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ECSTACY: A REVIEW OF MDMA AND MDA

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ABSTRACT

The Drug Enforcement Administration classified the drug methylenedioxymethamphetamine, MDMA, also known as Ecstacy, as a Schedule I controlled substance on July 1, 1985. The controversy surrounding the classification of MDMA is related to the question of its efficacy as an adjunct to psychotherapy and the larger issue of how to regulate the production and use of designer drugs. The authors review the literature on MDMA and its predecessor, MDA, a substance that differs from MDMA by one methyl group.

On July 1, 1985 the Drug Enforcement Administration (DEA) classified methylenedioxymethamphetamine (MDMA) as a Schedule I controlled substance on an emergent basis [1]. This classification has produced new controversy over "designer drugs"; new chemical analogs or variations of existing controlled substances that have psychedelic, stimulant, or depressive effects and high potential for abuse [2].

To understand the DEA decision to classify MDMA, it is also necessary to understand its predecessor, methylenedioxyamphetamine (MDA), a drug that differs from MDMA by one methyl group. This article will review the literature on MDMA and its companion, MDA.

While MDA and MDMA are considered designer drugs, their history indicates otherwise. There are three groups of drugs generally considered to be designer

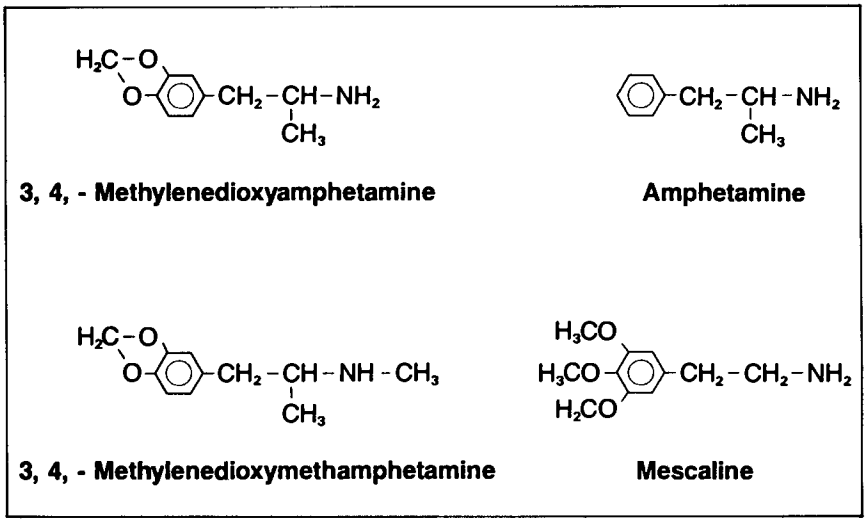

Figure 1. Chemical structures of MDA, MDMA, Mescaline and Amphetamine.

drugs. These are the fentanyl analogs, the meperidine analogs and MDMA. Unlike the fentanyl and meperidine analogs both MDA and MDMA were first synthesized in the early 1900s, prior to the advent of designer drugs. More recently, they have been rediscovered and appropriated by the producers of designer drugs. They are therefore, designer drugs by use rather than by history [3].

The DEA position on MDMA derives largely from the similarity of MDMA to MDA, and the existing literature on MDA. The structural and pharmacologic similarity of MDMA to MDA, and MDA's potential for abuse, constitute the most cogent argument for the emergency classification of MDMA, because there are very little research data on MDMA, itself [4]. Thus, it is necessary to understand the action of MDMA in terms of MDA, but it must be recognized that it is an assumption, rather than a fact, that these are near-identical drugs.

MDA was the drug known as Ecstacy prior to the advent of MDMA. It bears a chemical resemblance to mescaline, is related to saffrole, and is a psychoactive agent in mace and nutmeg [5]. After synthesis in 1910, MDA was noted to have hallucinogenic and stimulant properties and to aggravate Parkinsonism [6]. It was patented as an antitussive in 1956 [7], as an ataractic in 1960 [8] and as an anorexigenic in 1961 [9]. The anorexigenic properties have been subsequently confirmed by an animal study [10]. It was widely abused in the United States between 1960 and 1973, at which time the DEA successfully petitioned for its classification as a Schedule I drug. Though scheduled, it has remained a drug of abuse as indicated by report of its recent abuse in North

Carolina [11] and a DEA report of 1983 detailing sixteen clandestine laboratories manufacturing MDA between 1978 and 1981 [12].

TOXICITY OF MDA

The adverse effects of MDA are evidenced by eight toxicologically confirmed fatalities, resulting from blood levels of at least 100 ug percent, following the ingestion of quantities of MDA up to 1200 mg [13-17]. One fatality resulted from combined secobarbital and MDA ingestion [16]. Another death was accompanied by the clinical stigmata of amphetamine overdosage including disseminated intravascular coagulation, rhabdomyolysis, and acute respiratory distress syndrome, with toxicologic confirmation of MDA as the sole substance of abuse involved [17]. There are also reports of fatal and non-fatal toxic reactions to MDA that do not provide toxicologic confirmation of MDA ingestion [18-20]. Cimbura reports that a number of fatalities have occurred in Canada due to the sale of PMA, para-methoxyamphetamine, as MDA. PMA is approximately three times as potent as MDA and, if mistakenly consumed as MDA, could result in accidental overdosage [21].

A number of investigators have studied MDA toxicity in animals [22-28]. These studies suggest that toxicity is dependent upon dosage, route of administration, time of observation, and enantiomeric composition of the compound. Further, these animal studies suggest that protection against the toxic effects of MDA is afforded by phenobarbital, phentolamine, 6-hydroxydopamine, methylsergide, and possibly haloperidol, but not propranolol. This suggests that the toxicity of MDA is mediated by the alpha-adrenergic, dopaminergic, and serotoninergic but not beta-adrenergic systems. Additionally, the toxicity of the R(−) MDA enantiomer is at least partially mediated by conversion to alpha-methyldopamine [26]. A recent study using rats suggest that toxic doses of MDA cause degeneration of CNA serotoninergic neurons, loss of CNS serotonin receptors and decrease in serotonin and 5-HIAA levels [29]. These adverse effects on the serotoninergic system were already known for amphetamines [30].

In animal studies, MDA fatality has some of the characteristics of amphetamine toxicity, including a triphasic lethality curve and increased mortality with aggregate as opposed to individual housing [31-33]. These data coincide with the clinical fatality report by Simpson who noted amphetamine-like toxicity with MDA overdose [17].

Shulgin and Paton have suggested that it is conceptually possible for "MDA toxicity" to be confused with the toxicity resulting from the 3-aminobutane homolog of MDA. This homolog results when MDA synthesis is attempted from the free-radical form of piperonylacetone [34]. The concern of Shulgin and Paton was tested by Davis and Borne who found that the 3-aminobutane homolog had toxicity equal to MDA [35]. However, the toxicity of the homolog

was not blocked by phentolamine alone, but was blocked by phenobarbital, suggesting that this compound's mechanism of toxicity may differ from that of MDA.

The physical and behavioral toxic manifestations of MDA include: anergia, hypertension, tachycardia, mydriasis, dry mouth, increased muscular tension of the neck and jaw, bruxism, rigidity, seizures, diaphoresis, hyperthermia, panic, paranoid psychosis, exhaustion, coma, disseminated intravascular coagulation, rhabdomyolysis, acute respiratory distress syndrome, paresthesias of the extremities, insomnia, brief visual hallucinations, and diminished concentration [11, 13, 17, 18, 20, 36].

MECHANISMS OF ACTION

The effect of MDA on neurotransmitters has been assessed in a number of animal studies. These have demonstrated that MDA and its metabolites are releasers of norepinephrine and blockers of norepinephrine reuptake, similar to amphetamine, and these reports are substantiated by studies showing that various toxic effects of MDA can be blocked by cocaine, phentolamine, bretylium or 6-hydroxydopamine pretreatment [23, 24, 37-41]. Only one researcher failed to substantiate the protective effects of phentolamine against MDA toxicity and these results are probably explained by the use of an inadequate dose of phentolamine relative to MDA [24]. The noradrenergic action of MDA is most likely a product of its S(+) enantiomer and not its R(−) enantiomer [37, 41].

Dopamine may also be involved in MDA-induced effects, as haloperidol can prevent the hyperthermic effects of MDA [25]. About 2 percent of tritium labeled MDA is excreted as dopamine in mice [42]. However, since the formation of dopamine from MDA occurs by a demethylation process in the liver, it seems unlikely to account for the CNS effects of MDA [43].

Serotonin has also been implicated in MDA's action. MDA has affinity for the rat 5-HT receptor [42, 44]. At 1 micromolar concentrations, MDA is a potent releaser of 5-HT and methysergide significantly diminishes MDA mortality in mice [23, 45]. The serotoninergic effects of MDA may be specific to the R(−) enantiomer [44].

EEG studies on cats suggested predominately mescaline-like effects [46]. This is consistent with behavioral studies and clinical reports suggesting hallucinogenic properties for MDA. Behavioral studies suggest that the mescaline-like effects of MDA may be mediated specifically via 5-HT receptors [47]. MDA is also an MAOI [48], but the significance of this action of MDA is unclear.

BEHAVIORAL STUDIES OF MDA

A racemic MDA stimulus generalizes behaviorally to both CNS stimulant and hallucinogenic drugs. The hallucinogenic effects appear to reside in the R(−) enantiomer [49, 50] and result from serotoninergic actions [43, 44, 51-53].

The stimulant effects are probably specific to the S(+) enantiomer of MDA and may be mediated partially by the dopaminergic systems [25, 50, 52]. One study has failed to find MDA behavioral generalization to amphetamine, but this is likely due to the behavioral paradigm and the dosing schedule used [54]. Griffith has reported that MDA maintains self-infusion in monkeys at doses of 1-5mg/kg, which suggests the potential for psychological dependence to MDA [55].

MDA-TOXICOLOGY

Methods for the toxicologic identification of MDA exist. A thin layer chromatography (TLC) method using fluorescamine overspraying to identify phenylethylamine derivatives and subsequent gallic acid overspray to diminish MDA from MDMA at detection limits of 1 microgram has been reported [56]. A gas chromatography mass spectroscopy (GC/MS) assay to detect the 3,4-methylenedioxybenzylketone and 3,4-methylenedioxybenzylmethylketoxime derivatives of MDA has also been reported [57, 58]. DeMayo *et al.* have reported a colorometric test for MDA utilizing direct UV visualization [59].

BEHAVIORAL EFFECTS IN HUMANS

If MDA had only adverse effects it would not be a drug of abuse. In those who take the drug for its "positive" effects, typically at a dose of 100-200 mg, anecdotal reports describe a "warm glow," increased aesthetic sense, increased insight, heightened self-awareness, increased spirituality and sense of "oneness," diminished anxiety and defensiveness, increased desire for interpersonal contact, increased sense of well-being, and heightened tactile sensation [11, 36, 60]. Turek and colleagues conducted an open nonblind prospective study of MDA on volunteers. Following a 75 mg dose no significant change in vital signs was noted. A transient decrease in performance on the Digit Symbol Substitution test was found, but neither hallucinations nor change on the digit span subtest were noted [61]. However, 75 mg is a modest dose and not likely to be representative of effects found at the more substantial doses typical for MDA abusers.

MDA PSYCHOTHERAPY STUDIES

MDA has been used as an adjunct in psychotherapy in one patient who presented with depressive symptoms [62]. The patient was treated for six months using MDA three times at maximum doses of 120 mg/session. The depression was reportedly alleviated and exploration of personal and transpersonal unconsciousness accomplished. The author suggests that MDA may have "extreme significance for the field of psychotherapy and for the understanding of the

human personality." An open trial of MDA-assisted psychotherapy in eight volunteers has also been reported [60]. A 40 mg dose was used initially and thereafter 100 mg/session was utilized. It was concluded that "this compound may be of value in the facilitation of psychotherapy by virtue of its ability to enhance access to feelings and emotions without the distractions of sensory distortion." Yensen *et al.* reported an open trial of MDA assisted psychotherapy in ten neurotic patients using R(−) MDA [63]. MDA was used two to four times per patient over two to six months at initial doses of 75 mg and subsequent doses of up to 200 mg per session. No serious adverse consequences were reported but the drug became more LSD-like as doses increased. Yensen concluded that "MDA appears to be a useful adjunct to psychotherapy."

MDMA

MDMA was first synthesized by Merck in 1914 as an appetite suppressant, but was never marketed. As a street drug it is known as ADAM, XTC, MDM, and Ecstacy. Its formal chemical name is N,alpha-dimethyl-1,3-benzodioxole-t-ethanamine [64].

EPIDEMIOLOGY

Published epidemiologic data for MDMA are largely anecdotal. MDMA was reportedly popular among college students, specifically at SMU, a campus which has a ban on liquor [65]. The DEA has also reported encountering MDMA at its Dallas office in 50 mg tablets and has implicated MDMA in two deaths, 344 ER visits, and citation in twenty-two medical examiner reports [4, 66]. However, subsequently it has been stated that one of the deaths was actually due to the combined ingestion of MDA and alcohol. Also, MDMA was not toxicologically confirmed in the second death [64]. The DEA also cites paranoid episodes caused by MDMA intoxication. Unfortunately, no toxicologic confirmation of MDMA as the etiologic agent is offered in the DEA cases cited. Such confirmation is crucial as the actual content of street drugs may have little relation to the stated content [67]. Washton has reported psychosis requiring hospitalization in a patient who had abused MDMA for two years. However, no laboratory confirmation of MDMA abuse was offered [68]. Pharm Chem Lab has reported that only 27 percent of the MDMA submitted to them for analysis actually contained MDMA. The New York police lab has reportedly "rarely seen MDMA" and the San Francisco police lab saw five samples of MDMA in 1985 [68].

BEHAVIORAL EFFECTS OF MDMA IN HUMANS

MDMA's reputed popularity derives from effects such as positive mood changes, enhanced communication and intimacy, improved interpersonal relationships, increased self-esteem and elevated mood attributed to its usage.

One nonblind, uncontrolled study has found positive changes in mood, attitude, beliefs, relationships, occupation, spiritual-physical condition, and a transient decrease in substance abuse following MDMA-assisted therapy sessions. These effects followed doses of 150-225 mg [69].

However, MDMA ingestion has also been reported to cause tachycardia, an occasional "wired" feeling, jaw clenching, nystagmus, a nervous desire to be in motion, transient anorexia, panic attacks, nausea and vomiting, ataxia, urinary urgency, diplopia, insomnia, tremors, inhibition of ejaculation, and rarely, transient hallucinations [65, 69].

The evidence regarding MDMA's addictive potential is also scarce. MDA's ability to maintain self-infusion [55] is cited by DEA as evidence of MDMA's addictive potential, but no self infusion studies utilizing MDMA itself have been located by the authors.

MECHANISM OF ACTION

Preclinical research on MDMA is also scant. Glennon has reported that DOM, the hallucinogen which generalizes to MDA, does not generalize to MDMA suggesting that MDMA may not possess significant hallucinogenic properties [49]. However, the S(+) isomer of MDMA is a potent releaser of 5-HT in a whole rat brain synaptosome model, and, in a rabbit hyperthermia model for assessing psychotomimetic properties, S(+) MDMA was more potent than R(−) MDMA [45, 50]. Thus, the active S(+) isomer of MDMA is a 5-HT releaser, an action attributed to psychotomimetics, which suggests the potential of MDMA having psychotomimetic activity. Since the S(+) MDMA isomer has more potency in the rabbit hyperthermia model than the R(−) isomer, the opposite of MDA's isomeric activity, it is theoretically unlikely that MDMA's mechanism of action is via demethylation to MDA. However, no studies of MDMA metabolism have been located and demethylation, the process by which MDMA would be converted to MDA, is not an uncommon metabolic event. Amphetamine has been shown to generalize to MDMA, suggesting that MDMA does have stimulant properties [52]. MDMA was found to be two-thirds to three-and-a-half times less toxic than MDA and two to six times more toxic than mescaline as assessed by LD50 in various animals. Using the LD50 model, MDMA was less toxic than MDA in animals housed individually, but more toxic than MDA if animals were housed in aggregate fashion [70]. Thus housing conditions may have an impact on toxicity. Additional studies assessing route of administration, time of observation, and enantiomeric composition on toxicity are needed.

MDMA versus MDA

While MDMA has been assumed to be virtually identical to MDA in its action and thus in its toxicity, existent data suggests potential differences [64]. Clinical relief from adverse effects of MDMA with propranolol has been reported, whereas,

B-blockers have been reported ineffective in treating adverse effects of MDA [17, 69]. However, efficacy of propranolol for MDMA toxicity and lack of similar effectiveness for MDA could be a dosage artifact [25]. In the rabbit hyperthermia model for assessing psychotomimetic potential of a drug, the R(−) isomer was the active MDA isomer, whereas for MDMA the S(+) isomer was the most active. The studies of Nichols *et al.* suggest that R(−) phenethylamines and LSD bind to a common CNS receptor to induce psychotomimetic effects and this model would not predict hallucinogenic properties for an S(+) substituted phenylethylamine molecule [71, 72]. Thus, MDMA may have a different hallucinogenic mechanism of action than MDA or have a relative lack of psychotomimetic activity and in either case would be dissimilar to MDA. Dimethoxymethamphetamine, an hallucinogen, generalizes to MDA but not to MDMA suggesting at least a difference in hallucinogenic potency or a relative lack of hallucinogenic action for MDMA, in contrast with MDA [43].

DESIGNER DRUGS

The MDMA controversy is largely one of how to regulate the production and use of designer drugs. The DEA has exercised the only means of control at its disposal, emergency drug classification. Given the state of knowledge regarding the phenylethylamine designer drugs, this is the only approach possible. However, we suggest that this approach is likely to be cumbersome if "designer drugs" continue in vogue, as seems likely [73]. Simple modifications of MDA such as N-hydroxylation results in a psychoactive molecule which is not currently a Scheduled drug [72]. Similarly, 2,5-methylenedioxyamphetamine is theoretically likely to be a psychoactive drug, perhaps more psychotomimetic than MDA, yet not a controlled drug [44]. The work of Nichols' group suggests that any substituted phenylethylamine compound that is free of steric bulk on one side of the molecule at the C2 locus on the dioxole ring is likely to possess sympathomimetic properties [74].

General "classes" of compounds may require regulation to avoid the formidable task of individual classification of vast numbers of drugs. Further, seeking regulation of each new compound as it emerges from underground laboratories puts the consumers of these new drugs at increased risk as they become the subjects to test the safety of each new drug [73, 75]. Unexpected reactions in the synthetic process, the representation of one drug as another, or indiscriminate mixing of various drugs by dealer or consumer may result in increased morbidity and mortality to the consumer of the drug [21, 34, 76]. Other methods of bringing the designer drugs under control might include seeking classification of parent compounds or regulating the materials needed to synthesize various classes of drugs. Alternatively, a compendium of licit compounds might be formulated, and possession, synthesis, or consumption of compounds not listed would be illegal except at registered laboratories or

through prescription. Simultaneously or alternatively, the legal-economic cost to the consumer or possessor of the drugs might be increased to deter consumption.

Ultimately, additional research assessing mechanisms of action, metabolism, addiction potential and toxicity are needed to better understand the risks and benefits of these drugs and more intelligently guide their regulation. Further, if MDMA can enhance psychotherapy, careful research is required to demonstrate both its efficacy and safe dosing regimens.

CONCLUSION

Little is known about MDMA. Available data suggests that MDA and MDMA may differ significantly and leaves the question of efficacy for MDMA as an adjunct to psychotherapy unanswerable at this time. The controversy surrounding MDMA is part of the broader issue of how to regulate designer drugs and whether any of these drugs have medical-psychiatric utility. We suggest that the regulation of these drugs, the determination of their clinical utility, and clear understanding of their risks would be best served by further research as these are complex substances which appear to have multiple modes of action. Meanwhile, the regulation of these substances will need to occur on an individual basis until a more effective means of regulation can be implemented.

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