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REVIEW

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A bitter pill. Overview of ecstasy (MDMA, MDA) related fatalities

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Abstract *Rationale:* The issue of ecstasy-related fatalities has extensively attracted the attention of both the media and the general public, but less so of the scientific literature. *Objectives:* The aim of the present review is to focus on the epidemiological, clinical and pharmacological issues related to ecstasy fatalities. *Results:* Possibly due to a number of different reasons, the rates of ecstasy-related deaths seem to have peaked in recent years. MDMA metabolism is regulated by the levels of CYP2D6 and COMT (both exhibit some genetic polymorphism), and range of activity of these enzymes may account for some inter-individual differences in terms of toxic responses to the drug. A small increase in MDMA dosage can lead to a significant rise in drug plasma concentration. Due to their tolerance to MDMA psychoactive effects, some individuals may binge with dosages that may be the cause of serious concern. In experienced users, a reverse tolerance phenomenon can also be observed. Together with ecstasy, most of the misusers take a number of different compounds and the possible rationale of this style of consumption is commented upon here. Frequently, the lethal complications observed after acute MDMA administration can be the consequence of the occurrence of a serotonin syndrome and/or of sympathomimetic overstimulation (both conditions are exacerbated by environmentally induced overheating). *Conclusions:* A number of methodological problems can contribute to making difficult the interpretation of the role played by ecstasy in so-called ecstasy-related deaths, especially so if accurate information is not available.

Keywords Ecstasy · MDMA · MDA · Drug fatalities · Epidemiology · Drug mortality · Serotonin syndrome

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Introduction

The issue of ecstasy-related fatalities has extensively attracted the attention of both the media and the general public (possibly because of the young age of the victims), but less so of the scientific literature. This may result from several factors, including the alleged low numbers of victims involved compared with fatalities due to misuse of other illicit drugs (McKenna 2002) and multiple drug administration, which characterizes the typical occasion of use (Tossmann 2001). In fact, even the possibility that ecstasy alone can kill has been previously doubted (Giroud et al. 1997). However, ecstasy (MDMA; MDA) related emergency department visits increased progressively and dramatically during the 1990s (often doubling from year to year) and visits tended to be for overdoses and unexpected reactions (Landry 2002). Moreover, given the very large numbers of consumers involved (ecstasy consumption is second only to cannabis in a number of European countries; EMCDDA 2003) and the large dosages taken by some consumers (Schifano et al. 1998), it is imperative that the possible risk of ecstasy "overdose" is better evaluated and assessed. The aim of the present review is to focus on existing knowledge of the epidemiological, clinical and pharmacological issues related to ecstasy fatalities.

Epidemiological findings

Traditionally, most of the data pertaining to ecstasy-related fatalities have been based on case reports or small case series, and due to these uncertainties, estimates of the risk of using ecstasy vary considerably, from one death in 2000 first time users to one death in 50,000 (Gore 1999). More recently, however, reports on ecstasy related deaths have been based on "ad hoc" databases. During the period July to December 2000, a total of 66 medically examined cases in the USA tested positive for phenylethylamines, whilst Goldberger and Gold (2002) detailed toxicological findings of 22 cases which occurred in Florida in 2001

and 2002. Gill et al. (2002) commented on the causes of death of 22 MDMA positive fatalities occurring in New York between January 1997 and June 2000; although the size of their sample was small, results showed a 3-fold increase in the number of deaths in 1999 and 2000 with respect to previous years. Byard et al. (1998) retrospectively searched files of ecstasy deaths in South Australia from February 1992 to January 1997 and found only six fatalities, none of which was before 1995.

Schifano et al. (2003c) described their preliminary findings from England and Wales, where they identified 81 deaths related to taking ecstasy in the timeframe July 1997 to June 2000. Results of toxicological examination were made available in 75 cases; MDMA accounted for 68 (91%), MDA for seven (9%), and opiates or opioids for 44 (59%) of these cases. In 26 (38%) cases, one or more drugs (mostly hypnotics or sedatives) had been prescribed to the deceased patient. Most of the victims were males with a median age of 27 years. Recently, the same group presented a more detailed analysis of the same issue (Schifano et al. 2003b). They took into account data based on all information recorded in the National Programme on Substance Abuse Deaths (np-SAD) database (Ghodse et al. 2001, 2002, 2003), which regularly receives information on drug related deaths in addicts and non-addicts from coroners in England and Wales. A total of 202 ecstasy-related fatalities (which represents the largest sample of these deaths so far) occurred in the chosen timeframe (August 1996 to April 2002). The ratio of males to females was 4:1 and three out of four victims were younger than 29 (but one out of seven was younger than 19). In 17% of cases ecstasy was the sole drug implicated in death and in the remaining cases a number of other drugs had been found. According to toxicology results, MDMA accounted for 86% of cases and MDA for 13% of cases; single deaths were associated with MDEA and PMA.

Pharmacological and clinical pharmacological issues

Chemistry

MDMA (3,4-methylenedioxymethamphetamine) is one of the most well known phenylisopropylamine (PIA) compounds. MDMA potency (effective oral dose 100–160 mg) is similar to MDA. However, unlike MDA, the S(+) isomer of MDMA (effective dose 80–120 mg) is more potent than its *R*(−) enantiomer (effective dose estimated to be about 300 mg). MDMA and MDA are indirect potent releasers of serotonin and, to a lesser extent, of dopamine (Vollenweider et al. 2003; for a recent and thorough review of the issue, see also Green et al. 2003). An acute dose of MDMA can release around 80% of central serotonin stores (Green et al. 1995). The serotonin levels in the cytosolic area are directly related to the intensity (or lack of it) of MDMA-induced release of serotonin (Huether et al. 1997), and this may explain why ecstasy users tend to be polydrug users (Parrott 2001).

Pharmacokinetics and pharmacogenetics

The adverse effects of MDMA may be related to metabolism, and two overlapping metabolic pathways have been postulated. The first (and predominant) is carried out through the ring degradation by O-dealkylation to the corresponding 3,4-dihydroxy metabolites. The second pathway leads, via chain degradation, to MDA (Kovar 1998). Both MDA and MDMA metabolism is regulated by the levels of the hepatic enzyme CYP2D6. According to Tucker et al. (1994), about 5–9% of Caucasians are deficient in this enzyme, so that poor metabolisers may be at greater risk of toxic responses to the drug even at low doses (Ramamoorthy et al. 2002), but no data have confirmed these expectations so far (Gilhooly and Daly 2002). MDMA has been found also to be a potent inhibitor of CYP2D6 (Heydari et al. 2003).

The COMT enzyme is involved in the transformation of 3,4-dihydroxy-methamphetamine-HHMA (the main MDMA metabolite) to 4-hydroxy-3-methoxymethamphetamine-HMMA (Helmlin et al. 1996; Maurer et al. 2000; Segura et al. 2001). Approximately 25% of the Caucasian population have low COMT activity (Zhu 2002). HMMA may stimulate the release of the antidiuretic hormone vasopressin, so that excessive water retention, coupled with hyponatraemia, can be observed (Fallon et al. 2002; Forsling et al. 2002). Young women may be at greater risk (Parr et al. 1997; Budisavljevic et al. 2003). One could conclude that a range of COMT activity (due to genetic polymorphism) may explain some of the inter-individual differences in vasopressin secretion after MDMA consumption.

A small increase in MDMA dosage can lead to a significant rise in drug plasma concentration ("non-linear" pharmacokinetics; de la Torre et al. 2000). All of these factors taken together might lead to the conclusion that there may be, in at least some individuals, a significant lack of dose-response relationship after MDMA administration, and explain why toxic reactions may be unrelated to the amount taken.

The issue of MDMA lethal dosage

The LD_{50} in mice has been estimated to be between 80 and 115 mg/kg (Steele et al. 1994). According to the principles of interspecies scaling, small animal species require higher dosages of drug to achieve equivalent drug effects, so that Ricaurte et al. (2000) suggested that 20 mg/kg MDMA given to rodents is the equivalent of 5 mg/kg given to primates (and of even smaller dosages to humans). An average ecstasy tablet in the UK has been reported to contain 60–69 mg MDMA (Cole et al. 2002a). Consequently, in a 70 kg subject, one could conservatively conclude that, with the ingestion of some 20–30 tablets, the equivalent of the LD_{50} dose described in small animals can be achieved. Up to 40–50 ecstasy tablets have been described as the maximum dosage taken on a single occasion (Henry et al. 1992; Parrott 2001) and, at least in

the UK, heavy ecstasy consumers may binge with some 15–25 tablets per occasion (Parrott et al. 2001). Although there are pronounced individual differences with regard to the sensitivity to MDMA toxic effects, life threatening or lethal outcomes have been seen with concentrations between 0.11 and 7.0 mg/l (Theune et al. 1999). It is possible that other factors, such as aggregation in close environments (as in the case with clubs), together with high ambient temperature and possibly dehydration (Dafters 1994; Green et al. 1995), may play an important role in increasing the risk of a fatal outcome.

An active dose of MDMA is in the range of 1.35–1.8 mg/kg (which would make 1.5 ecstasy tablets in an average human being), and this would correlate positively with the intensity of MDMA-induced changes (Liechti and Vollendweider 2001). However, a significant proportion (35%; Cottler et al. 2001) of ecstasy users take the drug repeatedly in order to overcome the effects of short-term tolerance (Merrill 1996). It has been suggested that through destruction of the 5-HT distal axon terminals that subserve the desired MDMA entactogenic effects, its efficacy decreases over time (Parrott 2003). It is also possible that some individuals, whose serotonin levels are chronically low, will be attracted by higher dosages of ecstasy simply because MDMA is a potent serotonin releaser and this would give them, in the first few hours after administration, a much welcome serotonin "boost". Also, a reverse tolerance/sensitisation phenomenon can occur in experienced stimulant users, so that the behaviours associated with the most adverse consequences of ecstasy use (i.e. the serotonin syndrome) increase in both duration and intensity, whilst locomotor activity increases only in intensity (Green et al. 1995).

Pharmacological interactions

In most cases, ecstasy users take other drugs on the same night out. Furthermore, if light ecstasy users report comparatively light use of other illicit drugs, heavy ecstasy users usually display extensive drug histories (Fox et al. 2001) In 83% of the Schifano et al. (2003b) sample, the deceased took several psychoactive compounds (most frequently: alcohol, cocaine, opiates and amphetamines). People may have taken these different drugs to boost the effects of the single compound, so that one could wonder about the rationale of this polydrug abuse. Anecdotally, it appears that alcohol is taken with ecstasy at the beginning of the night to get a stronger/better high. In fact, MDMA, whilst in the presence of alcohol, shows more significant physiopathological effects (Pacifici et al. 2002). Cocaine, amphetamines and/or additional ecstasy tablets are taken to maintain arousal and a state of alertness (the MDMA entactogenic effects fade away in 2–4 h; Schifano 2000). Finally, opiates and/or high (i.e. sedatives) dosages of alcohol are taken in the last part of the night to calm down before going home, since the untoward after-effects of ecstasy (namely irritability and restlessness) persist well beyond the end of the empathogenic and entactogenic pleasurable effects (Curran and Travill 1997). Apart from the symptomatic relief from come-down effects, there are other reasons for polydrug use. First, ecstasy tablets are sometimes made up with different adulterants (e.g. ketamine, amphetamines: Spruit 2001). Second, with a chronic high dosage, ecstasy users experience a decrease of the desired effects over time, which could lead to exploration of use of other stimulants and hallucinogens.

In other cases, potentially fatal interaction of ecstasy can occur with prescribed medications. Antiretrovirals are potent inhibitors of CYP2D6, so that patients prescribed with HIV-1 protease inhibitors can experience prolonged effects from a small dose of MDMA (Henry and Hill 1998; Harrington et al. 1999). In other cases, the pharmacological interaction can determine the occurrence of the serotonin syndrome; this is the case with MDMA and moclobemide, which is taken to enhance the effects of ecstasy (Vuori et al. 2003). Fatal interactions with selective serotonin reuptake inhibitors (SSRIs) have been anecdotally described (Byard et al. 1998), possibly because some SSRIs (i.e. citalopram) can inhibit the CYP2D6 enzyme (Liechti and Vollenweider 2000). To intensify the ecstasy effects, some of the consumers take pre-party packages containing SSRIs (Schifano et al. 2003a), and this can facilitate the occurrence of the serotonin syndrome (Green et al. 1995).

Mechanisms of death

After acute ecstasy administration, a number of different physical complications have been reported: tachycardia, asystole, arrhythmias, hypertension, metabolic acidosis, cerebral haemorrhages, convulsions, coma, rhabdomyolysis, mydriasis, vomiting, diarrhoea, thrombocytopoenia, disseminated intravascular coagulation and acute kidney failure (Parrott 2001; Schifano et al. 2003b). The sympathomimetic stimulation is exacerbated by environmental conditions, that are in turn induced by the repetitive high frequency rhythm of the techno music itself (Parrott 2001). Environmentally induced overheating may further increase the rise in core temperature which is routinely seen with amphetamine-type stimulants, but the rise in body temperature is also somewhat independent from the setting in which the drug is taken. Febrile convulsions have been seen in children who accidentally ingest MDMA (Cooper and Eggleston 1997). Increased body temperature and excessive sweating was reported by some 90% of clubbers in the Davison and Parrott (1997) sample. Thirsty clubbers naturally tend to replace body fluids lost during sweating, but excessive intake of hypotonic fluids, coupled with an increase in vasopressin levels, may in turn cause the occurrence of lethal hyponatraemia (Budisavljevic et al. 2003). According to Parrott (2001), all ecstasy misusers develop a (mild, in most cases) serotonin syndrome after acute drug intake. The long-term psychobiological changes observed in humans can be the direct function of acute serotonergic overactivity (Parrott 2002). In fact, Soar et al. (2003)

found a significant positive correlation between both the average and the maximum dosage consumed by problematic (i.e. those who showed a number of psychopathological troubles) ecstasy drug users and scores on the serotonin syndrome questionnaire.

The serotonin syndrome, first described in rats (for a thorough review, see Green and Grahame-Smith 1976; Ener et al. 2003), is characterised in humans by a number of signs and symptoms: enhanced physical activity; sweating; incoordination; mental confusion; trismus; jaw clenching; agitation; hyperreflexia; hyperthermia; shivering; rhabdomyolysis; metabolic acidosis; myoclonus; tremor and nystagmus (Gillmann 1999; Schifano et al. 2003b). The serotonin syndrome seems to be the direct consequence of MDMA-induced 5-HT_1-like and 5-HT_2 receptor stimulation, which results in a marked increase of central serotonin levels (Liechti and Vollenweider 2001). Some of the MDMA acute effects (tachycardia, overarousal and hypertension) may well be due to more general noradrenergic/dopaminergic receptor stimulation (Hedetoft and Christensen 1999). Serotonergic release is intensified by parallel use of dopaminergic stimulants (Huether et al. 1997). In fact, Williams and colleagues (1998) suggest that the more serious complications (delirium, seizures, coma) are commoner when MDMA is consumed together with cocaine and amphetamines.

In patients with a history negative for viral hepatitis and alcohol abuse, the occurrence of a toxic acute hepatitis has been reported. This potentially fatal condition can be the result of an idiosyncratic response to MDMA (Henry et al. 1992).

Ecstasy ingestion alone, or in combination with other compounds, has been considered as a possible risk factor in road traffic accidents (Henry et al. 1992). Schifano (1995) described a case series of a few ecstasy consumers who showed, whilst under the influence of MDMA, bizarre and indirectly aggressive behaviours whilst driving (i.e. crossing red traffic lights in busy roads at high speed). Some of these phenomena (e.g. "surfing" whilst lying on the roof of a moving car; Hooft and van de Voorde 1994) may well be part of a collective ritual that is carried out at the end of a clubbing session. However, aggressive behaviours may also well be the consequence of a significant central 5-HT decrease (van Heeringen and Marusic 2003), a neurobiological condition that is found 4–6 h after MDMA ingestion (i.e. in the early morning hours; Schifano 1995; Hoshi et al. 2003). In a recent report, Webb et al. (2003) analyzed the causes of all deaths that occurred in England and Wales in the year 2000 and found that stimulants, including MDMA, particularly featured in traumatic accidents. Finally, the existence of an underlying natural disease acts as a contributory factor for the induction of a potentially fatal condition (i.e. arrhythmias, Dowling et al. 1987).

Treatment of somatic emergencies must be addressed as needed (for a complete review of this issue, see Green et al. 1995; Schifano et al. 2000).

The issue of increase in ecstasy-related fatalities

Initially reported between the end of the 1980s (Dowling et al. 1987) and the beginning of the 1990s (Henry et al. 1992), the rates of ecstasy-related deaths appeared to have peaked in most countries at the end of the 1990s. Schifano et al. (2003b) showed a 6-fold increase in the number of ecstasy-related deaths in England and Wales between 1996 and the beginning of 2002, and these figures showed a further increase by the end of 2002 (Ghodse et al. 2003). There are several possible reasons (not necessarily contradicting each other) behind this increase.

Consistent decrease in ecstasy prices over the years

The price of ecstasy in the UK has fallen rapidly over the last decade or so. In early 1994, the average price of a dose of tablets was £16.50 but by December 2001 this figure had more than halved to £7.00 (National Crime Intelligence Service 2002). The range of prices in London tends to be higher than in other areas, despite the fact that it is closer to the source of supplies, i.e. Belgium and the Netherlands. If the effects of inflation are taken into account, the fall in real terms is even greater. Prices are believed to have fallen further in 2002 (Schifano et al. 2003b).

Variability of content of ecstasy tablets

A number of different PIA compounds, which may be found in an "ecstasy" tablet, have entered both the European and the UK market (Ramsay et al. 2001; Bal and Griffin 2002). This may be the cause of concern, given that some of these "ecstasy-like" compounds can show a higher toxicity than MDMA per single tablet, significantly increasing the chances of ecstasy "overdose" (Felgate et al. 1998; Ghodse et al. 2002; Winstock et al. 2002). On the other hand, the decrease in MDMA content for a single tablet (which can happen with the variability of the market; Cole et al. 2002b) can determine an increase in number of tablets ingested. Given the non-linear pharmacokinetics of MDMA, this could result in a disproportionate rise in plasma levels.

Media attention

This may have increased both the level of alertness on the reporting agencies' side and prompted the set up of specific databases (Ghodse et al. 2003).

Finally, the constant and steady increase in ecstasy fatalities in the second part of the 1990s seems related, at least in the UK, to a more general increase in stimulant-related fatalities. Ghodse et al. (2003) showed that, whilst ecstasy-related deaths increased by 34% between 2001 and 2002, deaths related to amphetamine-like compounds

and cocaine use increased, in the same period, respectively by 60% and 47%.

Understanding the role of ecstasy in related fatalities

A number of methodological problems can contribute to making difficult the interpretation of the role played by ecstasy in so-called "ecstasy-related" deaths, and especially so if accurate information is not available.

The real content of so-called "ecstasy" pills has been the source of a vigorous debate. Schifano et al. (1998) described that in large samples (i.e. about 20,000 tablets) of ecstasy material seized, MDMA was found as an active ingredient in 85–90% of cases (whilst MDA was mostly found in the remaining cases). However, other reports (King 2000) have found that ketamine (usually mixed with other stimulants, e.g. caffeine, ephedrine, amphetamines) can account for up to 10% of seized tablets. Other reports (Baggott et al. 2000) have found that a significant percentage of ecstasy tablets seized did not contain MDMA as an active ingredient at all. To arrive closer to the source of the issue, Ramsey et al. (2001) analyzed solid dose formulations retrieved from an amnesty bin located at London club into which attendees were required to get rid of illicit drugs, or into which staff placed substances found during searches. They were able to identify 67% of tablets and found that about half contained "ecstasy-like" compounds (mostly MDMA). However, the issue is somewhat more easily interpreted where post-mortem findings can be made available. Schifano et al. (2003b) reported that toxicological confirmation of presence of ecstasy was found in 84% of cases (MDMA accounted for 86% and MDA for 13% of cases).

Polydrug abuse ingestion itself may act as a confounding factor. In general, ecstasy drug users tend to use not just cannabis, but a wide range of illicit drugs (Milani et al. 2000; Fox et al. 2001). The suggested polydrug occasional user model is characterized by at least three different psychoactive compounds taken on the same occasion (Tossmann et al. 2001). Consequently, even when MDMA is included in the list of the compounds found at post mortem, any conclusion of the role MDMA played in the mechanics of death can be difficult. One might think that co-occurrence of two stimulants (i.e. MDMA together with amphetamine and/or cocaine) could synergistically increase both dopaminergic and serotonergic stimulation, so that the serotonin syndrome is more likely to occur. Moreover, the mixed use of hallucinogens (i.e. ketamine and/or LSD together with MDMA) can increase the occurrence of intoxicated "behaviours", such as dangerous driving, with a consequent higher risk of a fatal outcome. However, it is also possible that concurrent use of sedatives (i.e. opiates) might somewhat mitigate the excess of sympathomimetic overactivity (Hunt 2003).

On other occasions, MDMA is the only drug found at post mortem and this occurs in up to 28% of cases (Ghodse et al. 2003). However, even in these cases, the controversial role of the individual's innate vulnerability, as might be conceived in those subjects who died having taken only one or just a few tablets (Braback and Humble 2001), must be taken into account as a concurrent cause.

Finally, to increase understanding of these phenomena, future studies should address not only coroners' reports but also the toxicology and pathology findings (normally available from the victims' files which are stored in the different coroners' offices throughout the country). Every file could then be studied and examined with the "psychological autopsy" technique, an approach that is already in use (Ghodse et al. 2003) to carry out in-depth studies of specific local situations. With this approach, detailed information about some important areas may possibly be elicited: medical and psychiatric history of the victims; full history of drug use; quantity of drugs taken on the last occasion and characteristics of venues attended (if any) prior to death.

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