81	81
2017	66	82,736,566	0.80	85
2018	51	80,385,811	0.63	92
2019	58	76,568,838	0.76	88
2020	42	74,684,752	0.56	95
Total	573	723,868,024	0.79	87

FTI, fatal toxicity index; DDD, defined daily dose

[a]The mean FTI for the 9-year period and the total percentage of prescribed users is displayed. Fatal toxicity index for zopiclone was calculated by relating the number of zopiclone intoxications to the sales of zopiclone (measured as dispensed DDD)

[b]Defined daily dose is the assumed average maintenance dose per day for a drug used for its main indication in adults (7.5 mg for zopiclone)

[c]The percentage of prescribed zopiclone-users among the fatalities is displayed for each year and in total

intoxications, 70% of cases had findings of opioids, and 55% had findings of benzodiazepines.

The median zopiclone concentration of all 573 cases was 0.47 µg/g in femoral blood (Fig. 4). The median concentration of zopiclone in suicides (0.66 µg/g) was significantly higher ($p < 0.01$) compared with the concentration in unclear cases (0.34 µg/g) and accidents (0.15 µg/g). The comparison was adjusted with Bonferroni corrections. The median concentration of zopiclone in monointoxications (0.79 µg/g; Table 2) was significantly higher ($p < 0.01$) compared with the median concentration of the remaining 530 fatalities (0.45 µg/g). The highest measured concentration was 12.0 µg/g (Fig. 4).

4 Discussion

4.1 Main Findings

This study shows that zopiclone contributed to 17% of all intoxication suicides autopsied in Sweden between 2012 and 2020. The 8% of monointoxications found in this study indicates that zopiclone is a substance with the potential of being lethal on its own. Although zopiclone fatalities are common in intoxication deaths in Sweden, they decreased at the end of the study period.

4.2 Time Trends

The declining number of zopiclone intoxications is in line with Swedish data on intoxication deaths in general [31]. The present study also found that the sales (measured in dispensed DDD) of zopiclone decreased between 2016 and 2020 in Sweden. A potential explanation for the reduction of zopiclone fatalities could be that medical professionals are more restrictive in prescribing the drug; there is evidence suggesting that limiting the access to lethal means is effective in the prevention of suicide [32, 33].

4.3 Demographics

Among all intoxication fatalities in Sweden, men constituted 65% of the deaths, which is in line with results from a Swedish publication on 6894 intoxication fatalities between 1998 and 2007 [34]. Interestingly, our study found that women and men were equally represented in fatal intoxications with zopiclone. Previous research has found women to be predisposed to insomnia [35]; in Sweden, women are prescribed more zopiclone, and drugs in general, compared with men, which could partially explain this finding [4]. We found that the proportion of suicides in intoxications with zopiclone (62%) was larger compared with the proportion in all intoxication fatalities (29%). The majority of suicides with zopiclone (56%) and suicides through intoxication in general (55%) found in this study were committed by women.

Table 4 The most frequent substance groups in count (*n*) and percentage (%) between manners of death found in fatal zopiclone intoxications

	Suicide			Unclear			Accidents		
Rank	Substance group	*n*	(%)	Substance group	*n*	(%)	Substance group	*n*	(%)
1	Hypnotics[a]	181	(51)	Hypnotics[a]	65	(55)	Opioids[d]	70	(70)
2	Antidepressants[b]	167	(47)	Antidepressants[b]	57	(48)	Benzodiazepines[c]	55	(55)
3	Benzodiazepines[c]	138	(39)	Opioids[d]	57	(48)	Antidepressants[b]	51	(51)
4	Opioids[d]	121	(34)	Ethanol[e]	52	(44)	Antiepileptics[f]	45	(45)
5	Ethanol[e]	120	(34)	Benzodiazepines[c]	45	(38)	Ethanol[e]	41	(41)

The groups of substances are mainly based on ATC codes

[a]Hypnotics: hydroxyzine, promethazine, propiomazine, alimemazine, buspirone, clomethiazole, melatonin, and diphenhydramine

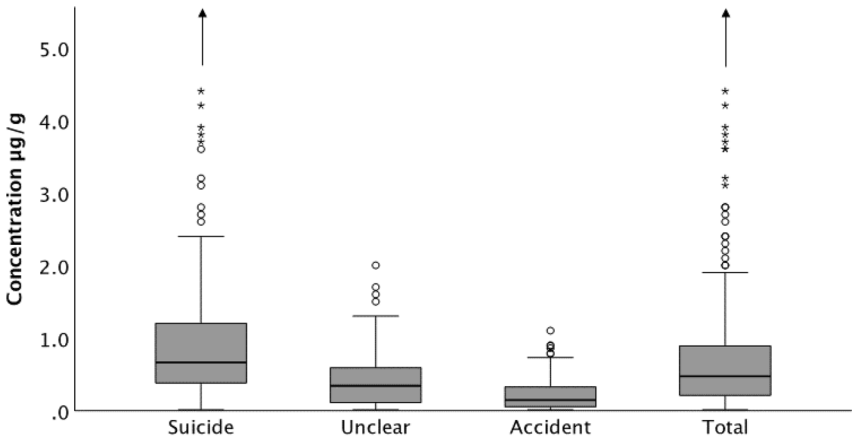
[b]Antidepressants: amitriptyline, nortriptyline, citalopram, fluoxetine, mianserin, paroxetine, venlafaxine, sertraline, mirtazapine, bupropion, duloxetine, vortioxetine, fluvoxamine, and clomipramine

[c]Benzodiazepines: alprazolam, diazepam, flunitrazepam, lorazepam, nitrazepam, temazepam, oxazepam, bromazepam, and flubromazolam

[d]Opioids: fentanyl, codeine, morphine, oxycodone, tramadol, methadone, buprenorphine, hydrocodone, tapentadol, dextropropoxyphene, ethylmorphine, and heroin

[e]Ethanol concentrations ≥ 0.2‰ in blood were included

[f]Antiepileptics: carbamazepine, clonazepam, lamotrigine, gabapentin, topiramate, levetiracetam, pregabalin, and valproate



	Suicide	Unclear	Accident	Total
Median	0.66	0.34	0.15	0.47
10th percentile	0.20	0.04	0.02	0.07
25th percentile	0.38	0.11	0.05	0.21
75th percentile	1.20	0.60	0.33	0.89
90th percentile	2.15	0.95	0.58	1.60
Max	12.0	2.00	1.10	12.0

Fig. 4 Postmortem concentrations of zopiclone in µg/g femoral blood between different manners of death among intoxications in Sweden between 2012 and 2020. Note that some of the highest concentration values are not displayed in the figure, illustrated by the arrows above boxes

The large portion of suicides in zopiclone fatalities and the overrepresentation of women in this group could potentially explain the equal representation of sexes in zopiclone deaths.

A speculative explanation for the large proportion of suicides in zopiclone deaths could be the correlation between sleep disturbances and depression. Insomnia is a common issue among individuals suffering from depressive symptoms [36], and sleep disturbances are important risk factors for suicide, even when adjusted for mental disorders [37]. This study found that 48% of zopiclone fatalities also had

findings of antidepressant drugs, and therefore, it is likely that a prominent proportion of the individuals had been diagnosed with depression. Since zopiclone is prescribed to patients with sleep disturbances, it could be speculated that the patient group suffers an increased risk for suicide, which could potentially explain the findings of this study. A randomized controlled trial found a greater incidence of depression among patients receiving treatment with hypnotic drugs compared with placebo [38]. It could be speculated that the treatment with zopiclone potentially increased depressive symptoms among the patients.

As mentioned, women were overrepresented in suicides both among all intoxications (55%) and in intoxications with zopiclone (56%). This result contrasts previous research on completed suicides, where men commit almost twice as many compared with women [33]. Evidence suggests that women tend to choose less violent methods of suicide [17, 39, 40], and intoxication with drugs is the most common suicide method for women in Sweden [31]. Women are considerably overrepresented in suicide attempts, which are more frequent than completed suicides [33]. When attempting suicide, intoxication with drugs is a common method, which could partially explain the large finding of women among intoxication suicides seen in this study. When specifically investigating intoxication suicides, there are previous studies finding women to be equally represented and overrepresented [16–18, 31, 34, 41], supporting the results of this study.

Individuals dying in zopiclone fatalities were older compared with all fatal intoxications in Sweden; the median age was 55 and 44 years, respectively (Table 1). This study found that women dying in the case of zopiclone intoxications was associated with older age, which has been seen in previous research of intoxication deaths [17, 31, 34]. Therefore, it could be speculated that the large representation of women among the zopiclone fatalities could explain the higher median age seen in this study.

Among individuals aged > 65 years, 76% of deaths were suicides, and in total they constituted about one-third of all suicides with zopiclone. The large representation of the elderly in suicides is in line with previous research [33, 40], and a Swedish study found that intoxication with drugs constituted about 40% of female and 16% of male suicides in the elderly population [16]. According to data published by the Swedish National Board of Health and Welfare, the largest group of patients receiving a prescription for zopiclone were > 84 years of age. In 2020, women constituted 65% of the patients aged > 64 years and prescribed zopiclone [4]. It could be speculated that the large prescription to the elderly and elderly women is a contributing factor to their representation in zopiclone suicides.

4.4 Monointoxications

In this study, 8% of the fatalities with zopiclone were monointoxications. Early clinical trials failed to show major morbidity or mortality in connection with zopiclone [1, 3, 7–10], and details regarding its toxicity have remained unclear. The present findings indicate that the use of zopiclone alone can have fatal consequences, especially among the elderly. Some previous studies on intoxication deaths have found fatalities with zopiclone as the sole toxicological finding, supporting the thesis that zopiclone can be lethal on its own [42, 43]. Acute toxicity from lone use of both Z-drugs and benzodiazepines has been shown to be common among intoxications presented at emergency departments throughout Europe [15].

The elderly (aged > 65 years) constituted 65% of all monointoxications and 80% of monointoxications, with no additional findings in this study. Among the monointoxications, 86% of deaths were suicides, and an explanation for the overrepresentation of the elderly could be that they apply more lethal means in their attempts to commit suicide [40], and therefore might have ingested higher dosages. Another theory could be that the frailty as well as comorbidities and polypharmacy of the elderly made them more susceptible to the toxicity of zopiclone.

4.5 Toxicology

The postmortem concentrations of zopiclone found in this study were in line with the results of previous research [42, 43]. A Swedish study on data between 1992 and 2006 found the median concentration of zopiclone in intoxications caused by one substance (0.80 µg/g) to be similar to the concentrations of the monointoxications in this study [42]. The same study also investigated the concentrations of zopiclone in fatal intoxications caused by multiple substances. They found the median concentration to be 0.70 µg/g, and the upper 90th percentile was 1.90 µg/g, which is slightly higher compared with the corresponding concentrations in the present study comprising all manners of deaths (median 0.47 µg/g and upper 90th percentile 1.6 µg/g).

The majority of zopiclone fatalities were caused by more than one substance. This phenomenon is seen when studying fatal intoxications in general where most deaths are caused by the synergic effects of multiple substances [12, 34, 41, 43]. Ethanol was the most common substance found, which is in line with previous data [13, 18, 41, 43]. For suicides and fatalities with an undetermined manner of death, the most common additional findings were hypnotics. Hypnotic and sedative drugs have previously been shown to be common toxicological findings in intoxication fatalities [16–18, 21, 43]. Our study found that 70% of all accidental zopiclone intoxications also had findings of opioids in the toxicological

analysis. Previous studies have found opioids to be common findings among accidental intoxications [21, 23, 44].

4.6 Fatal Toxicity Index and Prescribed Zopiclone Use

This study found the FTI to be 0.79 for zopiclone, and 0.06 for monointoxications, which corresponds with the findings of previous publications [29, 42, 45, 46] and can be considered quite low. Ojanperä et al. [29] reasoned that substances with an FTI > 1 had "an especially high toxicity" in relation to sales. Our interpretation of this result is that, although it is a common substance used in fatal intoxications, the number of zopiclone fatalities are somewhat low in relation to sales. Jönsson et al. [42] found other sedatives/hypnotics, such as propiomazine (FTI 1.49), flunitrazepam (FTI 1.43), and hydroxyzine (FTI 2.02), with higher FTI's compared with zopiclone. A publication by Geulayov et al. [47] utilized FTI to compare relative toxicity of substances in fatal self-poisonings and found zopiclone/zolpidem to be nine times more toxic compared with diazepam (odds ratio 9.14, 95% CI 5.01–16.65).

An interesting result of this study was that 87% of the fatalities had a prescription for zopiclone, indicating that most individuals received the substance from the Swedish healthcare system. The proportion of prescribed users remained relatively unchanged throughout the years, even when the sales of zopiclone started to decrease by the end of the study period. To our knowledge, the prevalence of prescribed use of zopiclone in fatal zopiclone intoxications has not been reported previously. However, Haukka et al. [48] investigated zolpidem (another Z-drug) within this context and found that 88% were prescribed users, a result similar to the findings of this study. In comparison with previous publications investigating other substances, such as tramadol or oxycodone, the proportion of prescribed users was lower compared with the 87% seen in this study [48, 49]. Tjäderborn et al. [14] also found that the prevalence of prescribed zopiclone (70%) and zaleplon (79%) use among impaired drivers was higher compared with other substances, supporting the results of this study.

The high proportion of prescribed zopiclone use potentially indicates that a more restrictive prescribing rate could serve as a preventive measure for intoxication deaths, especially when caring for patients with an increased suicide risk. However, sleep disturbances are known risk factors for suicide [37], and it could be speculated that treatment with sedatives is an important factor for suicide prevention. Prescribing potentially harmful substances to patients with an increased risk for suicide is a balancing act for medical professionals. Through identifying individuals with an increased risk for misuse as well as examining the potential harm of zopiclone, medical professionals can make more informed assessments when prescribing the substance.

4.7 Strengths and Limitations

A major strength of this study is the national standardization of forensic autopsies in Sweden. All autopsies are performed by one governmental institution, and the toxicological analysis is performed at one central laboratory.

Another strength is that each death was reviewed individually to conclude whether zopiclone contributed to the lethality of the poisoning or not. When uncertainties appeared, the autopsy reports were scrutinized. This method enabled an understanding of the role of zopiclone in fatal intoxications and prevented inclusion of incidental zopiclone findings.

One limitation of this study is the risk for circular reasoning when utilizing postmortem concentrations of substances to investigate the cause of death in potential intoxications. A high concentration of a substance could potentially make the forensic pathologist more inclined to assume that the death was caused by an intoxication and vice versa.

Another limitation of this study is the instability of zopiclone in vitro. If a sample is stored in suboptimal conditions, zopiclone can be degraded, resulting in lower concentrations or even undetectable levels [50]. A lower concentration of zopiclone could potentially make the forensic pathologist less inclined to consider zopiclone as a contributor to the lethality of the intoxication, which could have resulted in an underestimation of zopiclone intoxications.

This study only included cases with detection of zopiclone in femoral blood. This is a limitation since fatalities without access to femoral blood were excluded, which could have resulted in an underestimation of cases. However, femoral blood is the site least susceptible for postmortem changes and therefore optimal for studying concentrations of xenobiotics after death [51–53].

A prescription for zopiclone was defined as valid if it was dispensed within 1 year before the date of death in our study. A sensitivity analysis was carried out prolonging and shortening the time interval between the day for the last dispense and the death date, none of which had a relevant impact on the results in this study. When shortening the time interval to 6 months, the proportion of prescribed users of zopiclone was 84%; when prolonging the period to 1 year and 6 months, 88% of zopiclone fatalities were prescribed users.

5 Conclusion

The present study demonstrates that the toxicity of zopiclone can be fatal both on its own and in combination with other substances. Being a widely prescribed drug, zopiclone may serve as an accessible means for suicide. Most cases were

prescribed zopiclone, which potentially indicates that restrictions in the prescribing rate could serve as a preventive measure for intoxication deaths, especially when caring for patients with an increased suicide risk.

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Declarations

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Ethics Approval The study was approved by the Regional Ethics Review Board in Linköping, Sweden, No. 2016/489-31, including extension 2018/577-32.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Availability of Data and Material Data are available upon reasonable request, following applicable regulations, by contacting the corresponding author.

Code Availability Not applicable.

Author Contributions LT, SG, AKJ, and FCK conceptualized the research questions and designed the study. SG and AKJ coordinated the retrieval of data from registers. LT and CS performed the assessment of the individual cases. LT performed the statistical analyses under the supervision of SG and AKJ. LT wrote the original draft, and FCK supervised the work. All authors contributed to data interpretation and editing of the draft and approved the final version.

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