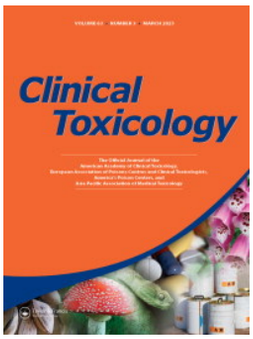

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# Differences in the clinical presentation of acute 3,4-methylenedioxymetamfetamine intoxication by co-intoxication and patient sex to European emergency departments

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## ABSTRACT

**Introduction:** This study hypothesized that 3,4-methylenedioxymetamfetamine intoxication presents with distinct clinical features and outcomes when combined with other substances of misuse, compared to mono-3,4-methylenedioxymetamfetamine intoxication. This study investigated the clinical presentation of acute mono-3,4-methylenedioxymetamfetamine intoxication, 3,4-methylenedioxymetamfetamine intoxication with exclusive co-usage of ethanol, and 3,4-methylenedioxymetamfetamine-co-intoxication with co-usage of other substances with or without ethanol, with a focus on patient sex differences.

**Methods:** A retrospective analysis was conducted using the Euro-DEN Plus database (2013–2022), which collects data on emergency department presentations with acute drug intoxication from 28 sentinel centres in 18 European countries. Odds ratios for clinical features were calculated for the three study groups with mono-3,4-methylenedioxymetamfetamine intoxication as the reference group. A sub-analysis explored patient sex differences in clinical features.

**Results:** Among 4,102 presentations, 3,4-methylenedioxymetamfetamine-ethanol intoxication ($n$ = 1,376) was associated with increased odds of agitation (OR: 1.34), drowsiness (OR: 2.30), and vomiting (OR: 1.85) compared to mono-3,4-methylenedioxymetamfetamine intoxication ($n$=359). 3,4-Methylenedioxymetamfetamine-co-intoxication ($n$=2,367) was associated with higher odds of bradycardia (OR: 3.14), psychosis (OR: 1.91), and coma (OR: 1.72). Mortality rates did not significantly differ across groups. Females reported a lower incidence of chest pain (OR 0.78) while reporting higher rates of vomiting (OR: 1.64), headache (OR: 1.61), and hypotension (OR: 1.89) compared to males.

**Discussion:** The variation in clinical manifestation of acute 3,4-methylenedioxymetamfetamine intoxication is associated with co-intoxication and patient sex. Co-intoxication with ethanol or other substances was associated with an increased incidence of more severe symptoms, such as agitation and psychosis, necessitating tailored management. These variations suggest the need for physicians to consider the type of co-intoxication and patient sex to optimize treatment strategies. Although co-intoxication affected the clinical trajectory, the mortality risk remains low.

**Conclusions:** Ethanol co-intoxication, co-intoxication with other substances of misuse, and patient sex were associated with varying clinical presentations in the emergency department, necessitating tailored treatment approaches.

## ARTICLE HISTORY

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## KEYWORDS

Euro-Den Plus; intoxication; MDMA; 3,4-methylenedioxymetamfetamine; polydrug use; recreational drug use; sex differences

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## Introduction

In recent decades, 3,4-methylenedioxymetamfetamine, commonly referred to as MDMA, "ecstasy", "XTC", or "Molly", has made a notable presence as a recreational drug across Europe and worldwide. Based on the latest national data available, the European Monitoring Centre of Drugs and Drug Addiction (EMCDDA) estimated that in 2023, 4.3% of European Union individuals aged 15–64 years had used 3,4-methylenedioxymetamfetamine at least once in their lives [1]. Amongst the 15–34-year-olds, who have the highest prevalence of drug use, 2.2 million (2.2%) had used 3,4-methylenedioxymetamfetamine in the past year [1]. Users report heightened sensory perception, increased energy, deepened emotional connection, enhanced sociability, and a sense of euphoria, making 3,4-methylenedioxymetamfetamine a popular drug in social settings, such as parties, raves, and music festivals [2]. However, the recreational use of 3,4-methylenedioxymetamfetamine is not without risk, and the number of deaths associated with 3,4-methylenedioxymetamfetamine in some European countries has been increasing over the last few years [3]. Concerns also arise from the substantially higher doses of 3,4-methylenedioxymetamfetamine in tablets currently available on the European retail market. While the average 3,4-methylenedioxymetamfetamine content per tablet was 100 mg in 2012, it increased to an average of 160 mg by 2022, with a peak average of 200 mg recorded in 2019 [1]. Patients presenting to the emergency department with acute 3,4-methylenedioxymetamfetamine intoxication exhibit a spectrum of clinical features, including tachycardia, hypertension, hyperthermia, dehydration, hyponatraemia, trismus, agitation, and seizures [4].

The severity and range of these presenting features depend not only on the dose of 3,4-methylenedioxymetamfetamine used but also on individual and environmental factors [5,6]. For example, a 2023 European Drug Emergencies Network (Euro-DEN) Plus study revealed that polydrug use serves as a contributing risk factor for critical care admission [7]. A 2021 report from the United States highlighted an increased risk of mortality among 3,4-methylenedioxymetamfetamine-intoxicated individuals after polydrug use [8]. The increased risk of mortality could be linked to interactions and severe acute intoxication resulting from the use of other substances of misuse [9,10].

Additionally, a 2022 Euro-DEN Plus study found sex differences in clinical features among patients with cannabis intoxication [11]. Given the widespread 3,4-methylenedioxymetamfetamine use among men and women [1], it is important to consider patient sex as a potential risk factor for 3,4-methylenedioxymetamfetamine-related clinical features [12]. For instance, females may have a higher vulnerability to hyponatraemia after 3,4-methylenedioxymetamfetamine use [13–15], with a significantly elevated risk of hyponatraemia-induced encephalopathy [14]. Despite suggestions in the current literature [16], there is a lack of definitive evidence on whether there are clinical differences in presentation after acute 3,4-methylenedioxymetamfetamine intoxication alone or in combination with other substances of misuse and/or patient sex.

This study aims to describe presentations to the emergency department with acute 3,4-methylenedioxymetamfetamine toxicity and to compare the characteristics and outcomes of these presentations for mono-3,4-methylenedioxymetamfetamine toxicity compared to polydrug toxicity and for males compared to females.

## Methods

### Study design

This retrospective study was conducted using the Euro-DEN Plus database. The Euro-DEN Plus project collects data on emergency department presentations with acute drug intoxication and contains in-hospital data from participating countries in Europe (European Union countries, Norway, Turkey, the United Kingdom, and Switzerland) [17]. The database aims to provide detailed information on the nature and extent of harm associated with the self-reported recreational use of drugs [12,17,18]. All presentations with clinical features consistent with acute drug toxicity and/or directly related to acute drug use are included. Presentations due to sole ethanol intoxication are not included. All presentations in the Euro-DEN Plus database from October 2013 to December 2022 were included in the analysis. For this study, cases were included if the primary reason for the emergency department visit was (related to) acute drug toxicity, and 3,4-methylenedioxymetamfetamine use was reported.

### Variables

In addition to documenting the specific substance(s) involved in the intoxication, this study gathered data on the following aspects: age, patient sex, ambulance arrival, time of presentation, ethanol co-usage, chest pain, palpitations, hypertension (systolic blood pressure ≥180 mmHg), hypotension (systolic blood pressure ≤90 mmHg), heart rate, bradycardia (heart rate <60 beats/min), tachycardia (>100 beats/min), headache, anxiety, agitation, hallucinations, psychosis, seizures, mental status (categorized as alert, drowsy, or comatose), vomiting, hyperthermia (body temperature ≥39 °C), hospital length of stay, and discharge outcome. Cases with missing values for any of the variables used in this study, including the variable for ethanol co-intoxication, were excluded. Presentations to the emergency department with 3,4-methylenedioxymetamfetamine intoxication were classified into three groups based on patient self-report. The first group, termed the mono-3,4-methylenedioxymetamfetamine intoxication group, included presentations where only 3,4-methylenedioxymetamfetamine was involved. The second group, termed the 3,4-methylenedioxymetamfetamine-ethanol group, included 3,4-methylenedioxymetamfetamine intoxications with exclusive co-usage of ethanol without any other substances of misuse. The third group, termed the 3,4-methylenedioxymetamfetamine-co-intoxication group, included 3,4-methylenedioxymetamfetamine intoxications with co-usage of other substances of misuse, with or without ethanol.

### Statistical analysis

Odds ratios were calculated by comparing the three groups with each other, using the mono-3,4-methylenedioxymetamfetamine intoxication group as the reference. Odds ratios for the development of clinical features were calculated using the frequency of each clinical feature. The interquartile range (IQR) was also calculated to summarize the data distribution. Utilizing the standard deviation and sample mean, 95% confidence intervals (95% CI) were computed for each odds ratio. An odds ratio was considered significant if its 95% CI range did not include an odds value of 1. Pearson's Chi-Squared test was used to calculate significant differences ($P$ value <0.05) between the three study groups for categorical values, excluding those expressed as odds ratios. The Kruskal–Wallis test was used for continuous variables.

### Sub-analysis of 3,4-methylenedioxymetamfetamine intoxication based on patient sex

A sub-analysis was conducted to examine the association of patient sex and clinical features in presentations with acute 3,4-methylenedioxymetamfetamine intoxication. Odds ratios for the risk of symptom development were calculated using the method described previously, with female sex used as the baseline. To mitigate the influence of other factors such as co-intoxication, the groups were stratified into mono-3,4-methylenedioxymetamfetamine intoxication, 3,4-methylenedioxymetamfetamine-ethanol intoxication, and 3,4-methylenedioxymetamfetamine-co-intoxication with co-usage of other substances, as outlined earlier. Given that the age range in the dataset was narrow, further analysis of the relationship between age and clinical features was not pursued, as any potential effects of age would likely be minimal and inconclusive.

### Software and reporting

The statistical software RStudio (© 2024 Posit Software, PBC, formerly RStudio, PBC) was used for the application of inclusion and exclusion criteria, definition of variables, and analyses of the outcomes. The code/syntax used in this study is available upon request. Reporting of results was done according to the "Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)" and "Reporting of Studies Conducted Using Observational Routinely Collected Health Data (RECORD)" guidelines [19,20]. All participating centres involved in the Euro-DEN Plus project have appropriate local ethical approval for data collection.

## Results

### Characteristics of acute 3,4-Methylenedioxymetamfetamine intoxication

After implementing the inclusion and exclusion criteria (Figure 1), a total of 4,102 cases with acute 3,4-methylenedioxymetamfetamine intoxication were included (5.8% of the 71,463 presentations in the dataset). Most were males ($n$ = 2,919, 71.2%), and the median age was 25 years (IQR: 21–31 years). The most common clinical features in the entire cohort were agitation ($n$ = 1,280, 31.2%), anxiety ($n$ = 1009, 24.6%), and palpitations ($n$ = 575, 14.0%). Most cases presented to the emergency department with concurrent use of ethanol ($n$ = 3,013, 73.5%). The complete descriptive statistics for this study cohort are outlined in Table 1. Table 2 displays the proportions of clinical features of the cohort.

A small portion of presentations ($n$ = 359, 7.8%) did not involve the co-use of other substances (Table 3). The most common substances co-used with 3,4-methylenedioxymetamfetamine were ethanol ($n$ = 3,013, 73.5%), cocaine ($n$ = 1,146, 27.9%), cannabis ($n$ = 682, 16.6%), and amfetamine ($n$ = 483, 11.8%), with a small proportion of presentations ($n$ = 349, 8.5%) having more than three substances in combination at once; cocaine ($n$ = 874, 29.9% versus $n$ = 272, 23.0%), gamma-hydroxybutyrate ($n$=227, 7.8% versus $n$=55, 4.6%) and lysergic acid diethylamide ($n$=85, 2.9% versus $n$=17, 1.4%) were more frequently reported among presentations in males compared to females. More information regarding co-intoxication can be found in Table 3.

The 3,4-methylenedioxymetamfetamine-co-intoxication group had the highest proportion of males, with 1,765 individuals (74.6%) (Table 2). Table 2 shows that compared to presentations with mono-3,4-methylenedioxymetamfetamine, those in the 3,4-methylenedioxymetamfetamine-ethanol group were associated with higher odds of tachycardia (OR: 1.36; 95% CI: 1.07–1.72), agitation (OR: 1.34; 95% CI: 1.03–1.74), vomiting (OR: 1.85; 95% CI: 1.25–2.76), and drowsiness (OR: 2.30; 95% CI: 1.69–3.12) and lower odds of chest pain (OR: 0.41; 95% CI: 0.28–0.60), hypertension (OR: 0.56; 95% CI: 0.40–0.79), anxiety (OR: 0.64; 95% CI: 0.49–0.83), and hyperthermia (OR: 0.48; 95% CI: 0.27–0.85). Furthermore, presentations with 3,4-methylenedioxymetamfetamine-co-intoxication were associated with a higher incidence of bradycardia (OR: 3.14; 95% CI: 1.15–8.64), psychosis (OR: 1.91; 95% CI: 1.14–3.23), and coma (OR: 1.72; 95% CI: 1.03–2.86) compared to a mono-3,4-methylenedioxymetamfetamine intoxication. However, these presentations had a lower proportion of hypertension (OR: 0.45; 95% CI: 0.32–0.62), tachycardia (OR: 0.67; 95% CI: 0.54–0.84), and hyperthermia (OR: 0.32; 95% CI: 0.19–0.56), compared to those with mono-3,4-methylenedioxymetamfetamine intoxication. No significant difference in other clinical features was observed between the three groups.

Finally, patients in the 3,4-methylenedioxymetamfetamine-ethanol group were associated with lower odds of admission to a psychiatric ward (OR: 0.30; 95% CI: 0.10–0.90) but were more likely to self-discharge (OR: 1.87; 95% CI: 1.25–2.79) compared to the mono-3,4-methylenedioxymetamfetamine group. Conversely, patients using additional substances of misuse were associated with higher odds of psychiatric ward admission (OR: 2.68; 95% CI: 1.17–6.14) and decreased odds of medical discharge (OR: 0.72; 95% CI: 0.56–0.92) from the emergency department compared to the mono-3,4-methylenedioxymetamfetamine group. No group was associated with increased odds for mortality. Of the 11 deaths in this study, five were associated with hyperthermia. The odds ratios between the three groups can be found in Table 2. There were significant differences in length of stay;

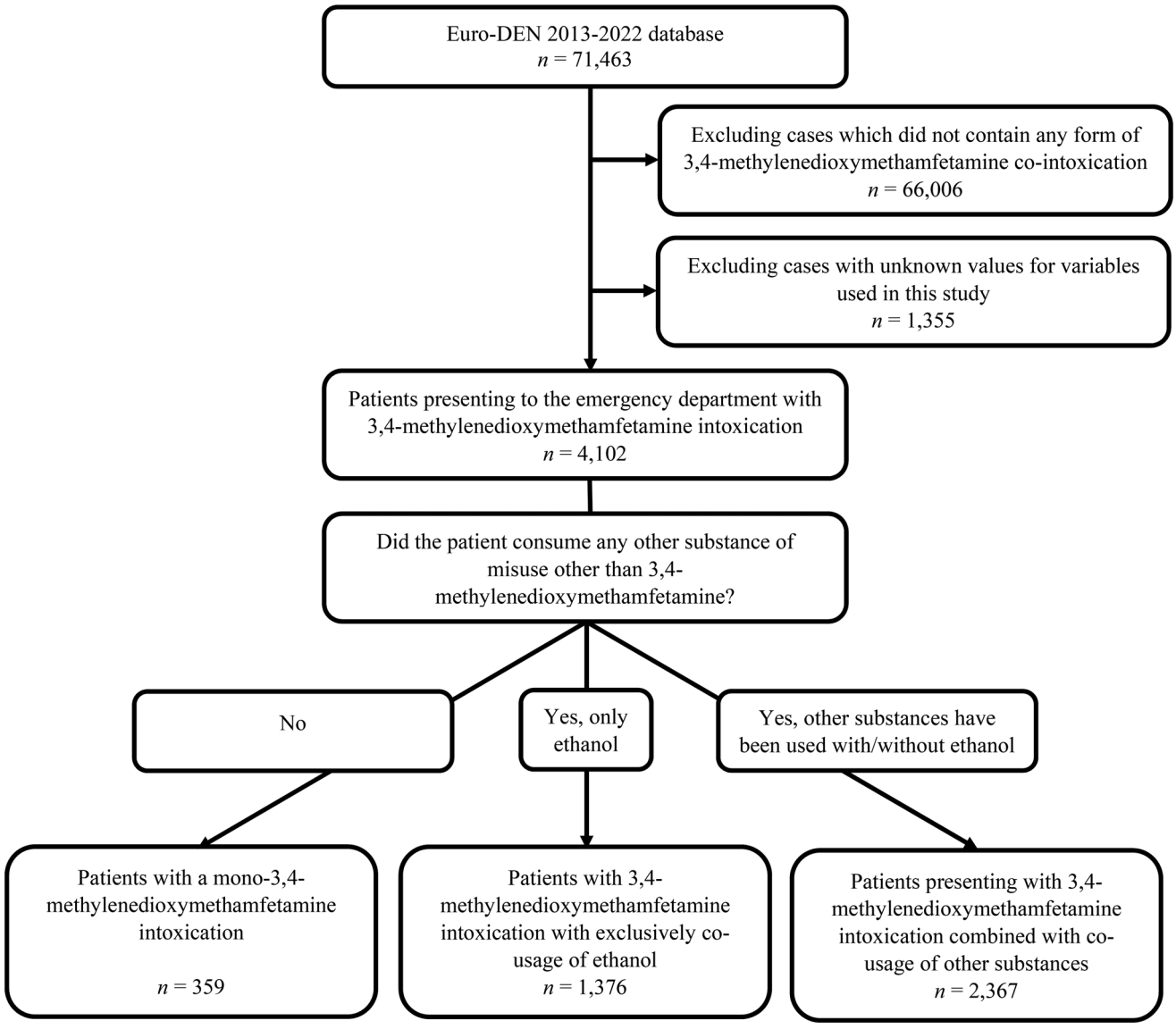


Figure 1. Flowchart with implementation of inclusion and exclusion criteria.

3,4-methylenedioxymetamfetamine 3,4-methylenedioxymetamfetamine-co-intoxication had the longest stay in the emergency department with a median of 4.3 h (IQR: 2.7–7 h), compared to 3.5 h (IQR: 2.4–5.1 h) for mono-3,4-methylenedioxymetamfetamine intoxication, and 3.8 h (IQR: 2.4–5.7 h) for 3,4-methylenedioxymetamfetamine-ethanol intoxication. There were no significant differences in length of stay among admitted patients between the three groups.

### *Sub-analysis on patient sex and 3,4-methylenedioxymetamfetamine intoxication associated clinical features by intoxication group*

Table 4 presents the patient sex differences and the odds of developing clinical features. Males were associated with increased odds of chest pain in all intoxication groups, except for the mono-3,4-methylenedioxymetamfetamine intoxication group, compared to females. Being male was associated with increased odds of seizures only in the mono-3,4-methylenedioxymetamfetamine group. Finally, being male was associated with decreased odds of developing hypotension and vomiting in all intoxication groups, although there was no significant correlation between hypotension and patient sex in the mono-3,4-methylenedioxymetamfetamine group.

## Discussion

This study examined how the co-usage of ethanol and other substances of misuse affects acute 3,4-methylenedioxymetamfetamine intoxication, alongside exploring the influence of patient sex on 3,4-methylenedioxymetamfetamine intoxication. The data indicated that almost all intoxications with 3,4-methylenedioxymetamfetamine involved co-intoxication with other substances of misuse (mostly cocaine, cannabis, and amfetamine), besides ethanol present in three-quarters of the presentations. 3,4-Methylenedioxymetamfetamine co-intoxication was associated with different clinical features compared to mono-3,4-methylenedioxymetamfetamine intoxication, depending on whether co-intoxication involved only ethanol or other substances

**Table 1.** Characteristics of the total study population ($n$ = 4,102), mono-3,4-methylenedioxymetamfetamine intoxication ($n$ = 359), 3,4-methylenedioxy metamfetamine-ethanol intoxication ($n$ = 1,376), and 3,4-methylenedioxymetamfetamine-co-intoxication with co-usage of other substances with or without ethanol ($n$ = 2,367).

| | Total study population | Mono-3,4-methylenedioxy metamfetamine intoxication | 3,4-Methylenedioxy metamfetamine -ethanol intoxication | 3,4-Methylenedioxy metamfetamine-co-intoxication with other substances | *P* Value |
|---|---|---|---|---|---|
| Age (years), median (IQR) | 25 (21–31) | 25 (20–31) | 24 (20–29) | 25 (21–32) | <0.001 |
| Male, *n* (%) | 2,919 (71.2) | 238 (66.3) | 916 (66.6) | 1,765 (74.6) | <0.001 |
| Arrived at the emergency department by ambulance, *n* (%) | 3,118 (76.0) | 222 (61.8) | 1,117 (81.2) | 1,779 (75.2) | <0.001 |
| Arrival time 22:00 – 07:59, *n* (%) | 2,281 (55.6) | 196 (54.6) | 905 (65.8) | 1,180 (49.9) | <0.001 |
| Ethanol ingestion, *n* (%) | 3,013 (73.5) | 0 | 1,376 (100) | 1,637 (69.2) | Not available |
| Length of stay | | | | | |
| Admitted (h), median (IQR) | 14.1 (6.5–33.8) | 13.3 (4.1–34.4) | 12 (6.9–30.4) | 16.2 (6.7–35.1) | 0.10 |
| Medically discharged (h), median (IQR) | 3.9 (2.6–6.5) | 3.5 (2.4–5.1) | 3.8 (2.4–5.7) | 4.3 (2.7–7.0) | <0.001 |

of misuse. Moreover, females more often presented with vomiting, headache, and hypotension, while males more often reported chest pain in almost every intoxication group.

While patients with mono-3,4-methylenedioxymetamfetamine intoxication displayed typical sympathomimetic features [21], co-intoxication with ethanol tended to dampen these features, likely due to the depressant effects of ethanol. Co-intoxication with ethanol was associated with decreased reporting of chest pain, anxiety, and hyperthermia and increased reporting of agitation, drowsiness, and vomiting.

A 2021 review [10] on the combined usage of 3,4-methylenedioxymetamfetamine and ethanol found eight studies that showed that co-ethanol usage attenuated the increase in body temperature in animals, likely due to vasodilation in cutaneous vessels. However, only one placebo-controlled study has specifically examined this interaction in humans, reporting a non-significant trend suggesting that co-exposure to 2–3 alcoholic beverages and 3,4-methylenedioxymetamfetamine 100 mg may reduce increases in body temperature [22]. The quantity of ethanol consumed in this study [22] may be lower than that typically observed in 3,4-methylenedioxymetamfetamine-intoxicated individuals presenting to the emergency department, suggesting that higher ethanol dosages could potentially have a greater attenuating effect on the increase in body temperature. However, as this study does not report precise ethanol dosages, this remains speculative. Furthermore, while animal studies have shown increased cellular stress [23], likely contributing to cardiotoxicity when 3,4-methylenedioxymetamfetamine and ethanol are combined, no such studies have been conducted in humans. One human study investigated the concentrations of norepinephrine and epinephrine and found no significant increase in these catecholamines with co-usage of ethanol compared to mono-3,4-methylenedioxymetamfetamine usage [22]. Despite animal studies suggesting a potential for cardiac toxicity, the observed reduction in chest pain in humans could be attributed to the depressant effects of ethanol, which may reduce patients' awareness of discomfort. However, since the study did not report specific ethanol dosages, this explanation remains speculative. Furthermore, two studies in mice [24,25] found an increased proportion of 3,4-methylenedioxymetamfetamine-induced anxiety when ethanol was consumed concurrently, which contradicts our results; however, ethanol is known to decrease reporting of anxiety in humans [26]. The exact mechanism for increased agitation, drowsiness, and vomiting remains unclear but could be attributed to the direct depressant effects of ethanol rather than the 3,4-methylenedioxymetamfetamine-ethanol combination.

Lastly, increased agitation may explain the higher associated odds of self-discharge in presentations with combined 3,4-methylenedioxymetamfetamine-ethanol intoxication, due to factors such as conflict with staff or impatience with the wait for treatment.

When assessing the 3,4-methylenedioxymetamfetamine-co-intoxication group, features suggestive of central nervous system depression were noted, including an increased odds of bradycardia and coma. These effects were potentially linked to co-intoxication with substances such as cannabis, gamma-hydroxybutyrate, benzodiazepines, ketamine, diacetylmorphine (heroin), and other opioids. Additionally, the 3,4-methylenedioxymetamfetamine-co-intoxication group was associated with an increased odd of psychosis, likely stemming from the consumption of hallucinogens, such as cannabis and lysergic acid diethylamide [27]. The increased odds of psychosis may also be partially explained by increased dopamine influx in the brain due to drugs like cocaine, which could induce psychosis in 3,4-methylenedioxymetamfetamine-intoxicated individuals [27,28]. A 2016 Euro-DEN Plus study [29] examined psychosis associated with acute recreational drug toxicity and reported increased odds after lysergic acid diethylamide, metamfetamine, and cannabis use, all of which were present within the 3,4-methylenedioxymetamfetamine-co-intoxication group. While all these factors might contribute to the increased association with admission to psychiatric wards, this study lacked the data to confirm this, as the Euro-DEN Plus database does not record the reason for admission. However, emergency medicine physicians should anticipate this increased need for psychiatric admission when evaluating a patient with 3,4-methylenedioxymetamfetamine-co-intoxication.

Finally, in our analysis, only a small number of patients died. 3,4-Methylenedioxymetamfetamine-co-intoxicated patients did not have an increased likelihood of admission to critical care or mortality compared to patients with

**Table 2.** The prevalence of clinical features and outcomes of the total study population ($n = 4{,}102$), mono-3,4-methylenedioxymetamfetamine intoxication ($n = 359$), 3,4-methylenedioxymetamfetamine-ethanol intoxication ($n = 1{,}376$) and 3,4-methylenedioxymetamfetamine co-intoxication with other substances with or without ethanol ($n = 2{,}367$), and their odds ratio compared to mono-3,4-methylenedioxymetamfetamine intoxication.

| | Prevalence | | | | Odds ratio | |
|---|---|---|---|---|---|---|
| | Total study population *n* (%) | Mono-3,4-methylenedioxymetamfetamine intoxication *n* (%) | 3,4-Methylenedioxymetamfetamine-ethanol intoxication *n* (%) | 3,4-Methylenedioxymetamfetamine-co-intoxication *n* (%) | 3,4-Methylenedioxymetamfetamine-ethanol intoxication odds ratio (95% CI) | 3,4-Methylenedioxymetamfetamine-co-intoxication odds ratio (95% CI) |
| Chest pain | 426 (10.4) | 45 (12.5) | 76 (5.5) | 305 (12.9) | **0.41 (0.28–0.60)** | 1.03 (0.74–1.44) |
| Palpitations | 575 (14.0) | 59 (16.4) | 199 (14.5) | 317 (13.4) | 0.86 (0.63–1.18) | 0.79 (0.58–1.06) |
| Hypertension | 373 (9.1) | 57 (15.9) | 132 (9.6) | 184 (7.8) | **0.56 (0.40–0.79)** | **0.45 (0.32–0.62)** |
| Hypotension | 129 (3.1) | 10 (2.8) | 39 (2.8) | 80 (3.4) | 1.02 (0.50–2.06) | 1.22 (0.63–2.38) |
| Tachycardia | 2,050 (50) | 191 (53.2) | 835 (60.7) | 1,024 (43.3) | **1.36 (1.07–1.72)** | **0.67 (0.54–0.84)** |
| Bradycardia | 96 (2.3) | 4 (1.1) | 11 (0.8) | 81 (3.4) | 0.72 (0.23–2.26) | **3.14 (1.15–8.64)** |
| Headache | 248 (6) | 26 (7.2) | 71 (5.2) | 151 (6.4) | 0.7 (0.44–1.11) | 0.87 (0.57–1.34) |
| Anxiety | 1,009 (24.6) | 103 (28.7) | 282 (20.5) | 624 (26.4) | **0.64 (0.49–0.83)** | 0.89 (0.7–1.14) |
| Agitation | 1,280 (31.2) | 96 (26.7) | 452 (32.8) | 732 (30.9) | **1.34 (1.03–1.74)** | 1.23 (0.96–1.57) |
| Hallucinations | 361 (8.8) | 30 (8.4) | 86 (6.2) | 245 (10.4) | 0.73 (0.47–1.13) | 1.27 (0.85–1.88) |
| Psychosis | 255 (6.2) | 16 (4.5) | 45 (3.3) | 194 (8.2) | 0.72 (0.40–1.3) | **1.91 (1.14–3.23)** |
| Seizures | 256 (6.2) | 23 (6.4) | 87 (6.3) | 146 (6.2) | 0.99 (0.61–1.59) | 0.96 (0.61–1.51) |
| Mental status | | | | | | |
| Alert | 2,736 (66.7) | 285 (79.4) | 887 (64.5) | 1,564 (66.1) | **0.47 (0.36–0.62)** | **0.51 (0.39–0.66)** |
| Drowsy | 1,090 (26.6) | 57 (15.9) | 416 (30.2) | 617 (26.1) | **2.30 (1.69–3.12)** | **1.87 (1.39–2.52)** |
| Coma | 276 (6.7) | 17 (4.7) | 73 (5.3) | 186 (7.9) | 1.13 (0.66–1.94) | **1.72 (1.03–2.86)** |
| Vomiting | 488 (11.9) | 31 (8.6) | 205 (14.9) | 252 (10.6) | **1.85 (1.25–2.76)** | 1.26 (0.85–1.86) |
| Hyperthermia | 97 (2.4) | 19 (5.3) | 36 (2.6) | 42 (1.8) | **0.48 (0.27–0.85)** | **0.32 (0.19–0.56)** |
| Discharge outcomes | | | | | | |
| Admitted to the critical care unit | 167 (4.1) | 15 (4.2) | 52 (3.8) | 100 (4.2) | 0.90 (0.5–1.62) | 1.01 (0.58–1.76) |
| Admitted to psychiatric ward | 116 (2.8) | 6 (1.7) | 7 (0.5) | 103 (4.4) | **0.30 (0.10–0.90)** | **2.68 (1.17–6.14)** |
| Admitted to other units | 564 (13.7) | 45 (12.5) | 173 (12.6) | 346 (14.6) | 1.00 (0.71–1.42) | 1.19 (0.86–1.67) |
| Medically discharged | 2,757 (67.2) | 261 (72.7) | 941 (68.4) | 1,555 (65.7) | 0.81 (0.63–1.05) | **0.72 (0.56–0.92)** |
| Self-discharged | 487 (11.9) | 30 (8.4) | 200 (14.5) | 257 (10.9) | **1.87 (1.25–2.79)** | 1.34 (0.90–1.98) |
| Death | 11 (0.3) | 2 (0.6) | 3 (0.2) | 6 (0.3) | 0.39 (0.06–2.34) | 0.45 (0.09–2.26) |

Values marked in bold are considered statistically significant because the odds ratios do not contain "1"' in the 95% CI.

Table 3. Frequencies of co-intoxication in males ($n = 2,919$), females ($n = 1,183$) and the total study population ($n = 4,102$).

| | Total study population *n* (%) | Males with 3,4-methylenedioxymetamfetamine intoxication *n* (%) | Females with 3,4-methylenedioxymetamfetamine intoxication *n* (%) |
|---|---|---|---|
| Drugs that were co-used with 3,4-methylenedioxymetamfetamine | | | |
| Ethanol | 3,013 (73.5) | 2,130 (73.0) | 883 (74.6) |
| Cocaine | 1,146 (27.9) | 874 (29.9) | 272 (23.0) |
| Cannabis | 682 (16.6) | 528 (18.1) | 154 (13.0) |
| Amfetamine | 483 (11.8) | 346 (11.9) | 137 (11.6) |
| Gamma-hydroxybutyrate | 282 (6.9) | 227 (7.8) | 55 (4.6) |
| Benzodiazepines | 275 (6.7) | 194 (6.6) | 81 (6.8) |
| Ketamine | 251 (6.1) | 189 (6.5) | 62 (5.2) |
| Metamfetamine | 181 (4.4) | 127 (4.4) | 54 (4.6) |
| Diacetylmorphine (heroin) | 146 (3.6) | 115 (3.9) | 31 (2.6) |
| Lysergic acid diethylamide | 102 (2.5) | 85 (2.9) | 17 (1.4) |
| Opioids other than diacetylmorphine | 76 (1.9) | 59 (2.0) | 17 (1.4) |
| Number of different drugs taken | | | |
| 3,4-Methylenedioxymetamfetamine alone | 1,735 (42.3) | 1,154 (39.5) | 581 (49.1) |
| 3,4-Methylenedioxymetamfetamine with one other different drug | 1,377 (33.6) | 1,007 (34.5) | 370 (31.3) |
| 3,4-Methylenedioxymetamfetamine with two other different drugs | 641 (15.6) | 479 (16.4) | 162 (13.7) |
| 3,4-Methylenedioxymetamfetamine with three or more other different drugs | 349 (8.5) | 279 (9.6) | 70 (5.9) |

mono-3,4-methylenedioxymetamfetamine intoxications, contrary to some existing literature [8–10]. However, 3,4-methylenedioxymetamfetamine-co-intoxicated patients were less likely to be medically discharged in this study. Discrepancies in mortality and morbidity outcomes between our findings and previous studies may be attributed to differences in the drug combinations, as well as differences in dosages involved in 3,4-methylenedioxymetamfetamine-related poly-intoxications. For instance, individuals using cocaine or gamma-hydroxybutyrate might use a higher dosage of different drugs or engage in more lethal combinations than those using 3,4-methylenedioxymetamfetamine, potentially resulting in higher rates of death in those groups.

Males were associated with a higher occurrence or likelihood of chest pain in all groups, except in the mono-3,4-methylenedioxymetamfetamine intoxication group and had increased odds of hypertension only in the 3,4-methylenedioxymetamfetamine-ethanol group. Similarly, in another Euro-DEN Plus study [11] on acute cannabis intoxication, males also showed increased odds for chest pain and hypertension compared to females, which was attributed to their tendency to consume higher doses of cannabis, potentially leading to more severe toxic effects. This pattern may also apply to 3,4-methylenedioxymetamfetamine. However, no studies measuring 3,4-methylenedioxymetamfetamine intake by gender are currently available. Additionally, males had a higher proportion of cocaine co-intoxication, which may partly explain the increased proportion of chest pain compared to females in the 3,4-methylenedioxymetamfetamine-co-intoxication group. Navarro-Zaragoza and colleagues [23] found increased cellular stress in mice after the combination of 3,4-methylenedioxymetamfetamine and ethanol. Given that men already have a higher baseline risk for cardiovascular issues [30], it is plausible that they reach the threshold for symptom development earlier than women when using ethanol in combination with 3,4-methylenedioxymetamfetamine, which may explain why chest pain is reported more commonly in males in the 3,4-methylenedioxymetamfetamine-ethanol group The associated increased risk of hypertension in males, found in this study, is consistent with findings from other studies that adjusted for confounding factors such as body weight and plasma 3,4-methylenedioxymetamfetamine concentrations, emphasizing the heightened risk of hypertension in males [5]. The reason for the increased odds of hypertension only in the 3,4-methylenedioxymetamfetamine-ethanol group is not explained by the current literature. Additionally, Dumont et al. [22] reported that 3,4-methylenedioxymetamfetamine and combined ethanol intoxication in humans did not demonstrate a significant association between ethanol consumption and increased blood pressure in 3,4-methylenedioxymetamfetamine users, which contradicts our findings. One possible explanation might be that males using alcohol concurrently consumed larger doses of 3,4-methylenedioxymetamfetamine and/or ethanol, resulting in dose-dependent increases in blood pressure [5]. Unfortunately, the Euro-DEN Plus database does not contain information on 3,4-methylenedioxymetamfetamine dosage.

In contrast to men, women more frequently experienced vomiting among all groups. One explanation might be that the current literature suggests an increased susceptibility to hyponatraemia in women due to 3,4-methylenedioxymetamfetamine-induced syndrome of inappropriate antidiuretic hormone release [13–15]. However, symptomatic hyponatraemia typically presents with a broader range of symptoms beyond just vomiting, including headache, decreased consciousness, and seizures. In this study, the women in the total cohort and the 3,4-methylenedioxymetamfetamine-ethanol group showed only an increased odds of headaches, whereas males in the mono-3,4-methylenedioxymetamfetamine group showed increased odds of seizures. Therefore, it is unlikely that vomiting in this context solely stems from hyponatraemia. Unfortunately, specific literature on the matter is currently lacking.

There are several limitations in this study. First, patients with 3,4-methylenedioxymetamfetamine toxicity are

**Table 4.** Clinical presentation in the total population ($n = 4,102$), mono-3,4-methylenedioxymetamfetamine intoxication ($n = 359$), 3,4-methylenedioxymetamfetamine-ethanol intoxication ($n = 1,376$) and 3,4-methylenedioxymetamfetamine co-intoxication with other substances with or without ethanol ($n = 2,367$), in relation to patient sex (with males as reference).

| Clinical features: Females versus males | Total study population (1,183 versus 2,919) | Mono-3,4-methylenedioxymetamfetamine intoxication (121 versus 238) | 3,4-Methylenedioxymetamfetamine-ethanol intoxication (460 versus 916) | 3,4-Methylenedioxymetamfetamine-co-intoxication (602 versus 1,765) |
|---|---|---|---|---|
| Chest pain, *n* (%) | **71 (6.0) versus 355 (12.2)** | 13 (10.7) versus 32 (13.5) | **8 (1.7) versus 68 (7.4)** | **50 (8.3) versus 255 (14.5)** |
| Chest pain, OR (95% CI) | **0.46 (0.35–0.60)** | 0.78 (0.39–1.54) | **0.22 (0.11–0.46)** | **0.54 (0.39–0.74)** |
| Palpitations, *n* (%) | 150 (12.7) versus 425 (14.6) | 25 (20.7) versus 34 (14.3) | 58 (12.6) versus 141 (15.4) | 67 (11.1) versus 250 (14.2) |
| Palpitations, OR (95% CI) | 0.85 (0.70–1.04) | 1.56 (0.88–2.78) | 0.79 (0.57–1.10) | 0.76 (0.57–1.01) |
| Hypertension, *n* (%) | 91 (7.7) versus 282 (9.7) | 18 (14.9) versus 39 (16.4) | **30 (6.5) versus 102 (11.1)** | 43 (7.1) versus 141 (8.0) |
| Hypertension, OR (95% CI) | 0.78 (0.61–1.00) | 0.89 (0.49–1.64) | **0.56 (0.36–0.85)** | 0.88 (0.62–1.26) |
| Hypotension, *n* (%) | **55 (4.7) versus 74 (2.5)** | 4 (3.3) versus 6 (2.5) | **19 (4.1) versus 20 (2.2)** | **32 (5.3) versus 48 (2.7)** |
| Hypotension, OR (95% CI) | **1.89 (1.32–2.70)** | 1.32 (0.37–4.76) | **1.92 (1.02–3.70)** | **2.00 (1.27–3.13)** |
| Tachycardia, *n* (%) | 607 (51.3) versus 1443 (49.4) | 60 (49.6) versus 131 (55.0) | 286 (62.2) versus 549 (59.9) | 261 (43.4) versus 763 (43.2) |
| Tachycardia, OR (95% CI) | 1.07 (0.94–1.23) | 0.81 (0.52–1.25) | 1.10 (0.87–1.39) | 1.01 (0.83–1.20) |
| Bradycardia, *n* (%) | **18 (1.5) versus 78 (2.7)** | 0 versus 4 (1.7) | 1 (0.2) versus 10 (1.1) | 17 (2.8) versus 64 (3.6) |
| Bradycardia, OR (95% CI) | **0.56 (0.34–0.94)** | Not available | 0.20 (0.03–1.54) | 0.78 (0.45–1.33) |
| Headache, *n* (%) | **96 (8.1) versus 152 (5.2)** | 13 (10.7) versus 13 (5.5) | **35 (7.6) versus 36 (3.9)** | 48 (8.0) versus 103 (5.8) |
| Headache, OR (95% CI) | **1.61 (1.23–2.08)** | 2.08 (0.94–4.55) | **2.00 (1.25–3.23)** | 1.39 (0.98–2.00) |
| Anxiety, *n* (%) | 315 (26.6) versus 694 (23.8) | 40 (33.1) versus 63 (26.5) | 102 (22.2) versus 180 (19.7) | 173 (28.7) versus 451 (25.6) |
| Anxiety, OR (95% CI) | 1.16 (1.00–1.35) | 1.37 (0.85–2.22) | 1.16 (0.88–1.54) | 1.18 (0.95–1.45) |
| Agitation, *n* (%) | 347 (29.3) versus 933 (32.0) | 29 (24.0) versus 67 (28.2) | 144 (31.3) versus 308 (33.6) | 174 (28.9) versus 558 (31.6) |
| Agitation, OR (95% CI) | 0.88 (0.76–1.02) | 0.81 (0.49–1.33) | 0.90 (0.71–1.15) | 0.88 (0.72–1.08) |
| Hallucinations, *n* (%) | 91 (7.7) versus 270 (9.3) | 9 (7.4) versus 21 (8.8) | 24 (5.2) versus 62 (6.8) | 58 (9.6) versus 187 (10.6) |
| Hallucinations, OR (95% CI) | 0.82 (0.64–1.05) | 0.83 (0.37–1.89) | 0.76 (0.47–1.23) | 0.90 (0.66–1.22) |
| Psychosis, *n* (%) | 71 (6.0) versus 184 (6.3) | 5 (4.1) versus 11 (4.6) | 15 (3.3) versus 30 (3.3) | 51 (8.5) versus 143 (8.1) |
| Psychosis, OR (95% CI) | 0.95 (0.71–1.27) | 0.89 (0.30–2.63) | 1.00 (0.53–1.89) | 1.05 (0.75–1.47) |
| Seizures, *n* (%) | 72 (6.1) versus 184 (6.3) | **3 (2.5) versus 20 (8.4)** | 27 (5.9) versus 60 (6.6) | 42 (7.0) versus 104 (5.9) |
| Seizures, OR (95% CI) | 0.96 (0.72–1.28) | **0.28 (0.08–0.95)** | 0.89 (0.56–1.43) | 1.20 (0.83–1.72) |
| Altered mental status (drowsy or coma), *n* (%) | 398 (33.6) versus 968 (33.2) | 22 (18.2) versus 52 (21.9) | 168 (36.5) versus 321 (35.0) | 208 (34.6) versus 595 (33.7) |
| Altered mental status (drowsy or coma), OR (95% CI) | 1.02 (0.88–1.18) | 0.79 (0.46–1.39) | 1.06 (0.85–1.35) | 1.04 (0.85–1.26) |
| Vomiting, *n* (%) | **187 (15.8) versus 301 (10.3)** | **18 (14.9) versus 13 (5.5)** | **88 (19.1) versus 117 (12.77)** | **81 (13.5) versus 171 (9.7)** |
| Vomiting, OR (95% CI) | **1.64 (1.33–2.00)** | **3.03 (1.43–6.25)** | **1.61 (1.19–2.17)** | **1.45 (1.09–1.92)** |
| Hyperthermia, *n* (%) | 35 (3.0) versus 62 (2.1) | 5 (4.1) versus 14 (5.9) | 16 (3.5) versus 20 (2.2) | 14 (2.3) versus 28 (1.6) |
| Hyperthermia, OR (95% CI) | 1.41 (0.93–2.13) | 0.69 (0.24–1.96) | 1.61 (0.83–3.13) | 1.47 (0.78–2.86) |

Values marked in bold are considered statistically significant (Odds ratios [OR] that do not contain "1" in the 95% confidence interval").
The odds ratio displays the likelihood of developing a clinical feature with males as reference.

fundamentally complex, with multiple factors influencing their presentations. These factors include the primary reason for presentation (e.g., due to chest pain or psychosis-related symptoms), severity of symptoms, prior medical history, and prior medication use. Additionally, genetic differences in the enzyme activity of cytochrome CYP2D6 influence the plasma concentrations and, hence, the responses to 3,4-methylenedioxymetamfetamine [6]. These factors were not taken into consideration since the Euro-DEN Plus database does not contain this information.

Second, more detailed information on the substances consumed, such as dosage or confirmation through toxicology screening, was not available. 3,4-Methylenedioxymetamfetamine, like other substances such as ethanol, exhibits a dose-response effect [5,10]. However, since most emergency departments do not measure plasma concentrations of the substances ingested, this variable was unavailable and could not be accounted for in our analysis. Moreover, since blood ethanol concentrations were not reported, we acknowledge the possibility that other alcohols, such as isopropanol, could have contributed to cases classified as ethanol intoxication. Additionally, the potential for misclassification of 3,4-methylenedioxymetamfetamine or other substances could not be fully excluded, as toxicology confirmation was often not performed in the emergency department. Reliance on patient self-reports may introduce inaccuracies, as patients may be unaware of all substances ingested. However, Wolfe et al. [31] compared self-reported substance use with laboratory testing for substances of misuse and found that the median positive predictive value for reported substance use in the emergency department was 0.68 (IQR: 0.44–0.86), while the median negative predictive value was 0.90 (IQR: 0.53–0.95) [31]. The authors concluded that self-reports provided a reasonably accurate assessment of intoxication profiles. Despite this, the reliance on self-reported data may still affect the precision of our findings regarding co-intoxication patterns and their associated outcomes. Misreporting, whether intentional or due to unawareness of all substances ingested, could lead to biased estimates of the

prevalence and effects of specific co-intoxications. This limitation might obscure certain associations or overstate others, reducing the reliability of conclusions about the relationship between 3,4-methylenedioxymetamfetamine co-intoxications and clinical presentations.

Third, precise drug composition, exposure dose, mode of use, pattern of use and first-time use can all affect the variations and severity of presentation, but such information was not gathered [2]. Furthermore, certain symptoms are subjective, leading to potential misclassification. Finally, multiple statistical tests were conducted in this study, which increases the risk of Type I errors (false positives). However, Bonferroni and Šidák corrections were not applied, as these methods can be overly conservative and increase the risk of Type II errors (false negatives) [32]. Given the exploratory nature of the analysis and the large sample size, the decision was made to prioritize a balance between controlling Type I errors and avoiding Type II errors. As such, no corrections for multiple comparisons were implemented.

## Conclusions

Ethanol co-intoxication, co-intoxication with other substances of misuse, and patient sex were associated with varying clinical presentations in the emergency department. Although three-quarters of 3,4-methylenedioxymetamfetamine-related presentations were discharged from the emergency department, they still pose a burden on healthcare services and carry risks of complications for some patients. Given the high prevalence of 3,4-methylenedioxymetamfetamine use in Europe, it is crucial to address and prevent these risks. Emergency physicians should be aware of the varied clinical profiles, as they can significantly impact patient outcomes and may require distinct treatment approaches. Most 3,4-methylenedioxymetamfetamine-related presentations reflect the dangers of polydrug use, highlighting the need for harm reduction messages for all drug users with an emphasis on the additional health risks due to drug combinations.

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