

Unintentional Opioid Overdoses Treated at University Clinic of Toxicology-Skopje in a Nine-Year-Period

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ABSTRACT

Background: The aim of this study was to assess the epidemiological profile of unintentional opioid overdoses, the prevalence and number of psychotropic substances involved in opioid overdoses.

Methods: This was a descriptive study, in which 180 participants were enrolled, and covered a nine-years-period. For collecting data was used the National patient electronic system "My term". The variables as gender, age, duration of opioid dependence, number of overdoses, type of substance, number of antidote ampoules, duration of hospitalization were analyzed. Severity of poisoning was made by using the Poison severity score.

Results: Opioid overdose cases were significantly higher among males than females. Mean age with standard deviation (SD) was 32.23 ± 6.71 years. Mean years (\pm SD) of duration of opioid use disorder was 11.60 ± 5.89 years. The most commonly used primary substance was methadone in 68.89% and heroin in 31.11% cases. Twenty patients were treated with mechanical ventilation because of the severe respiratory depression. Poison severity score was moderate in 51.11%, severe in 45.56% and fatal in 3.33% of the cases.

Conclusion: Most of the cases, predominantly males used one or two substances. The combination of methadone and benzodiazepine was most frequently used and the most common way was by injecting the abused substances. In most of the subjects PSS score was moderate and severe with no differences between genders.

KEYWORDS

opioids; overdose; Naloxone; Flumazenil; poison severity score

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INTRODUCTION

Opioid use disorders, fatal and nonfatal opioid-related overdoses (OODs) are significant public health problems. Accurate identification of OODs is essential to quantify the burden of the problem, evaluate risk-reduction strategies, monitor population-level outcomes, and improve prevention and quality of care (1).

Drug overdose continues to be a major cause of death, especially among young people in Europe, with recent data showing that it accounts for more than 3.4% of all deaths among Europeans between the ages of 15 and 39 (Eurostat, 2013). European countries have implemented a variety of approaches in their attempt to reduce overdose deaths at the national level using evidence-based interventions drawing on an understanding of individual and environmental risk factors. The type of substance used, the route of administration and the health of the user all have an impact on the risk of overdose. Most overdose deaths are linked to the use of opioids, primarily the injection of heroin (2).

Methadone is well established as an effective treatment of patients with opioid use disorder. However, the risk of sedation and respiratory depression with improper methadone dosing remains. Despite precautions for methadone prescription such as the dispensing of methadone under daily witnessed supervision in unstable patients and regular urine drug screen testing to verify compliance, fatalities associated with methadone have increased markedly across numerous jurisdictions in recent years (3).

Drug overdose mortality has reached unprecedented levels in the United States. Over the past two decades, drug overdose has more than tripled to become the leading cause of injury deaths in the US, outnumbering deaths from motor vehicle accidents and homicides according to data from the Centers for Disease Control and Prevention (CDC) / National Center for Health Statistics (NCHS). The epidemic shows no signs of leveling off: drug overdose mortality continued to rise through 2017, amounting to over 70,000 deaths in that year and increasing by 16 percent per year between 2014 and 2017 (4).

Compared with fatal heroin overdoses, the phenomenon of nonfatal overdose has been largely overlooked, apart from early reports based on intravenous drug user (IDU) surveys. Given that such surveys are subject to sampling bias, caution is required when attempting to determine the prevalence and characteristics of nonfatal overdoses from these samples. As such, the utilization of ambulance data may play an important role in determining the prevalence of nonfatal overdose. In addition, many heroin users who survive an overdose do not seek medical assistance (5).

Aims: 1. To assess the epidemiological profile of unintentional opioid overdoses over a nine-year period.

MATERIAL AND METHODS

DESIGN OF THE STUDY

This study has a descriptive design comprising a nine-year-period (2011–2019), and included a total of

180 patients with drug overdose, either illicit or prescribed opioids.

University Clinic of Toxicology is part of the biggest national tertiary care center, the Clinical campus “Mother Teresa” in Skopje, Republic of North Macedonia. This Clinic functions as an emergency center for internal diseases, which also includes the Toxicology department. Patients with opioid use disorder (OUD) come into the Institution/Hospital for one of the following reasons: overdoses with illicit and prescribed drugs, clinical examination and treatment of somatic diseases despite continuing opioid use, detoxification, withdrawal symptoms, or initiation of OUD treatment with the substitute buprenorphine. All participants underwent an interview and a complete clinical examination performed by the University Clinic of Toxicology specialists in internal medicine.

The National patient electronic system “My term” was used for collecting data. The variables: gender, age, duration of opioid dependence, number of overdoses, type of substance, number of antidote ampoules, duration of hospitalization were analyzed. Assessment of patient severity of poisoning was made by using the Poison severity score (PSS, Persson H et al., 1998) with the following score: none – 0 (no symptoms or signs related to poisoning); minor – 1 (mild, transient and spontaneously resolving symptoms); moderate – 2 (pronounced or prolonged symptoms); severe – 3 (severe or life-threatening symptoms); fatal – 4 (death).

SAMPLE

We analyzed patients with unintentional opioid overdoses who were treated as out/inpatients. The inclusion criteria were: 1. Overdoses with illicit and prescribed opioid drugs identified by a combination of three signs and symptoms referred to as the “opioid overdose triad”: pinpoint pupils, unconsciousness, respiratory depression. 2. Positive response to Naloxone, 3. History of patient positive for opioid use disorder. Exclusion criteria were the following: alternative diagnosis (e.g., trauma or infection), non-opioid drug poisoning. This study was in accordance the etic protocol for use of electronic data from the National electronic medical system provided to the University Clinic of Toxicology.

DATA ANALYSES

Data was statistically analyzed with the SPSS software package, version 22.0 for Windows (SPSS, Chicago, IL, USA). The qualitative series were processed by determining the coefficient of relations, proportions, and rates, and were shown as absolute and relative numbers. Quantitative series were analyzed with measures of central tendency (average, median), as well as with dispersion measures (standard deviation, standard error). Pearson Chi square test and Fischer exact test were used to determine the association between certain attributive dichotomies. Difference test was used for comparison of proportions. A two-sided analysis with a significance level of $p < 0.05$ was used to determine the statistical significance.

RESULTS

During the period of 9 years (2011–2019), we registered a total of 180 unintentional opioid overdose cases, and there were significantly more cases among males than among females. The highest proportion of unintentional overdoses, 26 (14.44%), was observed in 2014 and 2016 and the lowest, 7 (3.89%), in 2011. In 2015/16 we did not register any case of unintentional opioid overdose among females. The mean age of males was 32.51 ± 6.42 years and of females 29.79 ± 6.70, with no significant differences between genders (p = 0.0683). Also, there were no significant gender differences (p = 0.1784) related to the duration of opioid use disorder, which was 11.80 ± 5.95 vs. 9.89 ± 5.19 years in males and females, respectively. The number of previous overdoses were significantly more present among males compared to females (p = 0.0203), with maximum of 5 vs. 3 years, respectively (Table 1).

Tab. 1 General characteristics of the sample of unintentional opioid overdoses (2011–2019).

| Parameters | Gender | | | P |
|-------------------------------------|--------------|--------------|--------------|--------------------------|
| | Male | Female | Total | |
| Sample | | | | |
| N (%) | 161 (89.44%) | 19 (10.56%) | 180 (100%) | ¹ p = 0.0001* |
| Year of unintended opioid overdoses | | | | |
| 2011 | 6 (85.71%) | 1 (14.29%) | 7 (3.89%) | ¹ p = 0.0001* |
| 2012 | 24 (88.89%) | 3 (11.11%) | 27 (15%) | ¹ p = 0.0001* |
| 2013 | 20 (95.24%) | 1 (4.76%) | 21 (11.67%) | ¹ p = 0,0001* |
| 2014 | 18 (69.23%) | 8 (30.77%) | 26 (14.44%) | ¹ p = 0.0061* |
| 2015 | 23 (100%) | 0 (0%) | 23 (12.78%) | - |
| 2016 | 26 (100%) | 0 (0%) | 26 (14.44%) | - |
| 2017 | 17 (80.95%) | 4 (19.05%) | 21 (11.67%) | ¹ p = 0.0001* |
| 2018 | 18 (94.74%) | 1 (5.26%) | 19 (10.56%) | ¹ p = 0.0001* |
| 2019 | 9 (90%) | 1 (10%) | 10 (5.56%) | ¹ p = 0.0001* |
| Age | | | | |
| ± SD | 32.51 ± 6.42 | 29.79 ± 6.70 | 32.23 ± 6.71 | Z = 1.8226; |
| Min/Max | 20/55 | 15/47 | 15/55 | p = 0.0683 |
| Median (IQR) | 32 (28–37) | 29 (27–32) | 32 (28–36) | |
| Duration of addiction (years) | | | | |
| ± SD | 11.80 ± 5.95 | 9.89 ± 5.19 | 11.60 ± 5.89 | Z = 1.3454; |
| Min/Max | 2/32 | 2/27 | 2/32 | p = 0.1784 |
| Median (IQR) | 11 (8–15) | 9 (8–11) | 10 (8–14) | |
| Number of overdoses | | | | |
| ± SD | 2.04 ± 0.99 | 1.47 ± 0.71 | 1.98 ± 0.98 | Z = 2.3207; |
| Min/Max | 1/5 | 1/3 | 1/5 | p = 0.0203* |
| Median (IQR) | 2 (1–3) | 1 (1–2) | 2 (1–3) | |

¹ Difference test; Mann-Whitney U test = Z; * significant for p < 0.05

The number of substances used for unintentional opioid overdoses was one in 104 (57.78%) cases, two in 67 (37.22%), and three in 7 (3.89%) cases. Four and five substances were used only by 1 (0.56%) person each. Regarding gender, reported use of one or two substances

was 90 (55.9%) vs. 62 (38.51%) in males and 14 (73.68%) vs. 5 (26.32%) in females, respectively. The use of three and more substances was found only among male subjects.

The most commonly used primary substance for unintentional opioid overdose was methadone in 124 (68.89%) and heroin in 56 (31.11%) cases. Slow releasing morphine, Tramadol, alcohol, buprenorphine, amphetamine, and cocaine were found to be used only by male patients. The most frequently used combination was methadone and benzodiazepine (n = 59) and the most common way was by injecting the abused substances (Table 2).

We found no significant gender differences related to treatment, duration of hospitalization, and mechanical ventilation (p = 0.2559 vs. p = 0.1861 vs. p = 0.3911). Males were significantly more often treated with Naloxone compared to females (p = 0.0162), but this was not the case in the treatment with Flumazenil. The mean value of Naloxone antidote was 1.37 ± 0.74 mg (min/max: 0.04/4.4 mg). The mean value of Flumazenil antidote was 0.73 ± 0.3 mg (min/max: 0.5/1.5 mg). PSS score was moderate in 92 (51.11%) and severe in 82 (45.56%) of the cases with no percentage differences between the genders for p = 0.1320 vs. p = 0.2060, consequently. We found fatal PSS score among 6 (3.33%) male cases. Four patients received the methadone and benzodiazepine combination; the fatal outcome in one patient was as a result of using heroin, methadone, Tramadol and cocaine combination, and the last patient had fatal outcome as a result of methadone, benzodiazepine and alcohol combination (Table 2).

Tab. 2 Substances used and treatment of cases with unintentional opioid overdoses (2011–2019).

| Parameters | Gender | | | P |
|-------------------------|-----------------|------------------|------------------|---|
| | Male N = 161 | Female N = 19 | Total N = 180 | |
| Substance | | | | |
| Heroin | 48 (28.81%) | 8 (42.11%) | 56 (31.11%) | X ² = 1.198; df = 1; p = 0.2737 |
| Methadone | 113 (70.19%) | 11 (57.89%) | 124 (68.89%) | X ² = 1.190; df = 1; p = 0.2736 |
| Tramadol | 5 (3.11%) | 0 (0%) | 5 (2.78%) | - |
| Benzodiazepine | 57 (35.40%) | 5 (26.32%) | 62 (34.44%) | X ² = 0.622; df = 1; p = 0.4305 |
| Slow releasing morphine | 1 (0.62%) | 0 (0%) | 1 (0.56%) | - |
| Alcohol | 4 (2.48%) | 0 (0%) | 4 (2.22%) | - |
| Buprenorphine | 1 (0.62%) | 0 (0%) | 1 (0.56%) | - |
| Amphetamine | 2 (1.24%) | 0 (0%) | 2 (1.11%) | - |
| Cocaine | 3 (1.90%) | 0 (0%) | 3 (1.69%) | - |
| Treatment | | | | |
| Outpatient | 80 (49.68%) | 12 (63.16%) | 92 (51.11%) | X ² = 1.2909; df = 1; p = 0.2559 |
| Inpatient | 81 (50.32%) | 7 (36.84%) | 88 (48.89%) | |

| Parameters | Gender | | | P |
|---|-----------------|------------------|------------------|-------------------------|
| | Male N = 161 | Female N = 19 | Total N = 180 | |
| Duration of hospitalization (days) | | | | |
| ± SD | 3 ± 2.67 | 2 ± 0.01 | 2.93 ± 2.59 | Z = 1.3222; p = 0.1861 |
| Min/Max | 1/17 | 2/2 | 1/17 | |
| Median (IQR) | 2 (2-3) | 2 (2-2) | 2 (2-3) | |
| Number of Naloxone (ampoules 0.4 mg/ml) | | | | |
| ± SD | 3.41 ± 1.91 | 2.32 ± 1.11 | 3.29 ± 1.87 | Z = 2.4045; p = 0.0162* |
| Min/Max | 1/11 | 1/5 | 1/5 | |
| Median (IQR) | 3 (2-4) | 2 (2-3) | 2 (2-3) | |
| Number of Flumazenil (ampoules 0.5 mg / 5 ml) | | | | |
| ± SD | 1.46 ± 0.60 | 1.50 ± 0.58 | 1.47 ± 0.59 | Z = -0.2074; p = 0.8357 |
| Min/Max | 1/3 | 1/2 | 1/3 | |
| Median (IQR) | 1 (1-2) | 1.5 (1-2) | 1 (1-2) | |
| Poisoning severity score – PSS | | | | |
| moderate – 2 | 79 (49.06%) | 13 (68.42%) | 92 (51.11%) | ¹ p = 0.1320 |
| severe – 3 | 76 (47.21%) | 6 (31.58%) | 82 (45.56%) | ¹ p = 0.2060 |
| fatal – 4 | 6 (3.73) | 0 (0%) | 6 (3.33%) | - |
| Mechanical ventilation | | | | |
| Yes | 19 (11.80%) | 1 (5.26%) | 20 (11.11%) | ² p = 0.3911 |
| No | 142 (88.20%) | 18 (94.74%) | 160 (88.89%) | |

Pearson Chi-square test = X²; Mann-Whitney U test = Z; ¹ Difference test; ² Fisher exact test; * significant for p < 0.05

DISCUSSION

In this study we analyzed 180 patients with opioid overdose over of a nine-year-period. Of the total number of patients, 86 were inpatients, and the rest were treated in outpatient setting. The male population was predominant 89.44%. The mean age of the participants was 32.23 ± 6.71. The youngest was a female patient – fifteen years old and she experienced a heroin overdose. The oldest patient was a 55-year-old male. He overdosed with methadone and benzodiazepines intravenously.

Findings from one study of New South Wales, Victoria, Western Australia, and the Australian Capital Territory, reported gender distribution 70/30, with patients twice as likely to be males (6). This is consistent with other reports that showed that the heroin-using population is predominantly male. It was also reported that the mean age of heroin users was approximately 30 years (6). More recently, there has been some indication that the average age of users and the average age of initiation is decreasing (6). Warner-Smith et al. in their study noted that the decline in the average age of initiation does not necessarily indicate a corresponding decline in the mean age of heroin users (7). In studies reported by Darke and Loxley the average age of the male population was 27.7 years and of females 26 years (5). Ambulance data from Western Australia are similar to Queensland data, with a 2-year age difference between males (27.5 years) and females (25.6 years) (5). Previous studies have also found this approximate 2-year difference between the sexes (5). In our study there was a 2.7 years difference between males 32.51 ± 6.42

and females 29.79 ± 6.70. Males, older people and people with low socio-economic status are at higher risk of opioid overdose than women, as well as young people and people with higher socio-economic status (8).

Research has identified patient characteristics and prescribing practices that increase the risk of prescription opioid-related overdose and death (9). Patients with psychiatric disorders, and those using benzodiazepines or illicit drugs have higher risk of opioid-related overdose and death (9). Higher doses of prescription opioids are also associated with more overdose deaths (10, 11). Likewise, long-acting opioids are associated with an increased risk of non-fatal overdose (12). Among long-term opioid users in Medicaid, pharmacy shopping and overlapping prescriptions are associated with an increased risk of overdose (13). Additionally, for patients on opioid substitution therapy in England and Wales, methadone had a relative risk of overdose death of 6.23 when compared to buprenorphine. Among injection drug users in British Columbia, prescription opioid abuse was independently associated with overdose (14). Even in this study the most commonly used primary substance for unintentional opioid overdose was methadone in 124 (68.89%) and heroin in 56 (31.11%) cases. Of these, 86 patients were with prescribed methadone substitution therapy, and the remaining patients supplied drugs on the “black market”. The combination of methadone and benzodiazepine was most frequently used. In our study out of total heroin overdoses (n = 56), three patients combined heroin with Diazepam. Fifty-nine patients made a combination of methadone (overdose) and benzodiazepines. All patients administered substances intravenously. Liang in his study reported that persons at highest risk of overdose (adjusted hazard ratios of 2–3) received a daily MED of ≥100 mg regardless of the total dose or a daily MED of 50 to 99 mg with a high total MED >1,830 mg (15). In our study the mean value of the prescribed methadone dose was 90 mg.

A study conducted by Fox included 109 patients (35.5%) who had met criteria for severe respiratory depression. Ninety patients received Naloxone alone, 9 underwent endotracheal intubation alone, and 10 received both Naloxone and endotracheal intubation (16). Recently, in one study the authors examined insurance claims to derive risk factors for overdose or opioid-induced respiratory depression. They found that among various comorbidities examined, a history of a substance use disorder was closely associated with development of opioid-induced respiratory depression, with an odds ratio of 12.7 (5).

In our study antidote Naloxone was administered in all 180 patients, and Flumazenil was administered in 59 patients. Twenty patients were treated with mechanical ventilation because of the severe respiratory depression and six patients had fatal outcome.

LIMITATIONS OF THE STUDY

This study included only subjects who came to the clinic, and thus the generalizability of the results may be limited. There were six fatal outcomes, and therefore it was not sufficient to give information about the risk of mortality. In addition, in our study, we focused on unintentional

overdoses, but the data in the survey were self-reported by the patients. Substance users who experience an overdose are usually polydrug users; it is very difficult to distinguish which and how many drugs were used before an overdose episode.

CONCLUSION

Opioid overdose was predominant in the male population. There were no significant differences between genders related to treatment opioid overdose, duration of hospitalization, and mechanical ventilation and duration of opioid use disorder. The number of previous overdoses was significantly higher in the male population. Most of the study participants, predominantly males used one or two substances, and rarely more substances. The most commonly used primary substance for unintentional opioid overdose was methadone and heroin. The combination of methadone and benzodiazepine was most frequently used, and the most common way was by injecting the abused substances. There were no significant gender differences related to treatment, duration of hospitalization, and mechanical ventilation. In most of the subjects PSS score was moderate and severe with no differences between genders.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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AUTHOR CONTRIBUTIONS

N.S. designed the study, managed the literature searches and analyses. A. B. obtained data. V. V. S. undertook the statistical analysis and all the authors discussed the results. All authors revised and approved the final manuscript.

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