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3,4-Methylenedioxy analogues of amphetamine: Defining the risks to humans

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Abstract

The 3,4-methylenedioxy analogues of amphetamine [MDMA (“Ecstasy”, “Adam”), MDA (“Love”) and MDE (“Eve”)] are recreational drugs that produce feelings of euphoria and energy and a desire to socialize, which go far to explain their current popularity as “rave drugs”. In addition to these positive effects, the drugs are relatively inexpensive to purchase and have the reputation of being safe compared to other recreational drugs. Yet there is mounting evidence that these drugs do not deserve this reputation of being safe. This review examines the relevant human and animal literature to delineate the possible risks MDMA, MDA and MDE engender with oral consumption in humans. Following a summary of the behavioral and cognitive effects of MDMA, MDA and MDE, risks will be discussed in terms of toxicity, psychopathology, neurotoxicity, abuse potential and the potential for drug–drug interactions associated with acute and chronic use. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: MDMA; MDA; MDE; “Ecstasy”; “Adam”; “Love”; “Eve”; Recreational drug use; Toxicity; Psychopathology; Neurotoxicity; Abuse potential; Metabolic interactions

1. Introduction

Three methylenedioxy analogues of amphetamine (AMPH), namely 3,4-methylenedioxyamphetamine (MDA, “Love”) and its *N*-methyl derivative, 3,4-methylenedioxymethamphetamine (MDMA, “Ecstasy”, “Adam”) and *N*-ethyl derivative, 3,4-methylenedioxy-*N*-ethylamphetamine (MDE, “Eve”) have attracted a great deal of media attention in recent years (Fig. 1). They are illicit recreational drugs riding a second wave of popularity in Europe and North America as “rave” drugs, reflecting the common use of these drugs at dance clubs where the style of dance is prolonged and fast-paced to loud repetitive music. The first wave of popularity was recorded by the American press in the early 1980s, subsiding for a short time when MDA and MDMA were added to Schedule 1 of the US Controlled Drug Act in 1985. More recently, British newspapers abound with horror stories about young adults being hospitalized or dying after ingestion of these drugs, prompting one physician to dub the combination of MDMA and rave dancing as “the dance of death” [62].

As the use of the methylenedioxyamphetamines increased and data accumulated from animal studies, the perception that these drugs were fairly harmless began to be challenged [52]. Controversy arose regarding the significance of the results of animal research demonstrating morphological and functional changes to neurons after administration of these drugs and continues unabated. Retrospective methods and heterogeneity of drug use in the studied populations have hampered investigations in humans [37]. There also remains controversy over the original placement of MDMA and MDA on Schedule 1, with its categorization as having no accepted medicinal use. Having these drugs made illegal to possess has severely limited research efforts to identify and understand the mechanisms involved in any potential long-term central nervous system (CNS) effects in humans. Although considerable media attention has focused on these drugs and a large body of animal literature exists that suggests that they are selective 5-hydroxytryptamine (5-HT, serotonin) neurotoxins, few detailed assessments of risks inherent in the use of these drugs in humans exist. Differing opinions flourish, though, from dire predictions of long-term neurodegeneration [97] to noting that there remains no compelling evidence of long-term behavioral effects in either animals or humans [55,

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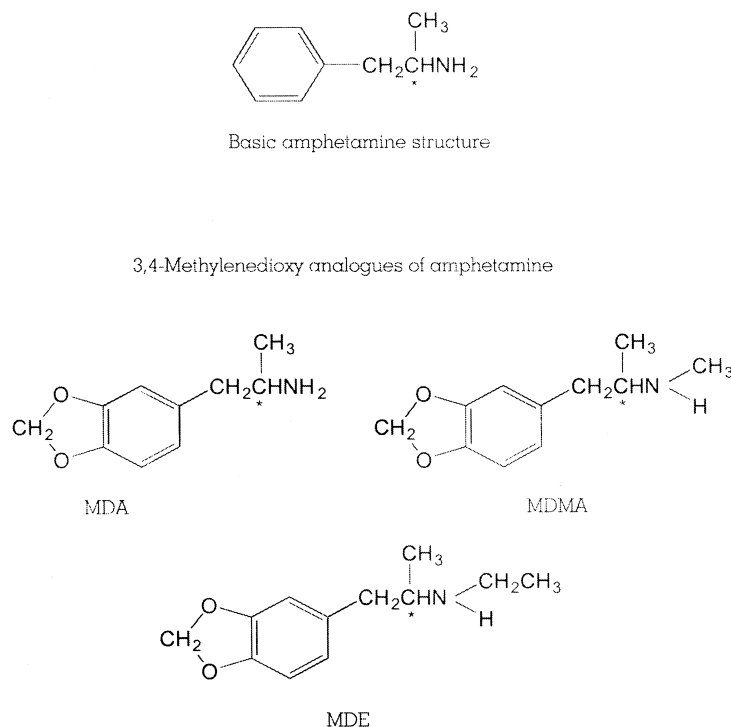


Fig. 1. Chemical structure of amphetamine and the three methylenedioxy analogues. Chiral centres denoted by *.

121, 126]. The goal of this article is to review the available literature on human use and animal data to trace the roots of the popularity of these drugs and to delineate the risks they engender with oral consumption in humans.

1.1. History

The first reported synthesis of a methylenedioxyamphetamine was that of MDA in 1910 by the German chemists Mannich and Jacobsohn [157, 145]. Its pharmacological properties were studied in animals in 1939 and included marked sympathomimetic effects, CNS stimulatory activity and convulsions at high doses [56]. MDA has been patented in turn as an antitussive (1958), an ataractic (1960) and an appetite suppressant (1961) [145]. The CNS effects in humans were reported by Alles [2], who described personally experienced increased auditory acuity and tactile awareness, and depersonalization. Naranjo et al. [102] recommended the use of MDA in psychotherapy for its ability to enhance emotions and empathy without producing sensory disruption or hallucinations. Its current popularity as a recreational drug and its name, the "Love" drug, arise from its emotion-enhancing qualities [157].

The first public recording of the preparation and properties of MDMA was a German patent filed in 1912 and issued in 1914 [145]. The first comprehensive report of the pharmacological actions of MDMA in humans appeared in 1978 [143, 145], but the drug had been used in clinical practice prior to that as an adjunct to psychotherapy for its ability to encourage openness of emotional expression and to

facilitate interpersonal communication and intimacy [144]. Greer and Tolbert [53] described the positive value of MDMA in therapy sessions with 29 patients.

Grinspoon and Bakalar [54] also supported the use of MDMA in clinical practice, classifying MDMA as a psycholytic agent or "mind loosening" agent, acting as a catalyst in the process of psychotherapy. They reported patients' claims of lasting improvement in their capacity for communication with others, in their capacity for insight and in their increased self-esteem up to two years after MDMA-assisted psychotherapy. Unfortunately for the clinicians who believed in the efficacy of MDMA in psychotherapy, MDMA became popular as a recreational drug in the late 1970s and early 1980s [144]. MDMA was actively promoted as a legally available euphoriant in Texas, with blatantly open sales in numerous bars and nightclubs [8]. Controversy over its use, its abuse potential and its potential for toxicity spilled over into the US media and was largely responsible for the placement of MDA and MDMA on Schedule 1 in 1985.

MDE became popular in the USA only after the placement of MDMA on Schedule 1 and enjoyed a brief expansion in use until the "designer drug" legislation of 1986 which outlawed the sale of analogues of controlled substances [10]. Although all three of these drugs have been Class A controlled substances in Britain since 1971, MDE and MDMA have attracted renewed popularity as illegal "rave" drugs in British and German nightclubs. The drugs are used in conjunction with rave dancing, i.e. prolonged episodes of hard and fast dancing within

a large group [37, 62, 154]. North American dance venues also report widespread use of MDMA and MDE at “rave clubs”.

1.2. Behavioral effects

MDA, MDMA and MDE have all been reported to produce very similar central and peripheral effects in humans. However, there are differences in potency, time of onset and duration of action. The central effects are described as an easily controlled altered state of consciousness, with heightened sense of well being, increased tactile sensations, increased perception of an inwardly focused experience and a strong desire to be with and converse with people, without significant perceptual distortion or hallucinations [2, 85, 103, 113, 144]. These subjective effects go far to explain their wide popularity as recreational drugs in such contexts as dance clubs and other social get-togethers. Over 80% of subjects ($N = 500$) approached to complete a questionnaire on the subjective effects of MDMA cited euphoria, increased energy and sexual arousal as positive drug effects [19]. Although MDA has been known to produce hallucinations at higher than typical doses, this effect appears to be either abolished or diminished to visual distortions rather than well-formed hallucinations by *N*-alkylation (as in the cases of MDMA and MDE) [85, 104, 112].

MDA is more potent than MDMA and MDE, with a typical dose range of 60–120 mg, while single doses of 100–200 mg (1.4–2.8 mg/kg) of MDMA and MDE are common [12, 85, 113]. The onset of effects ranges from 30 to 60 min with MDA to within 30 min with MDMA and MDE. Duration of action is longer for MDA (about 8 h) than MDMA (about 6 h) and MDE (about 3–4 h) [11, 104, 141, 145].

The peripheral effects of MDA, MDMA and MDE are largely sympathomimetic in nature, mediated by the release of norepinephrine. These effects include tachycardia, elevated blood pressure, mydriasis, tremor, palpitations and diaphoresis. Other common effects include increased salivation, bruxism (grinding of teeth) and trismus (tight jaw muscles) [70, 90, 112, 141]. These last two effects on facial muscles might be related to the release of 5-HT. The facial motor nuclei (cranial nerve VII) are innervated by excitatory 5-HT fibers. Micro-iontophoretic application of 5-HT produces a slow, depolarizing action accompanied by a modest increase in membrane resistance, which facilitates the excitatory effects of iontophoretically applied glutamate. The overall increased excitability of these motor neurons can persist for several hours after only a single application [1].

The most common reported after effects of MDA, MDMA and MDE are drowsiness, muscle aches and general fatigue, depression lasting 1–2 days, difficulty in concentrating, paranoia and short-lived anxiety and irritability [70, 90, 113, 162]. The after-effects increase with successive

doses, while the positive subjective effects diminish [53, 114, 146]. It was originally considered that the after-effects limit the frequency of use and tend to encourage variety in the choices of recreational drugs ingested [113]. This apparent sensitization seen in the unwanted after-effects and the tolerance that develops to the positive effects have been reinterpreted in a recent commentary as supportive evidence of neurodegeneration [98].

The unique subjective effects of MDA, MDMA and MDE ingestion have led to the suggestion that these 3,4-methylenedioxyamphetamines represent a novel class of drugs, labeled entactogens, distinct from psychomotor stimulants and hallucinogens [104, 105]. The term entactogen is derived from the Greek roots “en” for within or inside and “gen” meaning to produce or originate and the Latin root “tactus” for touch. Hence, the connotation of entactogen is that of producing a “touching within” [104], in reference to the drugs’ ability to promote inward reflection and positive self-assessment. The prototypic entactogen was the α -ethyl derivative of MDMA, *N*-methyl-1-(1,3-benzodiol-5-yl)-2-butanamine (MBDB). From previous work on structure–activity relationships which had showed α -ethyl substitution of DOM eliminated hallucinogenic activity, MBDB was proposed as an entactogen devoid of hallucinogenic properties and which supposedly had a less complex array of behavioral effects in comparison with MDA. Subjects given MBDB supported its entactogenic properties, reporting a pleasant state of introspection, enhanced communication and a pronounced sense of empathy, similar to MDMA except the onset of action was slower and more gentle with less euphoria [103]. Hermle et al. [63] supported the hypothesis that MDE also belonged to the novel entactogenic class. Comparisons of the effects of MDA, MDMA and MDE with those of psychomotor stimulants and hallucinogens have relied heavily on operant conditioning methodologies [6, 13, 44–46, 74, 103, 142]. Results from drug discrimination (DD) studies are equivocal, related to differences in the choice of training drug, the species, the schedule of reinforcement, the training regime, and the apparent stereoselectivity of behavioral effects, especially with MDA. Other behavioral studies in animals carried out in conjunction with postmortem neurochemical studies have also lent support to MDMA and MDA being distinct from psychomotor stimulants and hallucinogens [60].

1.3. Cognitive effects

There has been considerable interest in acute and long-term cognitive effects of the methylenedioxy analogues, especially with respect to learning and memory. Experimental data from animals have shown that species, dose and dosing regime are important factors in the ability of these drugs to produce cognitive effects. Low dose MDA (1.79–3.58 mg/kg) enhanced acquisition of conditioned nictitating membrane response in rabbits [127]. Rats repeatedly treated with high doses of MDMA showed no deficits on a number

of spatial memory tests [123, 126]. However, non-human primates appear to be more sensitive to decremental changes in cognitive testing. Acute administration of low dose MDMA produced deficits in tests of time estimation, learning and motivation, but had no effect on short-term memory or attention. However, chronic treatment with escalating doses of MDMA produced behavioral tolerance in these same operant tasks. The tolerance could still be demonstrated for some of the tasks when the animals were administered a challenge dose of MDMA 6–18 months after completion of chronic MDMA treatment [39, 40].

Recreational users of MDMA do not report specific changes in cognitive performance related to learning and memory [18, 19]. Varying degrees of “mental confusion” after acute MDMA ingestion have been reported, but no objective testing was included [28, 31, 52]. A single dose of MDE (140 mg) given to volunteers failed to adversely affect performance on several numerical tests [63]. Parrott et al. [111] compared regular MDMA users (10 episodes or more) and novice users (9 episodes or less) to control subjects. Performance on response speed and vigilance measures did not differ among the groups; however, both groups of MDMA users showed deficits on tests of immediate and delayed word recall.

1.4. Current recreational use

Data on the current prevalence of use of these drugs is sparse, although there are survey results that suggest that they continue to experience increasingly wider popularity. Frank [38] reviewed reports on clandestine laboratories seized by the Drug Enforcement Administration between 1978 and 1981. Although the most common drug being made during this period was methamphetamine (MAMPH) (378 out of 751 laboratories), 16 illegal laboratories were found to be specifically making MDA. Kirsch [75] reported that approximately 10,000 doses of MDMA were being distributed on a monthly basis by a single laboratory in California in 1976, and that number increased to 30,000 by 1984 and to 500,000 just prior to MDA and MDMA being placed on Schedule 1 of the Controlled Substances Act in 1985. In 1987, out of 369 college undergraduates interviewed at a major American university, 39% of the students admitted to having used MDMA at least once during the preceding year [112]. A random 1990 survey of illicit drug use by undergraduates at a British university revealed that 24% of those surveyed had used MDMA [27]. An opinion poll conducted in Britain reported that 31% of people between the ages of 16 and 25 had taken MDMA, mostly at dance clubs [59]. Over 90% of participants ($N = 135$) in a Glasgow dance scene had tried MDMA at least once [37]. Other epidemiological studies involving 15- and 16-year-old students have reported that 5–9% of the students had used MDMA [73, 97, 156].

1.5. Controlled studies in humans

Due to ethical considerations, the scant numbers of controlled studies in humans have used small numbers of subjects who have had prior experience with MDMA. Serum prolactin (PRL) and mood responses to intravenous L-tryptophan (Trp) were compared between MDMA users and healthy volunteers [118]. The PRL response to Trp showed a tendency towards being blunted in the MDMA group in contrast to the results obtained in rats showing an enhancement of the PRL response to fenfluramine after single or multiple doses of MDMA [115]. No differences were found between the two groups of human volunteers in terms of mood changes induced by Trp. Preliminary findings of the first FDA-approved Phase 1 study prospectively evaluating the effects of MDMA administration (0.25–1.0 mg/kg) in six subjects included modest increases in heart rate and BP and stimulation of secretion of both ACTH and PRL [55]. Volunteers administered MDE showed sleep electroencephalogram changes similar to those seen with amphetamine [50]. Neuroendocrine and cardiovascular effects produced by the acute doses of MDE were similar to those observed with MDMA [51].

2. Toxicity

2.1. Acute effects

In the early 1970s reports of fatalities associated with the ingestion of MDA began appearing. Reed et al. [119] reported postmortem findings of marked visceral congestion and edema and petechial hemorrhages on the surface of the heart following ingestion of MDA. However, toxicology revealed levels of MDA in brain and blood of 1 mg/100 ml, suggestive of an overdose. Simpson and Rumack [141] reported on a patient treated in a hospital emergency department after ingestion of MDA. The patient presented as unresponsive, with increased heart rate, hyperthermia, generalized rigidity, dilated pupils and hyperreflexia. After 24 h there was deepened unresponsiveness, increased pulmonary distress, decreased BP and continued hyperthermia resistant to any cooling techniques used. Prior to death, there was evidence of rhabdomyolysis and disseminating intravascular coagulopathy (DIC). Autopsy revealed diffuse pulmonary and cerebral edema. These authors compared the death with nine deaths reported after ingestion of another AMPH analogue, *p*-methoxyamphetamine (PMA), where all the patients presented with similar symptoms as were seen with MDA and also died without their conditions ever stabilizing [17].

There are many case reports that describe similar post-mortem and non-fatal clinical courses related to either MDMA and MDE use [7, 14, 16, 62, 128, 154, 155]. The clinical characteristics of mental status changes, restlessness, hyperthermia, hyperreflexia and myoclonus are

reminiscent of serotonin syndrome, defined by Sternbach [150] as a toxic hyperserotonergic state [31]. The dose ingested does not appear to correlate well with the severity of symptoms nor the clinical course. One fatality had a serum MDMA level of 1.26 mg/l, while another patient, whose serum level was 7.0 mg/l, received supportive treatments only and survived [14, 16]. Barrett and Taylor [7] reported on a patient who experienced severe rhabdomyolysis and DIC, yet blood levels of MDMA were only 0.2 mg/l. The number of prior exposures to the drug also does not seem to be a factor in clinical outcome. Coore [26] reported both pancreatic and hepatic necrosis in addition to rhabdomyolysis on postmortem examination of an 18-year-old first-time user of MDMA. MDE was originally thought to be less potent than the other two analogues and thus less likely to produce serious toxicity. However, as the use of MDE increased, more data became available to put this belief in jeopardy. Varying degrees of hepatic necrosis and myocardial damage were recorded in pathology reports from seven young men who died after exposure to MDMA or MDE [100]. Iwersen and Schmoldt [69] reported on two fatalities (one died in hospital of cardiovascular failure and the other died of self-inflicted injuries) directly associated with ingestion of MDE, although alcohol was involved in the case where the individual stabbed himself to death. The blood levels of MDE were 20.2 and 0.22 $\mu\text{g/ml}$, respectively.

Other effects of exposure to these drugs have been documented. Marsh et al. [88] reported two cases of non-fatal aplastic anemia following exposure to MDMA, both of which resolved spontaneously 7–9 weeks after presentation. Although changes in immune systems have not been reported in humans with these drugs, MDMA has been shown to have modulatory effects on a number of immune function parameters in rodents [66, 115]. MDMA use was implicated in a case of subcortical infarction evident within one hour of ingesting two tablets [57]. As the evidence mounted that the most serious acute toxic effects were related to the combination of hyperthermia and dehydration resulting from the use of these drugs in conjunction with extended periods of physical exertion, dance club owners encouraged users to take dance breaks in a cool room and drink water. However, this created a new set of problems from water intoxication and hyponatremia, which also proved to be potentially fatal [65, 89, 161].

It is difficult to collect accurate information regarding the numbers of deaths that can be ascribed directly to the ingestion of these drugs. Dowling [33] in his review of postmortem reports from July 1985 to March 1986 found 16 cases in the USA and Canada where MDMA or MDE were the underlying cause of death or were felt to have contributed to death. White et al. [160] reported 12 MDMA-related deaths in Australia in the past two years, but at least six of these were reported to involve PMA, either alone or in combination with MDMA. There have been 53 reported methylenedioxy analogue-related deaths in Britain [4].

While it is important to recognize that the number of deaths related to these drugs is relatively small when the frequency of use is considered, the lack of apparent relationship between dose and toxicity and the seriousness of the clinical presentation even when the patient survives suggest that these drugs do not deserve the “harmless” label and that educational programs are needed. Users and perhaps dance club owners need to be able to identify early signs of serious toxicity and to seek treatment when any of the signs are observed. The provision of sports drinks instead of plain water and scheduled breaks in the music rather than leaving the responsibility to “cool off” to the individual dancers could also be useful in the prevention of serious heat-related toxic effects.

The recommended treatments for toxic reactions related to the ingestion of MDA, MDMA and MDE are generally supportive, with ventilation assistance, cooling measures, anticonvulsants and fluid replacements. Rehydration is recommended, but the rate of correction must take into account the degree of existing hyponatremia [161]. Management of rhabdomyolysis also entails the restoration of depleted fluids and electrolytes, in addition to the alkalization of the urine and the administration of furosemide [136]. There remains controversy over the use of dantrolene, a drug used in the management of malignant hyperthermia [7, 154]. Watson et al. [159] reviewed six case histories of patients admitted after ingestion of MDA or MDMA and found that dantrolene did not affect the clinical outcome. Other pharmacological agents that have been used as supportive treatments include naloxone, chlorpromazine, haloperidol and chlormethiazole.

2.2. Chronic effects

Unfortunately there are no follow-up data available from the survivors of acute toxicity related to ingestion of any of the methylenedioxy analogues. Thus, potential long-term or permanent disturbances in liver function, thermoregulation or other systems affected by acute ingestion cannot be ruled out at this time. Some attempts have been made to look at long-term neurochemical changes from chronic use of MDMA. McCann et al. [92] examined 58 subjects with prior histories of recreational drug use, 30 of whom were also MDMA users while the other 28 served as controls. After a two-week abstinence from drug use, it was found that MDMA users had lower levels of 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of 5-HT, in CSF. There were no differences between controls and MDMA users in the levels of homovanillic acid (HVA) or 3-methoxy-4-hydroxyphenylglycol (MHPG), metabolites of dopamine (DA) and NE, respectively. Other researchers have not found such changes in 5-HIAA levels [113]. Differences in the subjects with differing degrees of MDMA exposure and differing tastes in other recreational drugs could account for the variability in results. In addition, levels of 5-HIAA have been shown to be affected by diet [29] and psychiatric

disorders, including depression [117]. The studies discussed above were conducted on subjects with prior histories of MDMA use so potential confounds such as diet or depression could not be controlled. Interviews with users yielded no reports of disturbances in such 5-HT related behaviors as sleep, mood or appetite [121].

2.3. Lethality studies

The US Army contracted studies to assess the lethality of a series of AMPH analogues in the 1950s, but it was 20 years later before the results were published by Hardman et al. [58]. Of the compounds tested, MDA was the most potent, especially in dogs and monkeys, with a LD₅₀ (a term that denotes the lethal single dose in 50% of the animals studied) of 6–7 mg/kg when administered by intravenous (iv) injection. In the rat, the LD₅₀ for MDA after intraperitoneal (ip) administration was 27 mg/kg, compared with 49 mg/kg for MDMA and 95 mg/kg for MBDB. Simpson and Rumack [141] reported LD₅₀ values for mice, comparing MDA, AMPH and PMA by various routes of administration. All three compounds were equipotent when administered iv or ip, but MDA was the most potent orally administered compound. Davis et al. [30] found no significant differences between the LD₅₀ values of MDA and MDMA after ip doses in mice. In support of placing MDMA on the Schedule 1 list, these authors pointed out that the LD₅₀ for MDMA was only 10 times the effective dose, while in comparison, for LSD the LD₅₀ was 100 times the effective dose. Non-human primates appear to be more sensitive than rodents to the neurochemical and neurotoxic effects of MDMA [3, 96], but lethality studies have not been conducted. A lack of apparent relationship between blood levels of MDA, MDMA or MDE and fatal dosages makes it difficult to establish a comparable LD₅₀ value in humans.

3. Psychopathology

In addition to the psychological risks inherent in the use of recreational drugs in general, the methylenedioxy analogues have been associated with a number of psychiatric symptoms. Numerous case reports document diverse symptoms arising from a variety of use patterns from a single dose to chronic use of MDMA. The symptoms include paranoid psychosis of varying duration, persistent anxiety, depression and panic disorder [90, 94, 95, 109, 137, 162]. Gouzoulis et al. [49] reported on a case of toxic psychosis in a volunteer after ingestion of MDE (140 mg). More recently, Cohen [20] highlighted the risk of suicide in two individuals who presented with very different histories, symptoms and outcomes. The first individual had a six-year history of MDMA use and complained of persistent depressive episodes with suicidal ideation and significant anxiety. A combination of psychotherapy and lorazepam was found to be the most effective treatment; however, follow-up at six months revealed continued thoughts of

impending doom. The second individual was believed to be a first-time user who became very depressed over a recent breakup with a girlfriend within three hours of ingestion and two days later died from a self-inflicted gunshot wound to the head. Cohen suggested that MDMA's ability to influence 5-HT systems might be acting as a catalyst to create the abnormal pattern(s) of 5-HT neurotransmission believed to underlie many psychopathological disorders, particularly mood disorders.

Some of the patients described in the various case reports had either a family history or personal history of psychiatric problems, suggestive of increased vulnerability. However, other patients had had no previous history, yet developed psychiatric disorders, sometimes requiring ongoing treatment for extended periods. Thus, genetic factors and pre-existing psychopathology may explain some but not all of the vulnerability factors involved in an individual's risk for developing serious psychopathology. Until more information is available, it would seem wise for users to have friends and/or family alert for signs of suicidality in the hours and days following ingestion.

4. Neurotoxicity

It is in the area of potential neurotoxicity in humans that the most controversy exists. There is a large body of literature from animal studies that demonstrates significant long-term neurochemical and morphological changes in 5-HT neurons in response to administration of the methylenedioxy analogues. Careful analysis of the data from the animal literature raises questions about their generalizability to humans and reveals some of the reasons why the controversy continues.

4.1. Criteria for neurotoxicity

Kleven and Seiden [77] summarized four criteria that have been most widely used to establish neurotoxicity of AMPH analogues: (a) long-lasting depletions of 5-HT or DA; (b) a decrease in high affinity uptake sites for 5-HT or DA; (c) decreased activity of synthetic enzymes for 5-HT or DA; and (d) alterations in neuronal morphology. All four of these criteria have been studied in relation to the methylenedioxy analogues in animals, and yet many questions remain. Schmidt [132] was one of the first researchers to publish data on the first two criteria. He demonstrated that a single dose of MDMA (10 mg/kg) in rats produced a biphasic effect, with acute depletion of 5-HT, most prominent at 3–6 h after administration and recovery seen by 24 h, followed by another phase of 5-HT depletion seen one week after drug treatment. The second phase of 5-HT depletion was accompanied by a decreased number of 5-HT uptake sites. The hippocampus and the frontal cortex were the most sensitive regions to the depleting effects of MDMA [134]. Dose-dependent decreases in tryptophan hydroxylase activity (the enzyme involved in the synthesis of 5-HT) have

Table 1
Summary of evidence of neurotoxicity after administration of MDMA

Reference	Species	Dosing regime; total dose of MDMA	Time-frame of measurements	Results in CNS
[108]	Rat	20 mg/kg sc twice daily × 4 d; 160 mg/kg	2 weeks later	Loss of fine 5-HT axons arising from dorsal raphé
[122]	Monkey	2.5–5 mg/kg sc twice daily × 4 d; 20–40 mg/kg	2 weeks later	↓ 5-HT and 5-HIAA, ↓ number and density of cortical 5-HT axons
[130]	Rat	Single dose 40 or 80 mg/kg po, 40 mg/kg po twice daily × 4 d; 320 mg/kg	18 h, 4 months	↑ Density of degenerating fiber terminals in caudate, ↓ number of 5-HT axons in hippocampus at 4 months
[68]	Monkey	2.5 or 10 mg/kg sc, twice daily × 4 d; 20 or 80 mg/kg	Day 2 and day 5; every 2 weeks for 16 weeks	↓ 5-HT and 5-HIAA, ↓ 5-HT uptake sites (only at 10 mg/kg)
[36]	Rat and monkey	Rat: 10 mg/kg ip q2h × 4 doses. Monkey: 5 mg/kg sc twice daily × 4 d; 40 mg/kg	Rat 52 weeks; monkey: 72 weeks	Loss of 5-HT uptake sites followed by altered reinnervation pattern, especially in monkeys
[80]	Rat	20 mg/kg sc twice daily × 4 d; 160 mg/kg	2, 8, 16, 32, 52 weeks	Full and partial recovery of 5-HT uptake sites, regionally specific
[129]	Rat	20 mg/kg sc twice daily × 4 d; 160 mg/kg	2, 8, 16, 32, 52 weeks	Rate and extent of recovery of 5-HT uptake and tissue concentration of 5-HT, regionally specific
[22]	Rat mothers and pups	20 mg/kg twice daily × days 14–17 of gestation; 160 mg/kg	1 week postpartum	↓ 5-HT and 5-HIAA in mothers, not pups
[140]	Human placental 5-HT cell line	0.4–1.2 mM	24 and 48 h	↓ Cell survival, evidence of DNA fragmentation and apoptosis

also been documented after administration of either MDA or MDMA [41, 72, 135, 152]. Using a number of different experimental methodologies, all three methylenedioxy analogues of AMPH have been shown to be capable of producing morphological changes to 5-HT neurons, with characteristic decreases in the number of 5-HT immunoreactive axons in a regionally specific manner, swollen varicosities at the proximal ends of fine and beaded 5-HT axons and fragmentation of the fine axonal fibers [5, 25, 130]. Although most researchers have failed to demonstrate that 5-HT cell bodies are adversely affected by these drugs, recent studies using a human serotonergic cell line showed that MDMA produced a apoptotic response in the cells by inducing DNA fragmentation [140]. O'Callaghan and Miller [107] used astrogliosis (assessed by increased levels of glial fibrillary acidic protein) as a positive index of neuronal damage in mice administered D-MDMA. Table 1 gives a summary of representative studies indicative of neurotoxicity induced by MDMA.

Many other workers in this field have replicated findings that support meeting the criteria to establish neurotoxicity as listed above, using differing doses and dosing schedules to highlight the importance of species, dose, route and frequency of administration to the neurotoxic potential of MDA, MDMA and MDE [8, 21, 25, 76, 84, 120, 151].

However, dose is the most controversial issue in relation to applicability to human users. A typical tablet of MDMA sold on the street contains approximately 100 mg and is taken as a single tablet per episode of drug use. This is the equivalent of 1.4 mg/kg per day for 1–2 days over a weekend. In the rat, the minimum dose that will consistently show long-term effects is 10 mg/kg twice daily for four days (total dose over four days is 80 mg/kg). However, many researchers used 20 mg/kg twice daily for four days (total dose 160 mg/kg) to demonstrate robust effects in the various 5-HT parameters. The equivalent doses in humans would be 1.4 g per day (or 14 tablets) for four consecutive days. However, it must be remembered that the overall metabolic rate in rodents is much higher than in humans and thus much lower doses in humans may produce similar neurochemical effects. Although non-human primates have been shown to be more sensitive to MDMA than rodents, the total dose over a four-day period used to demonstrate long-lasting deficits is typically 20–80 mg/kg [36, 68, 122]. The equivalent dose range in humans would be 1.4–5.6 g (or 14–56 tablets in a four-day period). Even the reported practice of “stacking” MDMA (taking three or more tablets at once) [136] does not come close to the equivalent doses, on a mg/kg basis, used in animal studies.

4.2. Recovery and reinnervation

The degree of recovery and the time required for recovery to occur after administration of these drugs also appear to be dependent on dose, dosing regime, specific biological marker examined, the brain region studied, the species and the specific methylenedioxy analogue. For example, Battaglia et al. [8] found full recovery of the number of cortical 5-HT uptake sites in rats by 12 months, following an initial 90% loss of the sites after MDMA (20 mg/kg twice daily for four days). Ricuarte et al. [124] reported partial recovery of the levels of 5-HT in rats 5 months after a drug treatment regime of 20 mg/kg twice daily for four days, then repeated one week later. In contrast, monkeys examined 14 weeks and 18 months after multiple doses of MDMA continued to exhibit profound loss of 5-HT uptake sites and decreased levels of 5-HT and 5-HIAA in specific brain regions [68, 124]. Molliver et al. [101] examined the time dependency of the degenerative changes and found that 24–48 h after drug treatment, both rats and monkeys treated with MDA exhibited swollen, distorted and fragmented cortical axon terminals as well as swollen proximal axon stumps. These authors proposed four phases of neurotoxicity produced by AMPH analogues such as *p*-chloramphetamine, fenfluramine (FEN), MDA and MDMA: (a) phase 1 involving transmitter release and depletion, which is immediate and reversible; (b) phase 2 involving irreversible axon degeneration seen 24–48 h after drug administration; (c) phase 3 involving regional denervation, which can persist for weeks or months; and (d) phase 4 where there is a slowly progressive regeneration and reinnervation over a year.

Fischer et al. [36] administered MDMA to monkeys and showed alterations in the pattern of reinnervation as assessed by numbers of 5-HT transporter sites 18 months later. In most brain regions, decreases in binding sites persisted, while in the hypothalamus there was evidence of hyperinnervation. Both Lew [80] and Sabol [129] and their colleagues showed dose- and regional-dependency on the rate and degree of recovery from neurotoxic lesioning with MDMA in rats. MDE has been shown to produce similar acute effects as MDA and MDMA, but the second phase of depletion and the loss of 5-HT uptake sites were either significantly attenuated or not apparent [71, 133, 152].

4.3. Implications for humans

Despite the need to use high doses of MDA or MDMA to demonstrate significant and long-lasting neurochemical and morphological changes, it would be foolish to dismiss the animal literature and conclude that these drugs have little neurotoxic risk for users. It is well known that the rate and degree of metabolism of many drugs varies considerably among the various species. In addition, many factors argue against a simple dose–response relationship in the neurotoxic potential in humans. The lack of a dose–

response relationship in the emergence of acute toxic reactions in humans suggests that other factors mediate individual responses to these drugs. An important factor that has been shown to enhance the neurotoxic capacity of MDMA in animal models is the ambient temperature [99], which could have direct implications for dance clubs where most of the use of these drugs is reported. Core temperature is also important in terms of neurotoxic potential, as demonstrated by animal experiments where deficits in 5-HT parameters were blocked by drugs that prevented MDMA-induced hyperthermia [35]. As indicated previously, individuals who had been treated for acute toxicity have not been systematically followed to assess potential longer-term neurotoxic effects. The issue of cumulative risk for neuronal damage in later life from repeated exposure in early adulthood has been discussed by a number of researchers, but there are few controlled studies that have set out to examine this. Some researchers have begun to address cumulative risk by using an escalating dose regime in non-human primates [40]. From the animal data, Ricuarte et al. [125] speculated that these drugs produce 5-HT neuronal death which might not become clinically evident until much later in life, in a similar fashion to Parkinson's disease, where at least 80% of DA-containing neurons must be destroyed before clinical symptomatology emerges. However, in Parkinson's disease there is cell death, whereas it is apparently only the 5-HT axonal fibers farthest away from the dorsal raphé nuclei that are most affected by the methylenedioxy analogues. The mechanisms underlying the apparent lack of effect of these drugs on 5-HT neurons arising from the median raphé are still not understood, nor are the implications of the reinnervation patterns of fine 5-HT fibers from dorsal raphé cells seen after MDMA administration. Most of the fibers arising from the dorsal raphé do not make discrete synaptic connections, but rather they act to modulate the release of other neurotransmitters [5, 34]. This could result in more subtle changes in behavior mediated by a number of other neurotransmitters, rather than those behaviors directly mediated by 5-HT, such as eating, sleep, thermoregulation and mood. In addition, there is increasing recognition that the mature CNS is capable of significant neuronal plasticity. Thus, the long-term outcome of damage to fine 5-HT axonal fibers cannot be accurately predicted.

There is a paucity of published neuroimaging data from animals or humans after acute or chronic administration that might shed some light on the potential for neuroanatomical structural damage from acute ingestion or cumulative effects from prolonged exposure to these drugs. However, some evidence is emerging that the hippocampus and parts of the basal ganglia might be selectively affected. Quantitative deoxyglucose autoradiography conducted weeks after high dose MDMA in rats revealed changes in labeled glucose uptake within the hippocampal pyramidal cell layers CA2 and CA3 [139]. Only one published case report was found that contained magnetic resonance imaging

(MRI) data [147]. This study described a woman who first presented with psychotic symptoms three days after taking one half tablet of MDMA, then went on to develop a specific disorder of episodic memory. The amount and duration of MDMA exposure was unknown and no acute toxic effects were noted at the time of ingestion. Neurological examination was normal as were the results of tests of language function and semantic memory. Brain MRI performed three weeks after onset of memory difficulties revealed bilateral hypertensive lesions of the globus pallidus, which had partially resolved when a second MRI was done two months later (although there was little clinical improvement). There was some suggestion of involvement of basal temporal structures, which include hippocampal regions, on the first MRI. Similar bilateral lesions of the globus pallidus were reported on a computerized axial tomography (CT) scan obtained from a man who was admitted in a comatose state with convulsions and hyperthermia after ingestion of a combination of heroin, MDMA, amphetamine and alcohol [149]. Postmortem histology performed five weeks later on the same male patient confirmed necrosis of the globus pallidus, in addition to extensive gliosis. These authors suggest that the globus pallidus and the hippocampus are rich in 5-HT releasing neurons and that local release of 5-HT produced by MDMA might have led to prolonged vasospasm and necrosis, resulting in the observed lesions and the deficits in memory.

Some researchers have used the clinical experience with FEN as the basis for minimizing the neurotoxic potential of the methylenedioxy analogues in humans [125]. FEN has been shown to be five times more potent at producing the same 5-HT deficits as is seen with MDMA, yet has been used clinically for more than 20 years as an anorexiatic in the treatment of obesity without any reported evidence of neurotoxicity (although there have been recent reports of cardiotoxicity particularly when given in combination with phentermine). However, recent data suggest that there are mechanistic differences in the neurotoxicity produced in animal models following administration of MDMA or FEN [23]. Thus, direct comparisons of relative risk are questionable.

5. Abuse potential

There is mounting epidemiological data that the methylenedioxy analogues of AMPH are being heavily used, which has prompted some researchers to investigate whether the analogues should be considered drugs of abuse. The relative or absolute abuse potential of MDMA, MDA and MDE has not been assessed in humans, but there are a number of studies in animals that would suggest that these drugs have at least moderate abuse potential in humans. Although there is controversy over the definition of “drugs of abuse” and members of this grouping can have

widely differing mechanisms of action, the ability to act as a powerful operant reinforcer and to produce psychomotor stimulation are considered fundamental properties [32]. Common behavioral paradigms used to study drugs of abuse in animals include exploratory locomotor activity, conditioned place preference, drug self-administration, intracranial self-stimulation and drug discrimination [32, 82].

All three analogues are capable of producing increases in locomotor activity, albeit to a lesser degree than the psychomotor stimulants like amphetamine and cocaine [48, 61, 93, 153]. Using a cocaine substitution procedure where stable cocaine self-injections were maintained prior to substitution with MDMA, both Beardsley et al. [9] and Lamb and Griffith [79] demonstrated non-human primates would self-administer MDMA. MDA was also shown to support self-administration in rats trained with cocaine [87]. The use of cocaine as a training drug followed by substitution with one of the methylenedioxy analogues, while a common practice in this type of experimental method, raises questions about the absolute abuse potential. However, this may be a moot point in that it is very rare to find exclusive MDMA, MDA or MDE users [37].

In intracranial self-stimulation studies, electrodes are commonly implanted in the medial forebrain bundle, an area believed to be involved in reward processes and in maintaining drug taking behaviors. Drugs are assessed as to their ability to increase the rate of self-stimulation and to lower the threshold of electrical stimulation required to maintain self-stimulation [81]. Hubner et al. [67] showed that MDMA, but not LSD, lowered the reward threshold in a dose-dependent manner, up to a dose of 2 mg/kg, with behavioral disruption seen at higher doses. Lin et al. [83] compared response rates and frequency threshold for nucleus accumbens self-stimulation among MDMA, D-AMPH and cocaine and found that MDMA decreased both the response rates and the frequency threshold. Methysergide reversed the inhibitory influence of MDMA on response rate but had no effect on the lowered frequency threshold, suggesting 5-HT involvement in the performance but not in the reinforcement-modulating effects of MDMA in this paradigm. Reward systems and related behaviors are considered to be mediated largely by DA [78]. The exact mechanisms involved and the multiple interactions between DA and 5-HT systems have been difficult to delineate and to assign relative importance to in terms of the long-term neurochemical effects. Intact functioning DA and 5-HT systems appear to be fundamentally important to the development of long-term 5-HT system deficits, but the contribution of individual systems and an indication of which are “upstream” or “downstream” of the primary effects(s) of the methylenedioxy analogues remain unclear. Beyond functional integrity, the complexity of the myriad of interactions among the various direct drug effects on neuronal components and among the indirect effects from the release of 5-HT makes it very difficult to assess the relative

contribution of single processes and discrete drug effects to the observed neurotoxic changes.

As mentioned previously, comparisons of the effects of MDA, MDMA and MDE with those of psychomotor stimulants have relied heavily on DD studies. Complete generalization in DD studies is seen amongst the individual methylenedioxyamphetamines [43, 131]. Some, but not all, laboratories have shown substitution with MDMA or MDA in animals trained with D-AMPH [13, 44, 45, 106, 138, 144]. Only MDA has been shown to be capable of substituting for a hallucinogen [43, 44]. However, hallucinogenic activity in general is difficult to study in animals, as hallucinogens produce behavioral disruption rather than activation and any specific behaviors associated with hallucinogens occur infrequently [42].

In summary, the animal data support the idea that MDA, MDMA and MDE share some of the reinforcing properties and ability to increase motor activity with known drugs of abuse like amphetamine and cocaine. Studies conducted in the early to mid-1980s examining patterns of use in university students suggested low abuse potential in that MDMA use was infrequent and not of long duration as the incidence of unwanted effects increased with repeated use [113]. However, the huge wave of current popularity and availability of these drugs has given rise to a number of chronic users who continue to ingest the drugs despite serious unwanted side effects and after-effects, suggesting higher abuse potential than originally considered.

6. Drug–drug interactions

There are a number of broad areas that merit consideration when assessing the potential for interactions between the methylenedioxy analogues and other exogenous or endogenous compounds. As indicated earlier, it is rare to find human subjects that are exclusive users of one of the analogues. Often, users choose a variety of recreational drugs, depending on availability, cost, setting and social group [37]. Thus, it is very difficult to appreciate the long-term implications given the possible interactions of the various drugs with each other used in combination at the same time or if the use of one drug enhances the potential toxicity of other drugs used at a later time. In addition, the purity and potency of single doses can be highly variable, such that assessing the actual cumulative exposure to a given drug is not possible. Users' testimonials should not be considered an accurate source of information to assess long-term or cumulative risk.

The other potential source of interaction between the methylenedioxy analogues and other drugs is at the level of metabolic enzymes. There is evidence that a number of cytochrome P450 (CYP) enzymes, including CYP2D6 and CYP3A4, are involved in the metabolism of MDA, MDMA and MDE [61, 158]. Competition for the same CYP enzymes is a source of many drug–drug interactions,

often having significant clinical implications. Both CYP2D6 and CYP3A4 are involved in the metabolism of multiple psychoactive drugs [116], giving rise to many possible drug–drug interactions when the methylenedioxy analogues are used in conjunction with other recreational drugs or other prescription drugs. The published report of users combining fluoxetine with MDMA [91] is an excellent example of potential metabolic interaction, in that fluoxetine is both a substrate and a potent inhibitor of CYP2D6 [47]. Higher than usual blood levels of MDMA for a longer period of time could result from the combination and increase the risk of acute toxicity and perhaps longer-term sequelae. The effects of combining MDMA and fluoxetine is complicated by another level of interaction. Fluoxetine, a potent 5-HT reuptake inhibitor has been shown to block the MDMA-induced transporter-dependent release of 5-HT in animals and prevent the deficits in 5-HT parameters produced by MDMA [86].

The possibility of various non-fatal degrees of hepatic necrosis associated with ingestion of any of the methylenedioxy analogues could have profound effects on the body's ability to metabolize and excrete the parent compounds and any biologically active metabolites. This could be an important area of potential risk in that there is evidence to support a role of specific metabolites as a mechanism involved in the neurotoxicity of these drugs [15, 24, 64, 110, 141, 148, 163].

Of course, such drug–drug interactions will be influenced by dose, dosing regimen and purity of the MDMA/MDA.

7. Conclusion

The goal of this review was to examine the reported and potential risks involved in the use of the 3,4-methylenedioxy analogues of AMPH in humans. It can be seen that these recreationally used drugs do not deserve the common belief that they are harmless enhancers of the rave dance experience. They constitute a potentially serious risk for acute toxic reactions that cannot be predicted by dose. The acute reactions carry with them significant morbidity and mortality. The neurotoxicity literature using animal models certainly suggests that there is potential for long-term neurochemical and neuroanatomical changes. Perhaps our inability to demonstrate deficits in humans is due to the limitations of our current technologies and assay methodologies applicable to human subjects rather than a lack of effect.

This review also serves to highlight some specific areas of research that require attention. It is imperative that systematic follow-up be done on individuals seen in emergency departments with acute toxicity. Aggregated neuroimaging data along with information about levels of monoamines and their metabolites and hepatic functioning could help to build a stronger body of literature than the current reliance on single case reports. The approval of controlled studies with MDMA in MDMA users will aid in this

direction. Animal studies are required using dosing regimens that follow more closely the pattern of human ingestion. For example, a conservative dose (in keeping with the species-specific factors such as drug sensitivity and rate of metabolism) administered 1–2 times per week on an ongoing basis and examining the animals for evidence of neurotoxicity at regular intervals would provide valuable information about the cumulative effects of the common pattern of human exposure to these drugs. Most of the literature reviewed above described almost a chemical lesioning methodology to reveal the various neurotoxic effects and thus does not address the issue of the relevance of frequency of use as a potential determinant involved in neurotoxicity.

Further information from controlled and follow-up studies in humans and dose-relevant animal studies will allow public health officials and other health care professionals to set up educational programs. Educational materials must accurately set out the risks these drugs represent to adolescents and young adults if they are to be believed. We need to move away from the scare tactics associated with some of the media coverage and provide reasoned information from which individuals can make informed choices about the use of MDA, MDMA and MDE and can recognize warning signs that require immediate medical attention both in themselves and their fellow “ravers”.

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