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Fatal and non-fatal health incidents related to recreational ecstasy use

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Abstract

Background: The recreational drug ecstasy (3,4-methylenedioxymethamphetamine) is currently used world-wide. Severe (including fatal) health incidents related to ecstasy have been reported but a risk assessment of acute non-fatal and fatal ecstasy-related health incidents has never been performed.

Methods: In the current risk assessment review, national data of non-fatal health incidents collected in the Netherlands were combined with the nationwide exposure to ecstasy, that is, last-year prevalence of ecstasy use. In addition, the annual number of ecstasy-related deaths in Great Britain (Scotland, Wales and England) was used to assess the risk of fatal ecstasy-related cases.

Results: In the Netherlands, the estimated risk of a moderate to severe acute health incident following the use of ecstasy is one in 900 pills (0.11%), whereas for cocaine it is one in 1600 doses (0.06%) and for gamma-hydroxybutyrate one in 95 doses (1.05%). With respect to ecstasy-related deaths in Great Britain, the estimated risk of ecstasy alone per user is 0.01–0.06%, which is close to the range of the fatality risk in chronic alcohol users (0.01–0.02%), amphetamine users (0.005%) and cocaine users (0.05%), but much lower than that of opiate use (heroin and morphine: 0.35%).

Conclusion: The current review shows that almost no data are available on the health risks of ecstasy use. The few data that are available show that ecstasy is not a safe substance. However, compared to opiates (heroin, morphine), the risk of acute ecstasy-related adverse health incidents per ecstasy user and per ecstasy use session is relatively low.

Keywords

3, 4-Methylenedioxymethamphetamine, ecstasy, recreative substances, stimulatory drugs, incidents, adverse effects

Introduction

Since 1970, ecstasy (3,4-methylenedioxymethamphetamine (MDMA)) has been used recreationally in the USA (Benzenhöfer and Passie, 2010; Sreenivasan, 1972) as a substitute for its analogue methylenedioxy-amphetamine (MDA). As part of the ‘War on Drugs’, the Drug Enforcement Administration (DEA) successfully petitioned in 1984 to have MDMA classified as a Schedule 1 illicit substance (DEA, 1984; Eisner, 1994). Shortly after, MDMA was banned world-wide.

Nevertheless, in the late 1980s recreational use of MDMA emerged in the USA and became one of the four most widely used illicit drugs. Similarly, in the UK and other European countries, recreational MDMA use spread along with the rave culture (Beck and Rosenbaum, 1994). Nowadays MDMA is no longer a niche or subcultural drug, but used worldwide recreationally by a broad range of mainly young (adult) people in nightlife settings, festivals, dance events and house parties. The popularity of MDMA was (and still is) mainly due to its low or absent dependence potential (Degenhardt et al., 2010) and the specific sensory, psychedelic and energising effects. The sensory effects facilitate sociability, empathy and ‘getting together’, whereas the energising effects allow vigorous and long-term dancing.

Worldwide, the use of ecstasy is emerging. According to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), in 2016, the last-year prevalence rates of ecstasy use in young European adults (15–34 years) and adults (15–64 years) was 0.3–7.4% and 0.1–3.6%, respectively (EMCDDA, 2018), with the highest rates (7.4% and 3.6%, respectively)

observed in the Netherlands (EMCDDA, 2018; van Laar et al., 2019). Recent surveys suggest a continued increasing trend in Europe, with five countries reporting higher estimates than in the previous comparable survey and nine reporting stable estimates (EMCDDA, 2017), though lately ecstasy use seems to stabilise in the UK where a small decrease was observed in 2015 (EMCDDA, 2017). The high level of ecstasy use seems to contradict its classification as a Class A substance. Confronted with these high consumption figures (see above), the large number of health-related incidents (Lameijer et al., 2018), and the emerging criminality related to the production of ecstasy, a re-evaluation of the drug policy with regard to ecstasy is needed. The current risk assessment of ecstasy was prepared to support policy makers in their efforts to develop an up-to-date and balanced ecstasy drug policy.

Ever since the scheduling of MDMA, the health risks involved in the use of MDMA have been the subject of heated debate. Some believe that the consumption of one dose will cause irreversible health damage (Parrott, 2013, 2014; Parrott et al., 2017), while others believe that MDMA is (relatively) harmless (Amoroso,

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Table 1. Correction factors used to calculate the adverse health risk of 3,4-methylenedioxymethamphetamine (MDMA) for non-fatal incidents.

	Item	Estimate	Multiplier
A	Nationwide coverage by MDI	33%	3.0
B	Pills per session	1.2	1.2
C	Sessions per year	4.0	4.0
D	Pills per year per user	4.8	4.8

MDI: Monitor Drug Incidents.

2018, 2019; Rogers et al., 2009). Especially in the international media, there is much concern about its safety. Indeed, numerous fatal MDMA-related deaths (MRDs) have been reported worldwide in emergency department (ED) reports (Dargan, 2008; EMCDDA, 2016; Horyniak et al., 2014; Rosenson et al., 2007; SAMHSA, 2013). The ED reports showed that most patients had used ecstasy in a large variety of doses and often in combination with other substances. The most severe clinical signs were hyperthermia and hyponatraemia.

The aim of this study is to present a systematic review of the fatal and non-fatal health incidents as reported in the scientific literature and other accessible sources to allow a science-based and balanced assessment of the health risks of ecstasy use, including fatalities. The risk of non-fatal incidents related to ecstasy use will be compared with the risk following cocaine and gamma-hydroxybutyrate (GHB) use, whereas the risk of fatal ecstasy incidents will be compared with the risk of fatalities related to alcohol use. Severe incidents are defined here as non-fatal adverse health incidents for which medical stabilization at an intensive care unit (ICU) was required.

Methods

Scientific reports, published between January 2000–April 2019, were retrieved using systematic searches in PubMed and Google Scholar. However, it appeared that only very limited data could be retrieved via PubMed. Only studies on fatal and non-fatal incidents with enough subjects ($n > 5000$) to adequately estimate the prevalence of last year ecstasy use in that population were included. Case reports, case series, ED reports and (other) papers not reporting exposure data, like last-year use prevalence, were regarded as inappropriate for our purpose. Throughout the text, acute adverse health incidents are defined as incidents, whereas severe incidents required medical stabilization at an ICU. One ecstasy pill is synonymous with one tablet of ecstasy.

Data, data quality and confounding variables

Most of the information about ecstasy intoxication is based on case reports, case series and retrospective audits. Various ED studies have reported ecstasy-related hospital admissions e.g. (Dargan, 2008; EMCDDA, 2016; Horyniak et al., 2014; Rosenson et al., 2007; SAMHSA, 2013). However, these studies were generally small and without information on the (last-year) prevalence of ecstasy use in the patients included and in users who did not visit the ED, making it impossible to calculate the risk per

user or per pill that was taken. Therefore, these studies were not able to answer our research question. Consequently, no eligible data were available in the scientific studies retrieved via PubMed, but some eligible information from governmental and non-governmental organisations could be retrieved via Google Scholar.

For non-fatal ecstasy-related incidents we could only make use of data collected by the Monitor Drug Incidents (MDI) programme in the Netherlands (Lameijer et al., 2018). The MDI dataset contains (a) data reported directly to MDI by first aid posts present at large parties and festivals, EDs, ambulance posts and forensic doctors, and (b) data from additional EDs, collected by the Injury Information System (Letsel Informatie Systeem (LIS)) (Panneman and Blatter, 2016). In the data directly reported to MDI, all incidents are categorised as (a) 'light' when adverse health effects of ecstasy are mild and the patient is well responsive, (b) 'moderate' when the patient is insufficiently responsive, and (c) 'severe' when the patient is non-responsive due to a (sub-) comatose state or aggressive behaviour, possibly in combination with abnormal vital signs. Insufficiently responsive or non-responsive was defined by a cut-off < 15 using the Glasgow Coma Scale (GCS), but the reports did not further specify the GCS scores for the sub-categories. The ED data collected by LIS are not specified according to severity category and, therefore, their severity distribution was derived from the ratios observed by EDs directly reported to MDI. Incidents involving foreign tourists were removed from the dataset.

The data collected by the MDI programme in the Netherlands (Lameijer et al., 2018) do not fully cover the Netherlands so that the multipliers depicted in Table 1 have been applied to estimate the nationwide number of ecstasy-related non-fatal incidents. Furthermore, we have used multipliers (see Table 1) to enable estimation of the risk per pill consumed.

Item A (nationwide coverage by MDI)

The MDI report mentioned the towns of the hospitals reporting to MDI and LIS (Lameijer et al., 2018). Based on the number of hospitals with an ED and inhabitants in these towns, it was estimated that MDI covers 70% of all incidents occurring in the Netherlands. For the current risk estimation, we applied a conservative estimate of the coverage by MDI of 33% (giving a multiplier for number of non-fatal incidents of 3.0).

Items B–D (pills per session and sessions per year)

According to the Antenne surveys, performed in the Netherlands among clubbers/'party goers', students and visitors of pubs and coffee shops (Benschop et al., 2015; Nabben et al., 2016, 2017, 2018), the level of use was 1.2 ecstasy pills per session on average on 4.0 days per year (median values). Thus, a conservative estimate of ecstasy use is four days (four sessions) per year, where 1.2 pills are used per session or 4.8 pills per year per user (giving a multiplier for number of non-fatal incidents of 4.8).

MRDs are systematically registered only in the UK. Unfortunately, MRDs are defined differently in Scotland and in England and Wales. In Scotland, the National Records of Scotland (NRS) receives information from the pathologist on (a) what drugs were thought to be implicated in or contributing to the death, and

Table 2. Number of non-fatal ecstasy-related adverse health incidents (percentage in parenthesis) in 2017 in the Netherlands, as reported by Monitor Drug Incidents (MDI) (Lameijer et al., 2018).

	Ambulances	EDs	Forensic doctors	First aid posts	Total
<i>Ecstasy-related^a</i>					
All	103	252	41	1351 ^b	1747
Light	22 (21)	61 (24)	25 (61)	976 (72)	1084 (62)
Moderate	51 (50)	124 (49)	15 (37)	300 (22)	490 (28)
Severe	30 (29)	67 (27)	1 (2)	74 (6)	172 (10)
Moderate – severe					662 (38)
<i>Related to ecstasy only</i>					
All	54	131	25	991	1201
Light	14 (26)	38 (29)	16 (64)	783 (79)	851 (71)
Moderate	31 (57)	63 (48)	9 (36)	178 (18)	281 (23)
Severe	9 (17)	30 (23)	0	30 (3)	69 (6)
Moderate – severe					350 (29)
<i>Related to ecstasy and other substance(s)</i>					
All	49	121	16	360	546
Light	8 (16)	23 (19)	9 (56)	193 (54)	233 (43)
Moderate	20 (41)	61 (50)	6 (38)	122 (34)	209 (38)
Severe	21 (43)	37 (31)	1 (6)	44 (12)	103 (19)
Moderate – severe					312 (57)

EDs: emergency departments.

^aRefers to total of incidents; ^b77% of total number of non-fatal incidents.

(b) what other drugs were identified post-mortem. In England and Wales, the Office for National Statistics (ONS) uses the definition of ecstasy-related deaths as follows: ‘that ecstasy was mentioned in the death certificate (other drugs may be mentioned as well)’ (ONS, 2018b). Both ONS and NRS include illegal, prescribed and legal substances in their poisoning deaths tables.

Results

Ecstasy-related non-fatal incidents

Many incidents related to ecstasy use have been described in the literature, but the majority of the studies did not report the prevalence of ecstasy use in the source population (e.g. the last-year use) and therefore these data are not suitable for an assessment of a risk of severe health incidents per user or per consumption session. The same holds for MRDs (see below). We could only retrieve two data-sets that were suitable to answer our research question about the risk of non-fatal ecstasy-related health incidents.

In the Netherlands in 2017, the MDI reported 5905 drug-related incidents of which 1747 were ecstasy-related (29.6%, see Table 2) (Lameijer et al., 2018). Table 2 shows that 1201 out of 1747 cases (69%) referred to use of only ecstasy. In the 546 incidents related to ecstasy in combination with one or more substances mostly alcohol and GHB (43% and 36%, respectively) were involved. Of all ecstasy-related incidents, 62% were light, 28% moderate and 10% severe. First aid posts – mainly present at large parties and festivals – reported most (77%) of the ecstasy-related incidents, of which 28% were moderate to severe. Of the 252 ecstasy-related incidents reported by EDs 76% were moderate to severe, indicating that ecstasy-related incidents reported by first aid posts were generally less serious than those reported by

EDs. Of the incidents related to ecstasy in combination with other substances, 57% were moderate to severe, whereas for those related to ecstasy alone the level was 29%. In addition, the fraction of moderate to severe incidents was higher if ecstasy had been consumed in combination with alcohol (35% vs 21%) (Lameijer et al., 2018).

Based on the MDI data, the Dutch Trimbos Institute recently estimated that yearly at least one in 250 ecstasy users (0.4%) seeks medical assistance due to any adverse health event following ecstasy use (Wijers et al., 2016). However, as outlined below, a more realistic incident risk can be calculated. First, most incidents are mild (62%, see Table 2) and resolve spontaneously or after some brief medical support at the first aid posts. More important are the moderate and severe incidents (moderate and severe) involving impaired responsiveness of users (Lameijer et al., 2018). Second, not all Dutch hospitals report to MDI and thus MDI does not collect all ecstasy-related incidents occurring in the Netherlands. Based on the number of inhabitants in the towns of the hospitals reporting to MDI, it was estimated that MDI covers 70% of all incidents occurring in the Netherlands. For the current risk estimation, we applied a conservative estimate of the coverage by MDI of 33%. Based on this estimate, the numbers nationwide in 2017 are: $3 \times 1747 = 5241$ ecstasy-related incidents with $3 \times 172 = 516$ severe ecstasy-related incidents. With 370,000 last-year ecstasy users in the Netherlands (van Laar et al., 2019), this represents an incidence rate of one incident in 70 (1.4%) and one severe incident in 710 (0.14%) ecstasy users (see Table 3). Third, the number of user days and the number of pills per session must be considered to assess the risk of an ecstasy-related incident. Based on reported ecstasy-use patterns, the risk of ecstasy-related non-fatal incidents per pill or session has been assessed (see Table 3). According to the Antenne survey from 2017 (Nabben et al., 2018), the averaged number of sessions among Dutch clubbers/‘party

Table 3. Risk estimation based on 1747 ecstasy-related incidents reported to Monitor Drug Incidents (MDI) by 370,000 last year users of ecstasy (assuming a coverage by MDI of 33%), the Global Drug Survey survey (GDS, 2019), and 11 m last-year consumers of alcohol in the Netherlands (van Laar et al., 2019).

Type of incident	Risk of a non-fatal incident	
	%	Per user/per dose
<i>Ecstasy-related incidents (MDI)^a</i>		
All incidents per user	1.4	1 in 70 users
All incidents per pill ^b	0.3	1 in 340 pills
Moderate to severe incidents per pill	0.11	1 in 900 pills
Severe incidents per pill ^c	0.03	1 in 3400 pills
Severe incidents per user	0.14	1 in 700 users
<i>Ecstasy-related incidents (GDS, 2019)^d</i>		
Emergency medical treatment required	0.6	1 in 160 users
Emergency medical treatment required (per pill)	0.125	1 in 800 pills
<i>Cocaine-related incidents (MDI)^a</i>		
All incidents per user	0.45	1 in 215 users
All incidents per dose ^b	0.12	1 in 850 doses
Moderate to severe incidents per dose	0.06	1 in 1600 doses
Severe incidents per dose	0.02	1 in 6000 doses
<i>GHB-related incidents (MDI)^a</i>		
All incidents per user	3.5	1 in 270 users
All incidents per dose ^b	1.4	1 in 70 doses
Moderate to severe incidents per dose	1.05	1 in 95 doses
Severe incidents per dose	0.47	1 in 212 doses
<i>Alcohol-related incidents^e</i>		
Assistance of ED required ^f	0.15	1 in 650 users
Severe incidents ^g	0.05	1 in 2000 users
Severe traffic accidents ^h	0.03	1 in 3000 users

ED: emergency department; GHB: gamma-hydroxybutyrate; ICU: intensive care unit.

^aPutatively occurring nationwide, based on an estimated coverage by MDI of 33% of all incidents.

^bBased on median number of four sessions yearly, where 1.2 ecstasy pill is consumed per session; for cocaine: four sessions yearly; for GHB: 2.5 sessions yearly.

^c21% Of incidents are severe: the patient requires medical stabilisation at the ICU.

^dDutch ecstasy users seeking emergency medical treatment in the last 12 months following ecstasy use (GDS, 2019).

^eBased on a total of 11 m drinkers in the Netherlands.

^fSome ED assistance was necessary in 17,800 alcohol-use-related accidents (van Laar et al., 2006).

^gIn 2017, 6000 alcohol-related intoxications required treatment in the ED (van Laar et al., 2006).

^hNearly 4000 severe alcohol-related traffic-related injuries required hospitalization.

goers' is 9.3 sessions per year; 45% used ecstasy four times per year, 35% 10 times per year and 20% more than 10 times per year (Nabben et al., 2018). The proportion of occasional users, i.e. those who used ecstasy only 1–2 times (sessions) per year, was 21%. Previous 'Antenne' surveys have been performed among students (Nabben et al., 2017), and visitors of pubs (Benschop et al., 2015) and coffee shops (Nabben et al., 2016) in the Netherlands who had used ecstasy in the last year. The aggregated results showed that about one-third (35–38%) of them were occasional users (1–2 sessions per year). Across the three groups, the use was 1.2 ecstasy

pills per session on average on 4.0 days per year (median values). Thus, a conservative estimate of ecstasy use is four days (four sessions) per year, where 1.2 pills are used per session or 4.8 pills per year per user. This rate is endorsed by the consumption rate of 5.0 pills per year per user as recently reported by the Global Drug Survey (GDS, 2019) (see also below). In other words: in the Netherlands with 370,000 last year ecstasy users 1.8 m (370,000×4.8) pills are consumed yearly giving an incidence rate of overall ecstasy-related incidents of one in 340 pills (1.8 m pills/5241 incidents) or 0.3%. In addition, based on the total of 516 (3×172; adjusted for 33% coverage) severe ecstasy-related incidents in 2017 (see Table 2), the incidence rate for severe incidents is one in 3400 pills (1.8 m pills/516 severe incidents) or 0.03%. Thus, the yearly estimated risk of a severe ecstasy-related incident is one in 717 ecstasy users (516 severe incidents in 370,000 ecstasy users) or 0.14%, whereas the yearly estimated risk of moderate to severe incidents (3×662; see Table 2) is one in 896 pills (1.8 m pills/1986 moderate/severe incidents) or 0.11%.

The data from the GDS, collecting regularly information from over 100,000 users via a Web-based questionnaire are, in this respect, of interest. The GDS, 2015 and GDS, 2019 reported an average worldwide frequency of ecstasy use of 8.0–9.7 and 5.0 (range: 3–10) times per year, respectively, and an average dose of 1.5 pills per session (GDS, 2015, 2019; Szigeti et al., 2018). The GDS estimates are close to an average dose of 1.5 pills per session and a use frequency of 8.8 times per year observed in the Dutch Party Panel Internet survey among 637 'party goers' (Peters, 2018). The GDS, 2017 report showed that the yearly number of days that ecstasy was used in the Netherlands, UK and Scotland was 7.9, 11.8 and 14.5, respectively (GDS, 2017). A subsequent survey from 2019 (GDS, 2019) reported a yearly number of days of ecstasy use in the Netherlands and England of 5.0 and 7.0, respectively (one pill per user day). The same survey from 2019 (GDS, 2019) reported a rate of hospitalisation following ecstasy use in the Netherlands of 0.6% (see Table 3).

Table 3 also shows the number of incidents reported in 2017 related to the use of cocaine and GHB (data about amphetamine were not collected by MDI), which appear to be considerably lower (3.0–4.5 times) than the number of incidents related to ecstasy use. However, the number of cocaine users (250,000 last-year users) (van Laar et al., 2019) is lower than the number of ecstasy users, and according to the Antenne surveys, cocaine is used 20% less frequently than ecstasy (median number of sessions per year: cocaine: 3.0–5.0; GHB: 1.0–4.0). Based on last-year prevalence rates, the risk for cocaine and GHB was estimated using a similar approach as the one used for ecstasy (see Table 2). Nationwide coverage of 30% and yearly use of cocaine and GHB is 4 and 2.5 yearly sessions (doses), respectively. Thus the estimated yearly risk of a moderate to severe incident following cocaine and GHB use is 0.06% and 1.05% per session (dose), respectively (see Table 3). This indicates that the use of one dose of cocaine and GHB gives a two-fold lower and 10-fold higher risk for a moderate to severe incident compared to the use of one ecstasy pill, respectively.

With respect to cannabis, the MDI reported that the number of moderate to severe incidents related to cannabis use was in the same range as that observed for ecstasy (36–68% and 36–74%, respectively). However, the number of cannabis users and their smoking frequency is much higher compared to ecstasy use. In

the Netherlands, 960,000 people have used cannabis in the last year (van Laar et al., 2019) (ecstasy: 370,000) and they used on average 200 joints per year (Snowdon, 2018) (ecstasy: 4.8 pills per year). As such, the risk of a moderate to severe health incident per joint (dose) is about 100-fold lower than ecstasy use (2.6-fold users and 42-fold yearly dose).

Ecstasy-related fatal incidents

The UK is the only country where fatal ecstasy-related health incidents are systematically recorded in death registers by the UK coroner (Schifano et al., 2003) though, unfortunately, toxicological data on the substances detected post-mortem are not always cited on the death certificate. As the last-year prevalence of ecstasy use in the UK is also known, the risk of MRDs in the UK can be estimated.

Throughout the UK, the annual number of MRDs (1993–2016: 853; annual mean of 37) have increased steadily in recent years (2010: 8; 2016: 65) (Handley et al., 2018; NRS, 2018). In England and Wales, the ONS reported in 2017 56 MRDs of which solely MDMA was implicated in 35 cases (ONS, 2018b). Based on 550,000 last-year ecstasy users (general population, 16–59 years; prevalence: 1.7%) (Home Office, 2018), the number of 56 MRDs gives an estimate of 0.01% per year or one MRD per 10,000 ecstasy users. Based on two ecstasy sessions per year and one pill per session (Home Office, 2018), the number of 56 MRDs gives an estimated risk of one MRD per 20,000 pills: risk per pill is 0.005%. MDMA was the only substance mentioned on the death certificate (no other drugs, but alcohol may also have been mentioned) in 35 MRDs (ONS, 2018b) so that the estimated risk of MDMA alone (per pill) is 0.003% ($35/(2 \times 550,000)$) (Table 4). However, the latest GDS survey (GDS, 2019) reported that the average ecstasy user in England had seven sessions per year with 1.7 pills per session, which would – assuming the same consumption rate in Wales as in England – reduce the risk per pill by a factor of six (11.9/2) to about 0.001% overall and 0.0005% per session with only ecstasy use.

In Scotland, 27 MRDs were reported in 2017 of which in three cases solely MDMA was involved (NRS, 2018). According to the latest Scottish Crime and Justice Survey 2014/2015 (ScG, 2016), last year prevalence of ecstasy use in Scotland (general population, 16–59 years.) was 1.3% (45,000 users). The frequency of ecstasy use per year is somewhat higher in Scotland than in England/Wales: 55% (Scotland) and 32% (England and Wales) of users had used more often than once or twice per year (Home Office, 2018; ScG, 2016). These figures implicate that the rate of MRD per ecstasy user in Scotland is six times higher than in England and Wales (0.06% and 0.01%, respectively). Based on two ecstasy sessions per year (one pill per session), the number of 27 MRDs in Scotland gives an estimated risk of MRD of 0.03% (one death per 3300 pills). Considering that in 2017 solely MDMA was involved in only three MRDs (NRS, 2018) (in 2014, 2015 and 2016: two, one and six MRDs, respectively), the estimated risk of MDMA alone in 2017 (per session) is 0.003% ($3/(2 \times 45,000)$). Table 4 also depicts the yearly risk of fatalities per user related to chronic alcohol use in the UK (0.01–0.02%), and to heroin+morphine use (0.35%), cocaine use (0.05%) and amphetamine use (0.005%) in England and Wales.

Discussion

Summary

A systematic search of the scientific literature showed that there were no publications on the risk of non-fatal and fatal ecstasy-related health incidents. For non-fatal incidents we could only use reports from the Netherlands, whereas for fatal incidents we only had reports from the UK. Concerning the overall risk of ecstasy use (all incidents), our estimate of one in 70 users based on available Dutch data is about three times higher than the previously calculated risk (one in 250 users: Wijers et al., 2016). In the Netherlands, the estimated risk of a moderate to severe acute health incident following the use of ecstasy is one in 900 pills (0.11%), whereas for cocaine it is one in 1600 doses (0.06%) and for GHB one in 95 doses (1.05%). In the UK, the estimated risk of MDMA-related mortality (MRM) for someone using only ecstasy is 0.01–0.06% per user, which is close to the risk of fatalities related to chronic alcohol use in the UK (0.01–0.02%), and to amphetamine use (0.005%) and cocaine use (0.05%), but lower than for opiate use (heroin and morphine; 0.35%) in England and Wales.

Data quality

It should be noted that the data we used in the current review – like data from most other studies – have serious limitations. First, though hyperthermia is the most commonly reported adverse effect of ecstasy use both in non-fatal and fatal cases (Rogers et al., 2009), the reports fail in general to document properly the circumstances and doses that induced the hyperthermia. Second, the 10th edition of International Classification of Diseases (ICD-10) was designed for uniform coding of diseases (WHO, 2010). Unfortunately, the registration of ecstasy-related ED attendances is poor because ecstasy-related health conditions are not well captured by the ICD-10 coding system, as ecstasy lacks a unique ICD-10 code, and in many countries ICD-10 codes are only given when patients are hospitalised beyond the ED.

Non-fatal incidents

The current review shows that the risk per pill of a moderate to severe ecstasy-related health incident in the Netherlands (0.11%) compares well with that reported for Dutch users in the GDS, 2019 survey (0.125%). Of those drug users who sought emergency medical treatment, 43% of ecstasy users were hospitalised (the figure for alcohol, cannabis and heroin was 60%, 53% and 61%, respectively), indicating a somewhat lower rate of hospitalisation after an ED visit for ecstasy than for the other three substances (GDS, 2019).

Despite the 1.5-times lower number of last-year users, the risk per dose of cocaine use appears to be about two times lower compared to ecstasy. This seems surprising because cocaine is often regarded to be more harmful than ecstasy (Nutt et al., 2007; van Amsterdam et al., 2010, 2015). However, the relatively higher harm of cocaine is mainly based on the effects of chronic use and its higher dependence potential. Of note with respect to the higher risk of ecstasy is the variability of MDMA-content in ecstasy pills, but not the purity of the ecstasy pills which for many years has been high (around 90%) (van Laar et al., 2019). Finally, the subjects

Table 4. Risk estimation based on the annual number of 3,4-methylenedioxymethamphetamine (MDMA)-related deaths (MRDs) in England and Wales and Scotland (56 and 27, respectively), and the number of last-year ecstasy users (550,000 and 45,000, respectively) in these countries.

	Risk of a fatal incident	
	%	Per user or per dose unit
MRDs		
England and Wales	0.010	1 in 10,000 users
England and Wales ^a	0.005	1 in 20,000 pills
England and Wales; solely MDMA ^b	0.003	1 in 33,000 pills
Scotland	0.060	1 in 1660 users
Scotland ^a	0.030	1 in 3300 pills
Scotland; solely MDMA ^b	0.003	1 in 33,000 pills
Other substances^c		
Opiates (heroin and morphine)	0.35	1 in 290 users
Cocaine	0.05	1 in 2000 users
Amphetamine	0.005	1 in 20,000 users
Alcohol-specific deaths^d		
England	0.011	1 in 9000 drinkers
Wales	0.014	1 in 7400 drinkers
Scotland	0.021	1 in 4900 drinkers
UK ^e	0.030	1 in 8200 drinkers
UK ^f	0.300	1 in 820 heavy drinkers
Other causes		
UK fatal road accidents ^g	0.0036	1 in 28,000 drivers

^aBased on two sessions yearly where one ecstasy pill is consumed per session (Home Office, 2018).

^bAnnual number of MRDs 2017/2018 involving solely MDMA England and Wales and Scotland was 35 and 3, respectively.

^cIn 2017, in England and Wales the number of fatalities related to heroin+ morphine, cocaine and amphetamine use was 1164, 432 and 91, respectively (ONS, 2018b) occurring in 335,000, 875,000, and 1.7 m users, respectively (Home Office, 2018).

^dDirect consequence of chronic alcohol use, such as alcoholic liver disease (ONS, 2017).

^e7697 Alcohol-specific deaths in 2017 in the UK (ONS, 2018c).

^fIn 2017 in the UK, 12% of males and 8% of females were frequent drinkers (those who drank alcohol on at least five days in the week before being interviewed) (ONS, 2018a).

^g1792 Fatal road accidents based on 50 m driving licenses.

reporting an incident related to ecstasy alone were relatively young (62% were <25 years.) compared with those reporting a cocaine related incident (only 24% were <25 years.). The lower age of ecstasy users may represent a higher risk because of less experience with substance use and a higher rate of risk taking.

The risk of an ecstasy-related incident may be increased by consumption of the drug under unfavourable or risky conditions (crowding, insufficient drinking, poor ventilation, excessive physical exertion) which may decrease the safe-dose level. Another risk factor is the consumption of high-dose pills, because it may lead to adverse health incidents due to overdosing. It remains as yet unclear whether high-dose ecstasy pills have increased the rate of ecstasy-related incidents. Based on self-reported effects of ecstasy pills from 5786 drug users and objective MDMA doses, it was shown that there is a dose-related effect

with adverse events like headache, hallucinations and agitation at doses above 120 mg per pill (Brunt et al., 2012). Though this observation suggests dose-dependency of ecstasy-related severe incidents, the Dutch Trimbos Institute recently reported no increase in serious incidents over the period 2015–2017 when high-dose MDMA pills (>65% of pills were dosed 150 mg or more) first appeared on the Dutch market (Lameijer et al., 2018). Possibly, users have meanwhile become more prudent and start for example every ecstasy session with half an ecstasy pill first before re-dosing, which has been shown to be a successful harm-reduction strategy (Fernandez-Calderon et al., 2019).

About half (56%) of ecstasy-related incidents in 2017 in the Netherlands were due to the combined use of ecstasy with other substances (mostly alcohol and GHB; in 36% and 43% of mixed-use cases, respectively) (Lameijer et al., 2018). This reflects the high prevalence of poly-substance use among ecstasy users (Home Office, 2014; Scholey et al., 2004; Wu et al., 2009). The proportion of moderate to severe incidents related to ecstasy in combination with other substances (57%) was higher compared to those related to ecstasy alone (29%), but this does not necessarily imply that the use of ecstasy in combination with (an)other substance(s) creates a higher harm level than the use of ecstasy alone. First, based on a pharmacodynamic interaction, sedating substances may decrease the acute toxicity of ecstasy. Stimulating drugs give excitation, whereas sedating drugs give inhibition (counteract) (Parrott et al., 2007). For example, MDMA is alerting and induces hyperthermia, whereas cannabis is sedating and induces hypothermia (Liu, 1974). On the other hand, stimulants (notably amphetamine and cocaine) may substantially enhance ecstasy's acute toxicity. Second, poly-drug users may show more risky behaviour than 'mono-drug' users.

Fatal incidents

The current study shows that the risk of a fatal incident following the use of solely MDMA in England/Wales and Scotland was the same: one in 33,000 pills (0.003%). However, the risk of MRDs irrespective of poly- vs mono-drug use was six-fold higher in Scotland than in England and Wales (0.03% vs 0.005%), suggesting regional differences in the concurrent use of other substances or riskier behaviour in Scotland (higher and more frequent dosing, unfavourable setting). Indeed, results from the GDS, 2017 survey suggest that ecstasy is used more often in Scotland (14.5 days per year) than in the UK as a whole (11.8 days per year) (GDS, 2017). However, the GDS surveys are selected samples with relatively many clubbers which may lead to an over-estimation of use and an under-estimation of the risk. Also some (relatively more) under-reporting in England and Wales cannot be excluded, because MRDs are defined in England and Wales as 'text search identified ecstasy written on death certificate' i.e. toxicological examinations are not necessarily carried out, whereas in Scotland MRDs are based on (a) what drugs were thought to be implicated in or contributing to the death, and (b) what other drugs were identified post mortem, which may result in a lower number of (false positive) MRDs.

Relative risk

It is not possible to compare the risk of a non-fatal incident following the consumption of one ecstasy pill with that of one alcoholic drink. The risk of alcohol-related incidents (mainly) relates

to the consumption of more than one drink, whereas the consumption of only one ecstasy pill may result in a serious incident. Presumably, the higher risk is due to the much higher mental and physical destabilising potency of one ecstasy pill compared to that of one alcoholic drink. Also, with respect to fatal incidents, ecstasy cannot be compared with alcohol. First, alcohol-related fatalities mostly result from prolonged excessive drinking (defined as more than 21 glasses per week for men and more than 14 glasses per week for women in the long-term), whereas ecstasy-related fatalities, except the traffic accidents, are the result of acute intoxications. Second, a considerable number of fatal cases have been described following the consumption of one ecstasy pill, which may partly be caused by unfavourable circumstances leading to hyperthermia. According to toxicological principles, the toxicity of ecstasy is dose-dependent, but a correlation between MDMA dose and mortality rate could not be established due to a paucity of data. Moreover, the numerous case studies collectively indicate that the dose of MDMA is poorly predictive of the severity outcome, whereas the extent and duration of hyperthermia are predictive (Gowing et al., 2002; Hall, 1997).

However, we can compare the risk of ecstasy with other recreationally used substances. It appears (see Table 4) that the estimated risk of ecstasy alone per user is 0.01–0.06%, which is close to the range of the fatality risk related to chronic alcohol use (0.01–0.02%), amphetamine use (0.005%) and cocaine use (0.05%), but much lower than that of opiate use (heroin and morphine; 0.35%). This finding is in agreement with the studies of King and Corkery (King and Corkery, 2010, 2018) who concluded that, based on an index of toxicity (calculated as the ratio of the number of deaths in England and Wales and availability over the period 1993–2016), the relative fatal toxicity of MDMA is close to that of amphetamine and cocaine/crack.

Limitations of this study

The risk assessment of non-fatal cases was mainly based on data of the Dutch MDI study. The MDI data refer to self-reported ecstasy use which is liable to bias, because shame and confusion in the patient may lead to incorrect and under-reporting (Monshouwer et al., 2016; Vreeker et al., 2017). Probably, the bias due to shame mainly applies to relatively innocent incidents, whereas for moderate and severe incidents the patient is more motivated to search for optimal medical treatment and to report all details. Furthermore, incorrect registration can jeopardise the quality of the dataset. For instance, once a hospitalised patient does not survive a severe ecstasy intoxication, clinical toxicological diagnostics are stopped leaving the cause of death unresolved and the case will not be reported as an MRD. In addition, when crowded at the treatment facility the pressure may contribute to suboptimal registration of the cases. Another limitation of this assessment is the poor registration of ecstasy-related incidents in the Netherlands, because only some of these incidents occurring nationwide are reported to the MDI. To enable the calculation of the number of non-fatal ecstasy-related incidents nationwide, we estimated the coverage of the MDI – based on the towns represented in the sample – at 33%. This figure represents a conservative and indicative estimate. Data of the GDS surveys were not eligible for the risk assessment, because they refer to selected samples with relatively many clubbers. The MRD rates, based on data from the UK, seem reliable though it cannot be excluded that (a) there was some under-reporting of cases, and

(b) ecstasy is used at a higher frequency (which would lead to lower risks per pill). As such, the risk rates presented in this paper are just the best estimates currently available.

Another limitation is that fatal cases are not routinely subjected to autopsy and full toxicological screening. Consequently, post-mortem toxicology data is not always available, nor consistently used for coding and monitoring of ecstasy-related deaths. Due to the lack of specific drug-related hospital and death records, under-reporting of ecstasy-related incidents in, e.g. the Netherlands, is evident. The next limitation is that most ecstasy use involves poly-substance use, i.e. users consume either concomitantly or simultaneously two or more psychoactive substances, including alcohol (Home Office, 2014; Scholey et al., 2004; Wu et al., 2009), which may affect the toxicity of ecstasy (for a review about drug interactions, see Mohamed et al., 2011). Indeed, when autopsies and toxicological analysis are conducted in MRDs, MDMA is rarely (up to 28% of cases) the only drug found in the blood of the deceased (Ghodse et al., 2001, 2003; Schifano et al., 2003). Examples of substances co-ingested with ecstasy are alcohol, stimulants, including cocaine and amphetamine, cannabis, benzodiazepines, GHB and LSD. Finally, both contaminated pills and ‘false’ pills (pills sold as ecstasy but containing no or little MDMA) may affect the risk of (fatal) incidents. Notably, ecstasy pills have occasionally been adulterated with p-methoxy-amphetamine (PMA) and p-methoxy-methamphetamine (PMMA) which are substantially more dangerous than MDMA because of their delayed effect (Steele et al., 1992).

Conclusion

Ecstasy use can be harmful and fatalities following ecstasy use have been reported. The estimated risk of any acute adverse health event in ecstasy users is about one in 70 users or about one in 340 pills consumed. However, this rate refers to all ecstasy-related incidents; for moderate to severe incidents, the estimated risk is about one in 900 pills consumed. Importantly, ecstasy users, including those in the Netherlands, are frequently poly-substance users (Home Office, 2014; Scholey et al., 2004; Wu et al., 2009), which is reflected in 31% of non-fatal incidents associated with the combined use of ecstasy and other substances (Lameijer et al., 2018). Given its widespread use, the number of MRDs is relatively low and the number of MRDs per user is comparable to amphetamine, cocaine and alcohol-specific deaths, but substantially lower than opiate-specific deaths (heroin, morphine). However, the use of ecstasy still implies a considerable health risk that should not be underestimated.

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