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Toxicological findings in overdose suicides 2016–21

ORIGINAL ARTICLE

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Background

More than 300 people die from an overdose each year in Norway, and the trend is rising. The proportion of suicides among overdose deaths has been 11–20 % over the past ten years, with the annual figure remaining relatively stable. The purpose of this study was to describe the demographics as well as the medications and substances used in overdose suicides.

Material and method

Data from forensic toxicology analyses performed at the Department of Forensic Medicine, Oslo University Hospital, were linked to the Cause of Death Registry. The cause and manner of death from the Cause of Death Registry were used to identify overdose suicides in Norway in the period 1 January 2016–31 December 2021.

Results

A total of 1383 overdoses were recorded in the dataset, and suicide was the cause of death in 251/1383 (18.1 %) cases. The average age was 51 years (± 16 years), and 135/251 (54 %) were women. Opioids were found in 235/251 (94 %) cases, with the most common being codeine (67/251; 27 %), oxycodone (63/251; 25 %) and tramadol (60/251; 24 %). In cases where opioids were found, benzodiazepines and/or z-hypnotics were identified in 181/235 (77 %) cases. A total of 109/251 (43 %) had taken antidepressants.

Interpretation

Autopsies following an overdose suicide often revealed more than one psychoactive medication with addiction potential, in addition to an antidepressant. These medications are used for chronic pain, sleep disturbances, anxiety and depression, as well as to treat substance use.

Main findings

A total of 1383 overdose deaths were identified for the period 2016–21, of which 251 (18.1 %) were suicides.

Opioids were the most common substance group in overdose suicides (235/251, 94 %).

The most common individual substances were zopiclone (70; 28 %), codeine (67; 27 %), diazepam (64; 26 %), oxycodone (63; 25 %) and tramadol (60; 24 %).

Polysubstance use was found in 240/251 (96 %) of the suicides.

Overdoses from illegal drugs and psychoactive medications with addiction potential are a serious social problem, with several hundred deaths annually in Norway. Over the past decade, suicides have accounted for 11–20 % of these deaths (1). The number of overdose deaths has increased since 2013, with a rate of 4.7–7.1 per 100,000 inhabitants in 2023 (2). The number of overdose suicides per year varies, but the trend during this period has remained stable, with no significant increase or decrease. Three times as many men as women die as the result of an overdose, but in terms of overdose suicides, the figure is higher for women (1). Overdose suicides account for approximately 40 % of all suicides by poisoning in Norway. An overdose is a type of poisoning involving the use of narcotic substances, including medications (such as opioids like codeine, oxycodone and tramadol) and illegal substances. The terms *drug-related deaths* and *drug-induced deaths* are used in the literature synonymously with *overdose deaths*. Fatal poisonings involving substances such as ethanol and medications like paracetamol, antidepressants or antipsychotics, are not included in the definition, nor in national overdose statistics (2).

The primary agents vary over time and between fatal and non-fatal overdoses. Ethanol is commonly found in hospital admissions for poisoning in general as well as fatal poisonings (2, 3). In non-fatal poisonings, paracetamol, GHB (gamma-hydroxybutyrate) and z-hypnotics/benzodiazepines are most common, while opioids are the most frequently used substance group in overdose deaths (3–5).

In Norway, forensic autopsies are performed for unnatural deaths, when criminality is suspected, when the cause of death is uncertain and may be due to suicide or an accident, or when the death is sudden and unexpected, according to the Prosecution Instructions (1986, sections 13 - 1, 13 - 2) (6). The

manner of death and cause of death (underlying cause) are determined by the autopsy pathologist based on toxicological analyses, information from the police, witnesses and the deceased person's family, as well as factors at the scene of the death. The autopsy report and death certificate are sent to the Cause of Death Registry.

In Norway, suicides are classified according to stringent criteria. This requires suicide notes, known suicide risk and any physical evidence at the scene to be considered when determining the manner of death. In the Cause of Death Registry, the manner and cause of death are coded according to the International Classification of Diseases, version 10 (ICD-10). For the underlying cause of death, Norway uses the definitions from the European Union Drugs Agency (EUDA): Intentional poisoning (suicide) (X61, X62), Poisoning of undetermined intent (Y11, Y12), Accidental poisoning (X41, X42), and Mental and behavioural disorders due to psychoactive substance use (F11–F19). Along with this, a code is used for the substance or substance group considered to be the primary agent (T40.0–T40.9, T43.6). Only opium, heroin, methadone, cocaine, LSD (lysergic acid diethylamide) and cannabis have their own cause of death code. All other substances are grouped into categories of chemically or pharmacologically similar substances and cannot therefore be identified from the Cause of Death Registry.

Few measures have been implemented to prevent overdose suicides. Developing effective preventive measures requires a thorough examination of the characteristics of this type of death. The purpose of this study was to examine overdose suicides, with a focus on which medications and substances were used shortly before death. The study examines forensic toxicology findings from the autopsy in conjunction with the official cause of death from the Cause of Death Registry, enabling a more detailed description of individual substances than a purely registry-based study would allow.

Do you need to talk to someone after reading this article?
If there is an immediate risk of suicide, contact emergency services. You can find more information and local resources at: findahelpline.com.

Material and method

Overdose deaths are considered unnatural deaths, and in Norway, a forensic autopsy is performed on over 90 % of such cases (3). All regional health authorities carry out forensic autopsies, and approximately 90 % of all biological samples undergo forensic toxicology analysis at the Department of Forensic Medicine in Oslo University Hospital. Standard analysis consists of screening for the most common substances and medications, as well as an

extended search for about 800 different substances. In certain cases, additional searches are conducted for several thousand substances using a reference library.

Forensic toxicology data from the Department of Forensic Medicine's laboratory journal system were linked with the Cause of Death Registry in order to include overdose suicides (X60, X61) between 1 January 2016 and 31 December 2021. Toxicological analyses are performed at St Olav's Hospital in Trondheim in approximately 10 % of the autopsies; these are not included in the study.

Categorisation of opioid and alcohol consumption

Codeine is metabolised into morphine in the liver. A morphine concentration lower than 10 % of the concurrent concentration of codeine was categorised as 'codeine consumption' in our study as opposed to 'morphine consumption'. Codeine is a natural constituent of opium and can therefore be detected in low blood concentrations after heroin use. Codeine consumption was therefore only included at concentrations > 1 µmol/L. Where morphine is found without simultaneous detection of heroin or its main metabolite 6-monoacetylmorphine (6-MAM), heroin use cannot be excluded due to the very rapid metabolism from 6-monoacetylmorphine to morphine. Findings of 6-monoacetylmorphine or a morphine/codeine ratio > 1 were categorised as 'heroin consumption' (7). Heroin is an illegal opioid, and in the context of reported 'opioid' and 'illegal substance' use, heroin will therefore be included in both categories.

Ethanol forms in the body postmortem. To detect actual consumption before death, the metabolites ethyl glucuronide and/or ethyl sulfate were used (8).

Analyses

Data are presented as mean values ± standard deviation for normally distributed data, otherwise as median (interquartile range) for non-normally distributed data.

Using RStudio (version 4.3.0), we created an UpSet graph to visualise the number of observed cases for the most frequently detected medication groups in various combinations.

Ethics

Permits were obtained from the Director of Public Prosecutions of Norway (Ra 11 - 40 ABG/abs 639.2), the Regional Committee for Medical and Health Research Ethics (2017/84/REK South East C, 2017/2475/REK South East C) and the Norwegian Data Protection Authority (11/00076 - 3/bso). All cases have been anonymised.

Results

A total of 1383 overdose deaths were recorded in the dataset. Of these, 251/1383 (18.1 %) were categorised as suicides and included in the study. Of these, 135/251 (54 %) were women. The average age was 51 ± 16 years (men: 48 ± 16 years; women: 53 ± 15 years).

Table 1 shows the most frequently detected substances and medications. Opioids were found in 235/251 (94 %) of the cases, with codeine being the most common opioid (67/251; 27 %). The individual substances zopiclone (70/251; 28 %), diazepam (64/251; 26 %), oxycodone (63/251; 25 %) and tramadol (60/251; 24 %) were most common. Illegal substances were found in 69/251 (28 %) cases and alcohol in 43/251 (17 %). Men were more frequent users of alcohol, heroin, cannabis and methadone than women, while women used codeine, antidepressants and antipsychotics to a greater extent than men (Table 1).

Table 1

Prevalence of the most common medication groups and individual substances in 251 overdose suicides. The substances were found in forensic toxicology samples analysed at Oslo University Hospital in the period 1 January 2016–31 December 2021. More than one substance may have been found in each case.

Substance	Total (%)	Women, *n* (%)	Men, *n* (%)
Total	251 (100)	135 (54)	116 (46)
Opioids[1]	235 (94)	123 (94)	112 (97)
Morphine[2]	43 (17)	29 (21)	14 (12)
Codeine	67 (27)	44 (33)	23 (20)
Oxycodone	63 (25)	35 (26)	28 (24)
Tramadol	60 (24)	34 (25)	26 (22)
Methadone	22 (8.8)	5 (3.7)	17 (15)
Buprenorphine	21 (8.4)	10 (7.4)	11 (9,5)
Benzodiazepines	153 (61)	79 (59)	74 (64)
Diazepam	64 (26)	33 (24)	31 (27)
Nitrazepam	45 (18)	27 (20)	18 (16)
Oxazepam	43 (17)	26 (19)	17 (15)
Clonazepam	43 (17)	23 (17)	20 (17)
Z-hypnotics	83 (33)	50 (37)	33 (28)
Zopiclone	70 (28)	42 (31)	28 (24)
Antidepressants	109 (43)	73 (54)	36 (31)

Substance	Total (%)	Women, *n* (%)	Men, *n* (%)
Citalopram	37 (27)	27 (20)	10 (8,6)
Antipsychotics	48 (19)	32 (24)	16 (14)
Quetiapine	29 (12)	19 (14)	10 (8,6)
Gabapentinoids	64 (26)	39 (29)	25 (22)
Pregabalin	44 (18)	27 (20)	17 (15)
Ethanol	43 (17)	19 (14)	24 (21)
Illegal substances	69 (28)	25 (19)	44 (38)
(Meth)amphetamine	20 (8.0)	8 (5.9)	12 (10)
Cannabis	28 (11)	9 (6.7)	19 (16)
Heroin[3]	25 (10)	7 (5.2)	19 (16)

[1]Shows the total prevalence of all detected opioids, including heroin, which is also an illegal substance.

[2]If morphine is found without simultaneous detection of heroin or the metabolite 6-monoacetylmorphine, heroin use cannot be ruled out due to the very rapid metabolism of 6-monoacetylmorphine to morphine.

[3]Heroin was considered to have been used if 6-monoacetylmorphine was found or if the morphine/codeine ratio was > 1.

Findings of opioid use remained relatively stable throughout the study period, with tramadol, oxycodone and codeine being the most common (Figure 1a). The detection rate of individual opioids showed little variation from year to year, with the exception of tramadol, which exhibited an increasing trend. Heroin and the opioids methadone and buprenorphine (which are used, inter alia, in opioid agonist treatment) were less common than other opioids. The prevalence of benzodiazepines decreased from 72 % to 61 % during the period (Figure 1b), accompanied by an increase in Z-hypnotics from 23 % to 36 %. The decline in benzodiazepines included a falling trend for clonazepam.

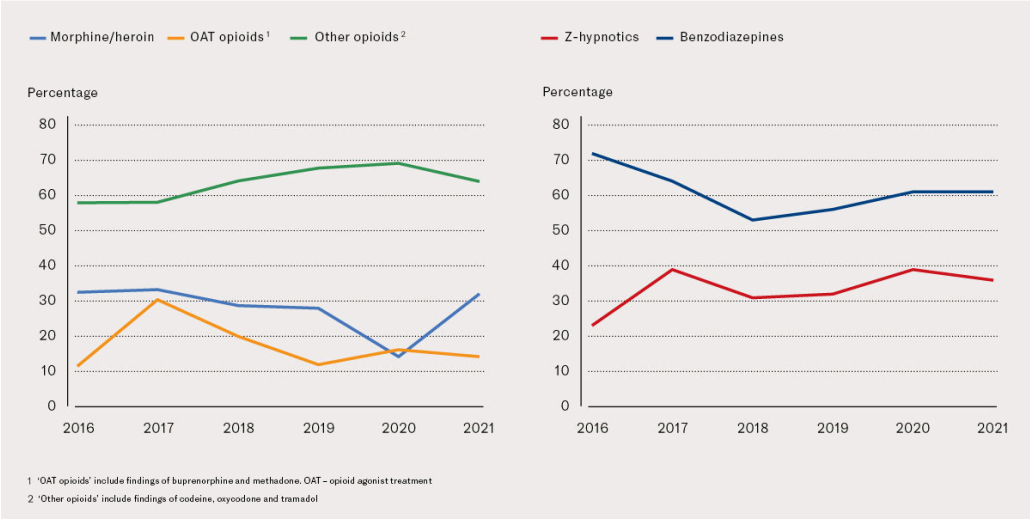

Figure 1 Annual proportion of various opioids (a), as well as benzodiazepines (clonazepam) and z-hypnotics (b), in forensic toxicology samples analysed at Oslo

University Hospital for 251 overdose suicides in the period 1 January 2016–31 December 2021.

Polysubstance use was detected in 240/251 (96 %) cases. The median number of identified substances was four (interquartile range 3–6). The highest number of substances detected in a single suicide was twelve. The opioid and benzodiazepine/z-hypnotic combination was most common, followed by additional findings of antidepressants and illegal substances (Figure 2). The opioid and benzodiazepine/z-hypnotic combination was found in 181/251 (72 %) cases, and the opioid and antidepressant combination was found in 102/251 (41 %) cases.

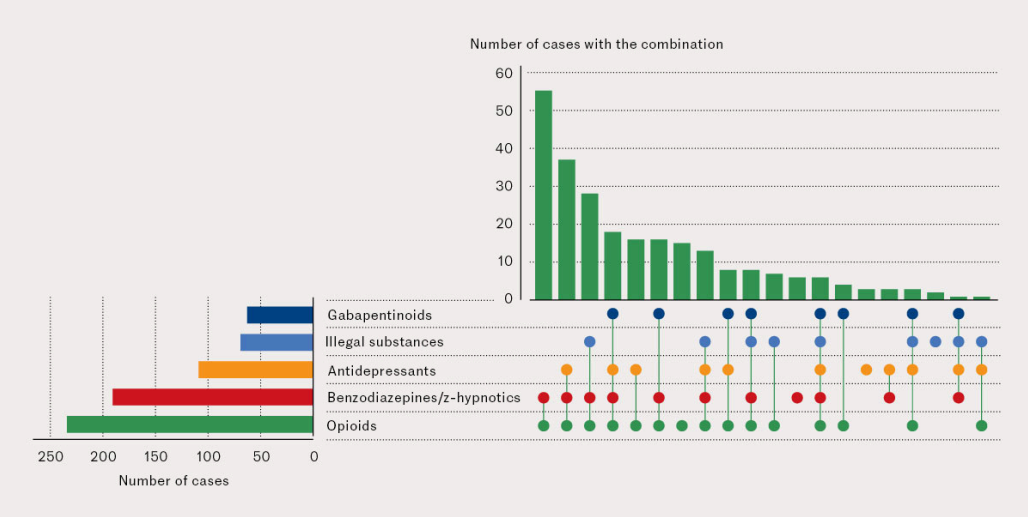

Figure 2 The UpSet graph of the frequency of detected combinations and individual findings of gabapentinoids, opioids, benzodiazepines and z-hypnotics, illegal substances and antidepressants in overdose suicides (*N* = 251) in forensic toxicology samples analysed at Oslo University Hospital in the period 1 December 2016–31 December 2021. The horizontal bar graph shows the total prevalence (in this case, of the substance groups opioids, benzodiazepines and z-hypnotics, antidepressants, gabapentinoids and illegal substances). The vertical bar graph shows the number of times a specific combination, marked with dots in the rows below, was found. The total prevalence of the benzodiazepine and z-hypnotic group is lower than the combined total prevalence for these substance groups inTable 1, as several samples were found to have both z-hypnotics and benzodiazepines.

Discussion

In this study of overdose suicides, the prevalence of opioids (94 %), benzodiazepines (61 %) and antidepressants (43 %) was high. Toxicological analyses found three or more psychoactive medications with addiction potential in most cases. Medications such as codeine, zolpidem, tramadol and oxycodone were more common than illegal substances like heroin, amphetamines and cocaine. Whether the medications were acquired illegally or prescribed by a doctor is unknown. Compared to overdose deaths and suicides in general, those who died from an overdose suicide were older, and a higher proportion were women (4, 9). The toxicological findings also differ significantly from other overdose deaths, with a lower prevalence of illegal substances and a higher prevalence of antidepressants (4).

Chronic pain conditions, substance use disorders and mental disorders are associated with an increased risk of suicide (10–12). Patients with serious somatic illnesses also have an elevated suicide risk, particularly in cases involving chronic pain (13). A previous report showed that those who take their own life are more likely to have a history of chronic pain and depression compared to those who die from other types of overdoses (14). The findings in our study show that medications used to treat pain, depression and mental disorders are common in overdose suicides. Antidepressants were found in many suicide cases. This has also been observed in Sweden, so is not unique to Norway (14).

Several countries have identified a correlation between increased opioid use and overdose deaths (15). Prescription opioids are more common in suicides than in other types of overdoses (4, 14). Codeine was the most frequently used substance in our study and is the most prescribed opioid in Norway (67/1000 inhabitants) (16). Findings of tramadol increased from 2016 to 2021, while oxycodone was found 3–5 times more frequently than tramadol and codeine, in relation to the number of users in the population (16). An increase in the use of oxycodone has been observed in recent years (17), and research shows that the increase in oxycodone prescriptions is associated with a higher risk of overdose (15, 18).

Use of psychoactive medications with addiction potential can lead to tolerance and dependence, and polysubstance use increases this risk (10, 19). Other adverse effects include impaired alertness and the risk of respiratory failure and death. Long-term use of narcotic substances such as opioids and benzodiazepines can impact brain function (20). This may include impaired mental processes and structural or chemical changes in the brain. Such changes can affect a person's ability to cope with challenges and stress, thereby increasing susceptibility to negative thoughts and impulses.

Opioids are often used together with benzodiazepines and z-hypnotics (21). This combination was the most common in our study. A median of four identified substances, all of which have an effect on the central nervous system, represents a high risk of interactions between the substances, and their combined effect can potentially be lethal. Treatment with multiple psychoactive medications with addiction potential is not recommended and should only be done under close monitoring when deemed necessary (22).

To prevent suicides and overdoses, it is important to identify high-risk groups. Norway's national overdose strategy aims to prevent overdose deaths in the country, but most measures primarily target users of illegal opioids (23). Although these measures have had a positive effect on heroin use, the number of overdose deaths has not significantly decreased in the last 20 years. It may be necessary to focus more on the use of psychoactive medications with addiction potential in addition to illegal substances. Preventive measures could include stricter prescription practices, smaller medication packages, campaigns for returning unused medications, close monitoring of patients, regular medication reviews, monitoring drug concentrations in the blood and a greater

emphasis on non-pharmacological treatments (24). Rapid access to psychiatric services is also crucial for prognosis and outcomes in many mental disorders and for suicide prevention.

Strengths and limitations

This study examined toxicological findings alongside causes of death from the Cause of Death Registry, thereby generating information on substance and polysubstance use that could not be identified from the registry alone. Furthermore, the dataset covers all of Norway, with the exception of Central Norway. As cases in Central Norway only account for about 10 % of the national total, we consider the results of this study to be transferable to the national level.

The study does not include links to data in the Norwegian Prescribed Drug Registry, which would provide information on the prescribing of medications. Future studies should examine prescription records for the deceased, and consideration should be given to making this information available to pathologists.

Distinguishing between an overdose suicide and a natural death can be challenging. Consequently, not all suicides are reported to the police. In these cases, no forensic autopsy is performed, leading to underreporting. Additionally, where there are no clear indications that a lethal overdose was intentional, the pathologist may categorise these as an overdose death with 'undetermined intent' or an accident. The number and proportion of suicides among overdose deaths are therefore a minimum estimate.

Conclusion

It may be important to consider suicide prevention measures for users of psychoactive medications with addiction potential. In this study, autopsies of overdose suicides often found more than one psychoactive medication with addiction potential in addition to an antidepressant. These medications are used to treat chronic pain, sleep disorders, anxiety and depression, but they are also used by patients with substance use disorders.

The article has been peer-reviewed.

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