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Deaths associated with MDMA in the period 2000–2019

ORIGINAL ARTICLE

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BACKGROUND

The use of MDMA (3,4-methylenedioxymethamphetamine), also known as ecstasy, has increased in Norway in recent years. Since MDMA has the potential to be toxic and cause death, we studied whether increased availability and use correlates with the increase in MDMA-associated deaths.

MATERIAL AND METHOD

The study includes post-mortems with findings of MDMA in blood, linked to information about cause of death from the Norwegian Cause of Death Registry. These data were compared with the number of arrested drug drivers with MDMA detected in their blood as well as annual seizure statistics from Kripos (The National Criminal Investigation Service) in the period 2000–2019.

RESULTS

In the period 2000–2019, MDMA was detected in 142 fatalities, and the cause of death was known for 132 of these. The number of annual MDMA-associated deaths varied from 1 to 18. The median MDMA concentration among the fatalities increased from 1.9 µmol/L (interquartile range (IQR) 0.9 to 5.0) in 2000–2004 to 3.8 µmol/L (1.4 to 12.0) in 2015–2019. In 47/132 (36 %) of cases, MDMA and other central nervous system (CNS) stimulant drugs contributed to the death. Among arrested drug drivers with detected MDMA, the annual number of detected cases was 7–262 in this period, but the median concentration remained stable.

INTERPRETATION

MDMA may have contributed to numerous deaths in Norway. Increased availability, increased use and increased strength of contents seem to be significant.

Main findings

The number of deaths associated with MDMA (3,4-methylenedioxymethamphetamine) annually in Norway has increased from 2014 and has risen in parallel with an increased number of MDMA seizures.

The percentage of fatalities with toxic MDMA concentrations and the percentage with a combination of 4 or more other recreational drugs were twice as high in 2015–2019 compared to 2000–2004.

The number of arrested drug drivers with MDMA in their blood increased from 2014, but MDMA concentrations in these people were stable in the period 2000–2019.

MDMA (3,4-methylenedioxymethamphetamine), also known as ecstasy, has been used as a recreational drug since the 1980s. Ecstasy can also contain other, related compounds (1). Its use in Norway peaked in around 2000 (2), and there were reports of numerous deaths and potentially long-term neurotoxic effects (3–5). Use then fell until 2010, but has increased steadily, and is now higher than in the early 2000s (2, 6).

MDMA is a potent central nervous system (CNS) stimulant. Single intake of a common user dose is associated with low acute toxicity, but long-term use is associated with higher frequency of psychiatric illness and cognitive impairment, although causality is unclear (4). At high doses, there is increased risk of serotonin syndrome and cardiovascular toxicity (7). MDMA can also cause rhabdomyolysis and resulting renal failure, as well as impacting the coagulation system with an increased risk of blood clots and internal bleeding (8).

A common user dose contains 50–150 mg 3,4-methylenedioxymethamphetamine (1). If several doses are taken or there is a small increase in dose, autoinhibition of the CYP2D6 enzyme can lead to considerably higher MDMA concentrations (9–11). Concentrations in blood may rise slightly after death due to post-mortem redistribution of MDMA from organs/tissue (12).

In terms of poisoning, it would not be possible to define a concentration level that is lethal for everyone, and polydrug use is a further complicating factor (13). We used our pharmacological knowledge about the effects of MDMA as a basis to investigate whether MDMA-associated deaths may be related to the dose ingested, and whether concentrations found in these deaths have changed over time. We looked at cases of reported fatal MDMA poisoning to define a limit that may indicate an increased risk of poisoning (5, 14, 15). A lack of data on LD_{50} and TD_{50}, which are commonly used measures of acute toxicity, means that a limit must be set based on clinical judgement and the available literature. Based on this, we defined MDMA concentrations above 5 µmol/L as potentially toxic. This is consistent with concentration levels in the literature (14).

In this study, we investigated the incidence of MDMA-associated deaths in Norway over a 20-year period and compared this with the incidence of MDMA among arrested drug drivers, which represents a population that provides information about trends in drug use in Norway (2). We also compared these incidences with the seizure figures in the 20-year period to investigate whether there was a connection. Our hypothesis was that increased availability and use correlates with an increase in MDMA-associated deaths. The following four secondary objectives were defined for the study: i) calculate the percentage of fatalities and of arrested drug drivers with MDMA detected in their blood, ii) compare the median MDMA blood concentrations in fatalities with that in

arrested drug drivers, iii) compare the percentage with MDMA blood concentrations above 5 µmol/L in fatalities with that in arrested drug drivers, and iv) compare the seizure figures in the 20-year period with the number of MDMA-associated deaths and incidence of the substance among arrested drug drivers.

Material and method

Post-mortem examination is required in cases of sudden and unexpected death, with toxicological analyses of around 900 recreational drugs, medicinal products, metabolites and toxins in the blood (16–18). The samples are analysed at the Department of Forensic Sciences, Oslo University Hospital, with the exception of samples from post-mortems in Central Norway (approx. 5–10 % of all post-mortems in Norway are performed at St Olav's Hospital, Trondheim University Hospital, and these are not included in the study). The analysis situation did not change in Norway in the study period. In certain cases, an extended search for around 9,000 substances is performed.

Post-mortems in which MDMA was detected

Amphetamines, including MDMA and its active metabolite 3,4-methylenedioxyamphetamine (MDA), have been included in the analysis panel throughout the period concerned. All post-mortems in the Department of Forensic Sciences in the period 2000–2019 in which MDMA was detected in blood were included in our study and linked to information about cause of death in the Norwegian Cause of Death Registry.

The Norwegian Cause of Death Registry uses ICD-10 diagnostic codes (19). The following codes were related to recreational drug use and overdoses in this data set: F11, F15, F19, X41, X42, X44 and Y14 (20). No other drug-related codes were found. Due to a change in practice in the Norwegian Cause of Death Registry's coding, the F-codes (so-called dependence diagnoses) were mainly used before 2003, and the X- and Y-codes after that (21). The X- and Y-codes refer to straightforward poisonings, with the following number describing whether the poisoning was an accident, suicide or undetermined intent, and the code is paired with a primary intoxicant (the substance/substance group that is likely to have caused the death). Like many other substances, MDMA does not have a specific diagnostic code. So information cannot be extracted directly from the Norwegian Cause of Death Registry about how many deaths have been judged to be due to MDMA, which are included in an umbrella group with code T43.6 or in F15, poisoning by or dependence on stimulants other than cocaine. Deaths with other underlying cause of death codes besides drug-related, where T43.6 was recorded as a contributory cause of death, but not the actual cause, are also described.

The post-mortem cases are referred to hereafter as 'fatalities'.

Drug driving where MDMA was detected

In cases of suspected drug driving in Norway, the Department of Forensic Sciences has national responsibility for forensic toxicology analyses. This was unchanged throughout the study period. The analysis panel consists of over 40 psychoactive substances (2), and MDMA and other known recreational drugs have been analysed throughout this period.

All cases with findings of MDMA in blood samples from arrested drivers suspected of drug driving in the period 2000–2019 were included. This group is referred to hereafter as 'arrested drug drivers'.

Seizure of MDMA

The number and quantity of MDMA seizures tells us about the availability of MDMA in Norway, and this information is provided by Kripos (The National Criminal Investigation Service) based on seizures made by the police and customs (22, 23). For seizures of powder, Kripos assumes a purity of 85 % and converts this to tablets with 150 mg active substance. Purity is determined using chromatographic analysis.

Ethics

For the post-mortem data, approval was given by the Norwegian Director of Public Prosecutions (Ra 11 - 40 ABG/abs 639.2), the Regional Ethics Committee (2017/84/REK sør-øst C, 2017/2475/REK sør-øst C) and the Norwegian Data Protection Authority (11/00076 - 3/bso). All cases were de-identified. MDMA findings in arrested drug drivers are anonymous statistics from the Department of Forensic Sciences. Samples from arrested drug drivers are owned by the Norwegian Director of Public Prosecutions, and the applicable data processing agreement does not require any further approval for such use. An overview of seizure figures (statistics) from Kripos is openly published data.

Results

In the period 2000–2019, MDMA was detected in 142/34,639 (0.4 %) of fatalities and 2,377/101,896 (2.3 %) of arrested drug drivers. In ten cases, the national ID number was incorrect or missing and could not be linked. A total of 132 cases had a known cause of death. Figure 1 shows that the percentage of detected cases with MDMA findings in fatalities fell from 2000–2004 to 2010–2014, and rose in the period 2015–2019. There was a similar trend for arrested drug drivers.

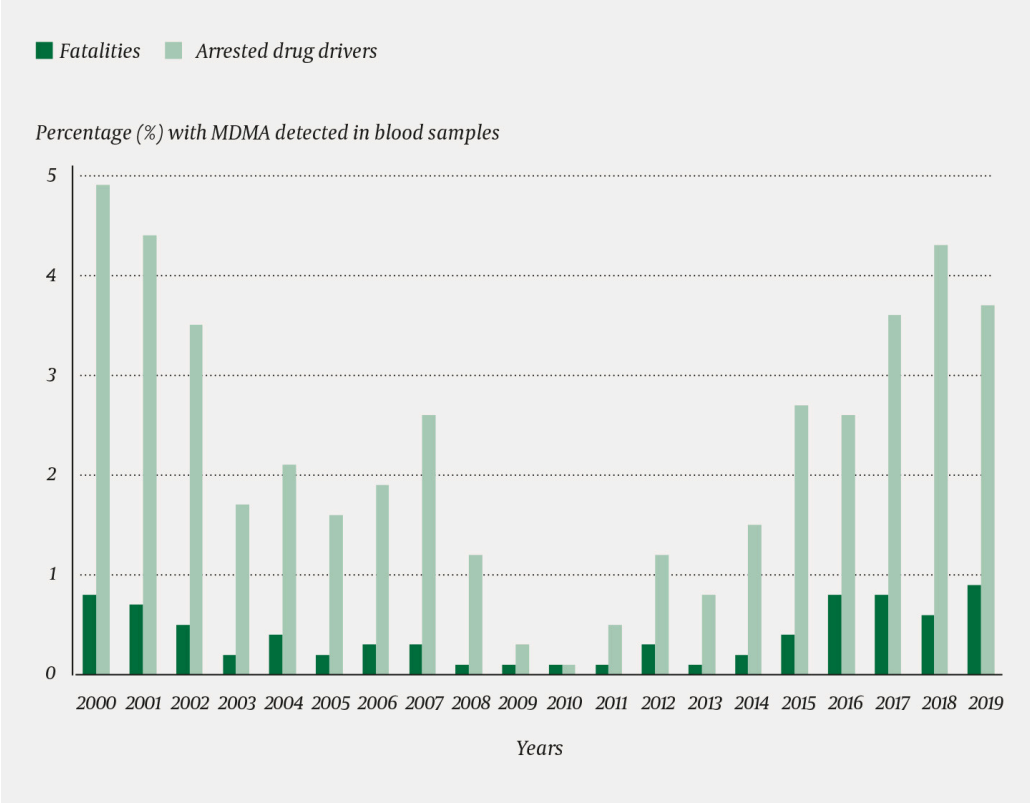

Figure 1 The percentage of fatalities and arrested drug drivers with MDMA detected in blood each year in the study period 2000–2019.

The median age of fatalities increased from 26 years (IQR 20 to 31) in 2000–2004 to 32 years (25 to 37) in 2015–2019. There was a smaller change among arrested drug drivers in the same periods, from 24 years (21 to 29) to 27 years (23 to 35). Men made up the majority in both groups throughout the study period (fatalities: 101/132 (76 %); arrested drug drivers: 2,103/2,377 (89 %)).

From 2010 to 2019, the number of seizures increased from 79 to 1,134 and the quantity from 4,400 tablets to 260,700 (22). According to Kripos, the strength of seized powder and crystalline material varied but was often high (average of 84 % in 2019) (22). In the 2000s, the usual content of the tablets was considerably lower (approx. 100 mg/tablet) than in 2019 (177 mg/tablet) (22).

Figure 2 shows the distribution of MDMA concentrations (median and interquartile range) over 5-year periods among fatalities in the study period. The median concentration among fatalities increased from 1.9 µmol/L in 2000–2004 to 3.8 µmol/L in 2015–2019. Similarly, Figure 3 shows the distribution of MDMA concentrations among arrested drug drivers. These were relatively stable over the 20-year period.

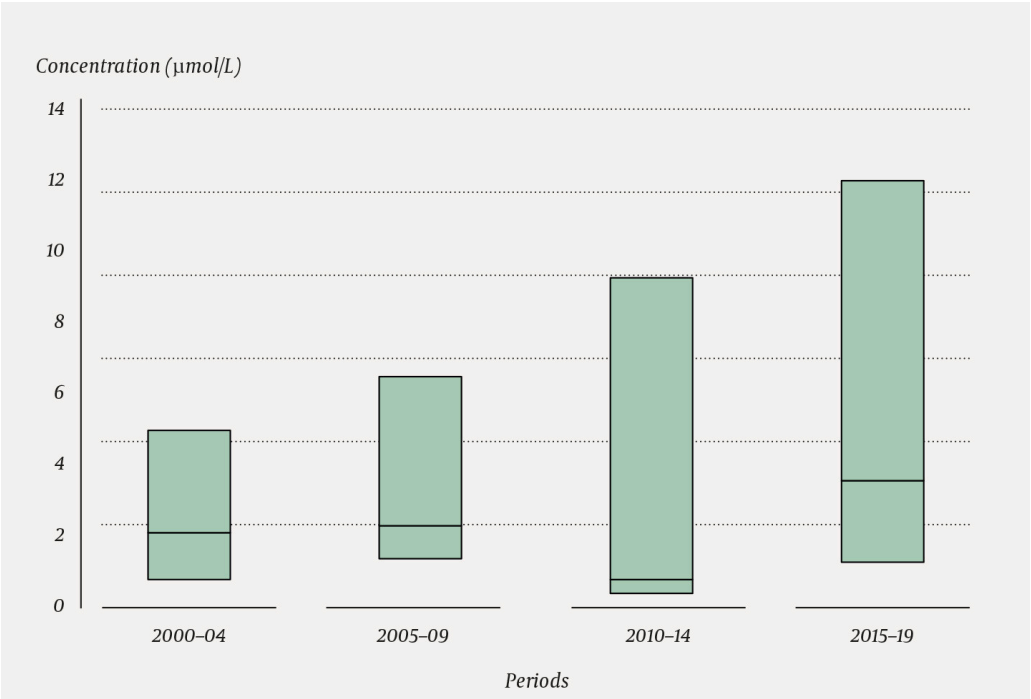

Figure 2 Distribution (median and interquartile range) of blood MDMA concentrations among fatalities per 5-year period in the study period.

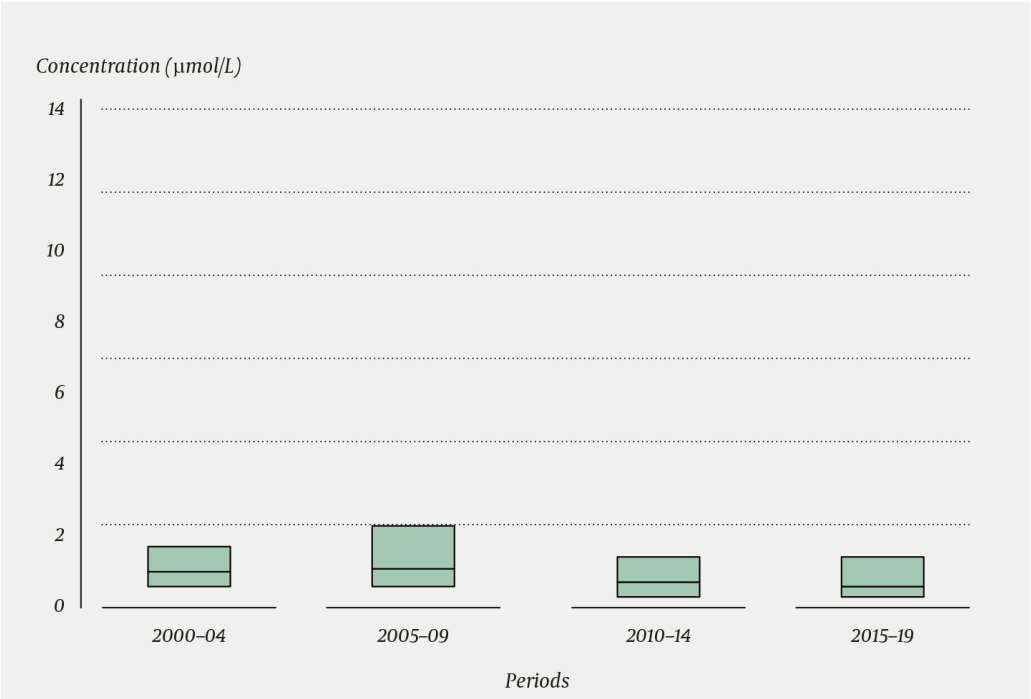

Figure 3 Distribution (median and interquartile range) of blood MDMA concentrations among arrested drug drivers in 5-year periods.

The percentage of fatalities with MDMA concentrations higher than 5 µmol/L in the period 2000–2004 was 11/46 (24 %). This increased significantly to 31/68 (46 %) in 2015–2019. There was no significant difference among arrested drug drivers in the two periods (2000–2004: 15/701 (2.1 %); 2014–2019: 19/1,096 (1.7 %)).

Among the fatalities, MDMA was always detected with polydrug use, most often amphetamine and/or methamphetamine. The percentage of post-mortems in which four or more additional substances were detected has increased from the first five-year period (2000–2004: 11/46 (24 %)) to the last five-year period (2015–2019: 32/68 (47 %)). Among arrested drug drivers, there was also an increase in the percentage of cases where four or more additional substances were detected (from 228/488 (32 %) in 2000–2004 to 486/629 (44 %) in 2015–2019).

Among the fatalities with known cause of death, 94/132 (71 %) were categorised as overdoses. T43.6 was stated as the primary diagnosis in 33/94 cases (35 %), and the code F15 was stated in 2/94 cases (2 %) – so 35/94 (37 %) of the overdoses were caused by ingestion of MDMA and/or other CNS stimulants. A total of 20/33 cases (61 %) where T43.6 was stated as the primary intoxicant occurred during the last five years of the study period.

MDMA was detected without other amphetamines in 14/35 (40 %) of the fatalities with T43.6 or F15 as the cause of death code. Among these, the median MDMA concentration was 13.0 µmol/L (IQR 5.5 to 25.5). In the remaining 21/35 (60 %) of fatalities, the median MDMA concentration was 5.3 µmol/L (3.3 to 13.0). The median amphetamine concentration (total of amphetamine and methamphetamine) was 16.0 µmol/L (6.1 to 32.8).

Among the causes of death where overdose was not the primary cause, 38/132 (29 %) were transport and drowning accidents, suicide and intentional self-harm (not caused by overdose), murder and diseases of the circulatory system, but recreational drug use was considered to be contributory to the death in 12 of these. There were consequently a total of 106 deaths related to recreational drugs: 94 overdoses and 12 cases where recreational drug use was an indirect contributory factor to the death. MDMA and/or other CNS stimulants were associated with the death in 35 and 12 cases respectively.

Discussion

MDMA may have contributed to or caused numerous deaths in Norway in the last decade. The percentage of post-mortems with findings of MDMA and use of underlying cause of death code F15 or T43.6, but without findings of concomitant use of other CNS stimulants, was higher in the last 5 years than in the first 15 years of the study period. The percentage of arrested drug drivers in Norway with MDMA detected in their blood has risen in the same period. The number and quantity of seizures has increased in parallel.

Over half of the deaths investigated with overdose as a cause of death occurred in the last five years. In addition, considerably higher MDMA concentrations were detected in post-mortem samples during this time compared with previously. This may be due to the ingestion of several user doses, autoinhibition of metabolism and/or higher-strength tablets/powder (22).

Detection of MDMA in arrested drug drivers in Norway fell in the 2000s, at the same time as the number of MDMA-associated deaths decreased. One possible explanation for the decrease was successful international regulation of a

precursor in MDMA production. The incidence in Norway increased again from 2011. In recent years, levels have exceeded those seen in the early 2000s.

The median age of arrested drug drivers and fatalities increased during the study period. At the same time, studies show that the user group has changed from the previous 'MDMA wave'. Then use was associated with young people at raves/house parties, but today the substance is largely used by an older, more affluent group without a link to any specific subculture (24). However, the party users have not entirely gone away (25). According to figures from the Norwegian Institute of Public Health (2018), use among young people aged 16–34 years has been higher than use of cocaine and amphetamine in the same age group in recent years.

Some of today's MDMA users have reported that they view ecstasy as different to – and more dangerous than – MDMA, despite MDMA being the main active substance in ecstasy (24). This new subpopulation is more likely to describe MDMA as a safe drug with positive properties, which may contribute to the substance extending to communities and user groups that would not otherwise have used illegal recreational drugs. Since the user groups are changing, there is a need for a different type of information and approach to prevention than during the ecstasy wave of the 2000s.

MDMA was usually detected in combination with other recreational drugs, and the number of cases in which four or more additional substances were detected has increased in the latter part of the study period. This combined use may partly explain the increase in the number of deaths. Polydrug use can make it difficult to determine which recreational drug caused the death (13), and it is probably the combination of several substances that is key.

The incidence of MDMA among arrested drug drivers and in unnatural deaths cannot be used to say anything general about the use of MDMA in Norway. However, our study shows that there has been an increase in the number of MDMA-associated deaths, where the substance may have contributed to or caused the death, at the same time as blood concentrations of MDMA have been increasing. Therefore, it is important that today's users, healthcare professionals and authorities are aware that MDMA has the same effects as before and can result in poisoning and death, and that the risk of fatal overdose increases when other recreational drugs are used at the same time (14).

A strength of our study is that toxicological findings are combined with information about cause of death from the Norwegian Cause of Death Registry. Since MDMA does not have its own code for indicating this as the cause of death, statistics from the Norwegian Cause of Death Registry alone could not be used to state the annual number of MDMA deaths. A limitation of our study, and also in the pathologists' determination of the cause of death, is that in cases where multiple CNS stimulants have been detected it can be difficult to determine the exact contribution of the various substances to the deaths.

Conclusion

MDMA may have contributed to or caused numerous deaths in Norway in the latter part of the period 2000–2019. In addition, the number of arrested drug drivers with MDMA in their blood has increased. This may be due to increased

availability of the substance on the Norwegian market. The percentage of fatalities with toxic MDMA concentrations was considerably higher at the end of the study period compared to the start.

The article has been peer-reviewed.

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