MDMA in Psychiatry: A Review of Preliminary Findings

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MDMA: A Review

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Abstract:

MDMA (methylenedioxymethamphetamine) is a psychoactive phenylisopropylamine with some features in common with both the amphetamines and the classic psychedelic drugs, but cannot be effectively placed within either category. Uncontrolle clinical studies demonstrate that the compound increases affectivity, enhances communication, and decreases abuse of addictive substances, without perceptual changes, disorientation or ego-disruption. Abuse, dependance, and adverse reactic have not been reported in the scientific literature. Restrictive legislation currently being proposed would prevent much-needed controlled clinical studies of the optimal use of MDMA in psychiatry.

INTRODUCTION

Methylene dioxymethamphetamine (MDMA) is an N-methyl derivative of methylenedioxyphenylisopropylamine (MDA). They are both synthesized from compounds related to safrol, an aromatic compound found in high concentrations in nutmeg (Stafford, 1983). MDMA was first synthesized by Merck, in Germany, in the early part of this century (Anon, 1914).

MDMA was first investigated as a potential psychotoxic compound by the Army, in the middle 1950's. Like mescaline, one of the most psychoactive compounds in peyote cactus, MDMA is a phenylisopropylamine, and as such, was considered a "mescaline analog" (Hardman et al, 1973). By implication, then, MDMA was considered among the so-called "psychedelic" drugs.

TERMINOLOGY

There is significant liability involved in labeling MDMA as a true psychedelic compound. Perhaps it may be of some use, then, to diverge here, in order to address this particular issue of nomenclature before proceeding much further in this paper.

"Psychedelic" is a term that has been associated primarily with the "LSD-like" compounds, as described by Martin and Sloane (1971). They can be distinguished from other centrally-acting drugs that can also under certain conditions, induce perceptual distortions (e.g. anticholinergic compounds such as atropine), paranoid and other delusions (e.g. as in chronic, high-dose amphetamine administration), and other alterations of cognition, behavior and affect (e.g. bromides and opiates). They are capable of, when pathological effects are

absent or minimal, "reliably inducing or compelling states of altered perception, thought and feeling that are not (or cannot be) experienced otherwise, except in dreams or at times of religious exhaltation" (Jaffe, 1980, pp. 563-564). Psychedelic compounds include the indolealkylamines (lysergic acid diethylamide--LSD, diethyltryptamine--DET, dimethyltryptamine--DMT, and psilocybin and psilocin--in the psilocybian mushrooms), and some of the phenylisopropylamines (Mescaline, DOM, DOET). "Psychedelic," however, as much as describing particular psychological effects elicited by these drugs, also has partaken of an association with the subculture out of which their use emerged in the 1960's. Osmond defined psychedelic as "mind-manifesting," (Grinspoon and Bakalar, 1979, p. 8), a purposefully vague term, and at the time, the most value-free. Others, however, struck by these drugs' primarily perceptual effects, labelled them "hallucinogenic" or "illusogenic." "Psychotomimetic" or "psychotogenic" are other terms used by investigators attempting to relate drug-induced states to functional psychotic illness, an attempt that has consistently been unsuccessful (Strassman, 1984).

MDMA does not appear to be a true psychedelic compound, by virtue, primarily, of the psychological effects ascribed to its use in humans, as will be detailed later in this paper. Therefore, labeling MDMA as a psychedelic obscures the relevant issues that need be addressed in determining abuse and use potential for this compound.

PHARMACOLOGY

Nervous tissue studies of MDMA are at the most rudimentary stage Only one paper has been published regarding this issue, by Nichols, et al (1982). This group found that MDMA was a potent releaser of serotonin from rat whole brain synaptosomes. The relevance of this finding is unknown. The psychedelic drugs (e.g. LSD) have generally been found to inhibit serotonergic cell-firing via either pre- (Mace, 1979) or post- (Jacobs, 1983) synaptic mechanisms. Amphetamines, on the other hand, primarily release dopamine and norepinephrine from synaptic regions (Moore, 1977).

BEHAVIORAL EFFECTS IN ANIMALS

MDMA has been studied somewhat more from a behavioral pharmacologic point of view, but still, this work can only be described as preliminary.

It is important to keep in mind some caveats regarding behavioral studies of psychoactive compounds in animals. LSD was found to be nonspecifically active in animal models run by Sandoz Laboratories (Hofmann, 1983), and was initially abandoned as not having any noteworthy effects. This would indicate that the most appropriate manner of understanding clinical effects of drugs in man, especially psychological effects, is in man. Further evidence for this is in Hardman's report (Hardman, et al, 1973), wherein massive doses of mescaline in monkeys produced no "hallucinogenic behavior." Mescaline is clearly a psychedelic compound in man. MDMA, on the other hand, produced "hallucinogenic behavior" in monkeys, in contradistinction to its clinically described effects, wherein no hallucinations are experienced.

Glennon, et al (1982) have attempted to demonstrate that the "discriminative properties" paradigm is an effective way of predicting "psychedelic" effects of compounds. In this model, animals are starved to 80% of their body weight, trained to press a bar for food in association with a psychedelic drug (in this case, DOM), and then studied to see what other drugs will elicit bar-pressing at the same rate as DOM (compared to saline placebo). MDMA was not found "psychedelic" in this paradigm. In a later paper (Glennon and Young, 1984), this group describes generalization of MDMA to MDA, although their statistical handling of the data is not described. MDMA was also found to generalize to amphetamine. The significance of these findings is unclear, although the authors speculate that N-methylation of MDA (to MDMA) decreases its "hallucinogenic" (i.e. generalizability to DOM) properties, while making it more similar to amphetamines (i.e. generalizing to amphetamine).

Even Glennon, however, with Nichols, sum up this research with the following comment: "It is unlikely that any non-human model will be developed which can reliably predict (psychedelic) properties in advance (of human research). This is simply due to the large number of possible component processes involved...." (Nichols and Glennon, 1983, p. 100). Shulgin and Nichols also remark concerning the difficulty in generalizing from animal behavioral studies to clinical findings: "The need for animal toxicology and metabolic information is not less than it has ever been, but it must be remembered that the ultimate purpose of research in this area is to alleviate human illness and provide for human needs." (Shulgin and Nichols, 1974, p. 80).

Another important point to distinguish is that between toxic and non-toxic effects. Massive doses of any compound can be toxic--i.e. cause death in high enough doses. The ability to demonstrate toxic effects of a drug does not make it only a "toxic" drug, however. For example, digoxin, the aminoglycoside antibiotics and lithium carbona- are all quite toxic at high doses, but therapeutic ranges have been established and utilized in clinical medicine with great success. Th major stumbling block in distinguishing toxic effects from pharmacologic effects in animals with regard to psychoactive chemical is the inability to measure an animal's subjective state. DOM and MD/ may generalize to each other, but this may be due to a multitude of properties which the two drugs may share (for example, the ability to increase heart rate or blood pressure, rather than subjective effects). In other words, they may not be generalizing to anything that has to do with psychological effects. The clearest example of the difficulty in generalizing animal models to human ones regarding psychoactive drugs is, perhaps inadvertantly, made by Hardman in his toxicity paper on mescaline and its analogs: "There may be some advantages to using dogs for screening substances for psychotomimetic activity. Most investigators have more experience in recognizing normal and abnormal behavior in dogs than in monkeys. The monkey frequently exhibits stoic behavior in response to stress, and he may successfully conceal his anxiety and altered perceptions" (Hardman, et al, 1973, p. 306 italics mine). It is difficult to impugn psychodynamic motives to animal behavior, let alone "psychedelic effects" in them.

HUMAN PHARMACOLOGY

The human pharmacology of MDMA has not been addressed in the published scientific literature. However, Downing[2], in an unpublished manuscript, describes the following experiment and physiological effects of MDMA: He describes the effects of MDMA (0.8-1.9 mg/pound), given orally, to 21 experienced MDMA users, as well as their responses on a screening questionnaire. All subjects were free of significant medical and/or psychiatric disturbances. Ages ranged from 20 to 58 years (with an average of 31), with educational experience being, on the average, four years of college. There were 13 men and 8 women. During the drug administration part of the study, various physical parameters were monitored. Cardiovascular responses including an increase in systolic and diastolic blood pressure, and an increase in heart rate, usually occurred with maximal levels attained within 30-60 minutes. No subjective symptoms were noted in this regard. Blood pressure was less than pre-drug values within six hours, and often was less than pre-drug values 24 hours after drug exposure. No hypotensive reactions or complaints were noted. No effects of MDMA on blood chemistry were noted.

All subjects showed pupil dilatation with preserved light reflexes. Eight of twenty-one had nystagmus, with most cases resolving within four hours. Two had equivocal nystagmoid movements at 24 hours. Six subjects had jaw-clenching, and four of these cases were resolved by four hours. One had mild persistence of this symptom at 24 hours. Deep tendon reflexes were enhanced in 8 subjects--all cases resolved within four hours. Gait disturbance and incoordination was noted in about one-half of the subjects. All reported increased

sensual awareness; one had nausea and vomiting at three hours; none showed any abnormalities of urinary or defecatory functions; no headaches were noted; appetite was suppressed in all for the day.

SUBJECTIVE EFFECTS

Subjective effects in humans have been described in a small number of publications, many of which are not generally available. Kueny[3], in a work written while a student at the Pacific School of Graduate Psychology, describes an increase in openness of communication and non-defensiveness in all nine subjects. Subjects were not psychiatrically ill, and all experienced the effect of the drug in positive ways. No hallucinatory, delusional or disorienting effects were noted. No physical side effects were described. No distortions of sense of self were experienced. All the above-mentioned reactions (which were absent) are typically seen in many "psychedelic" experiences. No adverse reactions were noted acutely or after long-term follow-up.

Greer[4], in the most extensive clinical study to date on MDMA, used 75-150 milligrams in 29 subjects recruited from without his psychiatric practice. Subjects were carefully screened for physical and severe psychiatric problems.

Subjects felt more in touch with their emotional life, and those of others; enhanced communication, positively enhanced attitudes and feelings, and non-defensiveness were experienced by 27/29 subjects. No significant adverse physical effects were noted. The lack of classic psychedelic effects (hallucinations, perceptual distortions, disorientation, delusional material, fragmentation of the sense of

self) were again noticeably absent. Follow-up demonstrated improvement in all subjects with diagnosable (DSM-III) psychiatric disorders.

Downing's study revealed that psychologically, no subjects had impaired consciousness. Most reported feelings of euphoria and increased energy. There was no post-session depression, as can occur with high-dose amphetamine experiences. There was no confusion, nor auditory or visual hallucinations. Twenty-four hours after drug exposure, significant, though milder, mood elevation persisted.

Other reports of subjective effects are essentially anectdotal and are consistent with Shulgin's general remark that MDMA appears to evoke "an easily controlled altered state of consciousness with emotional and sensual overtones...Psychological sequelae are virtually non-existent." (Shulgin, 1978, p. 292).

THERAPEUTIC USES

No published reports in the psychiatric literature address the use of MDMA in acutely psychiatrically ill individuals. However, Greer's, Downing's and Kueny's work document generally positive effects, after drug sessions, in a number of intrapsychic and interpersonal areas. These include increased energy and mood after drug use, decreased anxiety and tension, positive changes in attitude and self-image, improved interpersonal relationships at work and/or with loved ones, improved work efficiency and job satisfaction, increased creative and/or therapeutic activities, decreased substance use (including cigarettes, alcohol, marijuana, and cocaine), increased committment to life goals, and more directness in seeking desired activities and avoiding undesired ones.

Based on his extensive experience with MDMA, Greer believes this compound to be most helpful as a facilitator of communication betweer emotionally-involved people (e.g. couples, psychotherapist and patient). He also states that based on the fact that half of his subjects decreased their addictive-substance use, that MDMA may have therapeutic use in this regard as well.

ADVERSE REACTIONS

Reports of adverse reactions to psychoactive drugs are very difficult to evaluate from most of the salient psychiatric literature. In a recent review of research on the adverse reactions to the psychedelic drugs, it was demonstrated that even in the case of LSD, medically-sanctioned studies, using carefully administered doses and purity of drugs, with well-screened and followed-up subjects (both patients and controls), demonstrated a remarkable lack of adverse reactions (Strassman, 1984). Of significance is the fact that scheduling LSD and other psychedelics as Schedule I drugs drove all work with these compounds underground, did nothing to decrease the use of these drugs (in fact, may have increased the romantic allure of using them), and eliminated any bonafide psychiatric research with these substances. In other words, decreased therapeutic work was being done in the area, with increased black market use.

There are remarks concerning the incidence of adverse effects of MDMA in Greer's report. One of the 29 subjects experienced significant post-session psychological difficulties, of an identical nature to what he had been troubled with years before, prompting Gree. to speculate that there is an indication that "MDMA may predispose people to a recurrence of previous psychological disabilities"[4]

(p. 11). This subject re-entered psychotherapy and, in retrospect, stated: "It probably was a good thing. It speeded up processes that needed to happen"[4] (p. 4). Similar complaints are heard everyday by therapists working with subjects who find facing their problems temporarily painful and anxiety-provoking, in non-drug-facilitated psychotherapy.

All subjects in Greer's study reported mild difficulties during or after the sessions, either of a physical or emotional nature. All but one (previously mentioned) lasted less than a week, except for one case where the subject increased his weight by fifteen pounds over a few weeks. Twenty-two of twenty-nine subjects experienced jaw-clenching acutely, (probably related to the drug's sympathomimetic effects). No psychosis, serious depression, or suicide attempts occurred.

Management of all subjects with acute undesirable emotional effects was successful, using, at most, minimal psychological support, and they often resolved spontaneously. Oral benzodiazepines and/or propanalol decreased jaw clenching and other sympathomimetic effects.

In Downing's report, some short-term attention deficits were noted during the peak of the drug experience. Judgement was described as impaired based on what appeared to be idiosyncratic answers to hypothetical problems at one and two hours. The specifics of these impaired responses, however, are not given. Downing summarized these findings by stating that nystagmus and gait and coordination disturbances during most of the (approximately) four-hour session would indicate that tasks requiring hand-eye coordination (e.g. driving, operation of potentially dangerous machinary) should be avoided for the duration of the acute exposure, and perhaps for the

better part of the experimental day. Increases in blood pressure and heart rate would speak against using this compound in individuals whose medical conditions would be excacerbated by such changes (e.g. ischemic heart disease, hypertensive cardio-vascular disease, a history of cerebrovascular accidents, etc.). No "flash-back-" like phenomena have been reported with MDMA, whereas, in the case of classic psychedelic compounds, 15-77% of individuals who have taken LSD report some flashbacks (i.e. transient re-experiencing of the subjective experience of the drug-induced state) (Strassman, 1984).

ABUSE POTENTIAL

There are no reports in the literature of MDMA abuse, dependence, withdrawal or overdose. Several authors have described tolerance to the psychological effects of repeated MDMA use[4,5] (i.e. more undesirable effects and less desirable ones with increased use). The emotional intensity of the MDMA experience also appears to dissuade repetitive use. No authors have seen cases of MDMA dependence, although it is clear that some abuse potential exists, as in the case of all potentially pleasurable experiences.

Downing reported the results of his screening questionaire and also documented lack of MDMA abuse or dependence: Average duration of MDMA use was 2.3 years, with subjects having taken the drug between 1 and 15 times in the past. Frequency of use ranged from every month to every seven months. Almost all used other "recreational" drugs, including alcohol, marijuana, and cocaine. "Mental defects" experiences during reported prior MDMA use were described as minimal and difficult to interpret. Downing, therefore, concluded that MDMA

appeared to be used sparingly by his subjects, and was not associated with craving, dependency, over-use or adverse reactions, based on self-report in his screening questionnaires.

There is an increase in government and media reported use of "MDMA" among the population. As was the case with LSD, the authenticity of the drugs, its dose and adulterants, is rarely, if ever, known. Shulgin's recent publications document the ease with which adulteration can occur (Shulgin and Jacob, 1982a, b). Besides the obvious problem of documenting actual MDMA use, the relationship between drug use and psychological symptoms, as described in the case of the much more powerful and qualitatively different drug, LSD, is very difficult to make without "pre-morbid" data on character, psychopathology, and other drug/alcohol use, etc. (See Strassman, 1984, for a more detailed description of a suggested set of criteria for evaluating the "adverse reaction" literature).

SUMMARY AND RECOMMENDATIONS

For a summary of what appear to be the most salient similarities and differences between MDMA and the "classic" psychedelic drugs, Table I may be of some help.

(Insert Table I here)

It appears that MDMA has psychological effects in man. These have generally been described as cognitive and emotional, and are quite different than those of the "classic" psychedelic drugs. Carefully supervised clinical work with this compound demonstrates no abuse potential and minimal difficulties with adverse reactions. Psychotherapeutic use of this drug appears as its major role in medicine, although data from uncontrolled studies is limited. Abuse,

dependence, severe toxicity, and adverse reactions in the general public have not been reported in the literature. When it does, as it is bound to be, the critical reviewer should ask about identity of drug, setting in which it was taken, previous psychiatric, legal, and substance abuse history, and the temporal relationship between drug use and symptoms.

Animal data has not been particularly helpful with regard to "abuse potential" or "psychologic" effects of MDMA. Animal data has documented that MDMA can have toxic effects at high doses (as can most compounds). It appears to have some effects in common with MDA and amphetamine in animals, but what these similarities actually are cannot be determined, especially with regard to the question of psychological/subjective effects.

The available scientific evidence does not support the contention that MDMA has high abuse potential. Available scientific evidence provides some support for the drug being a promising adjunct to individual and conjoint psychotherapy and in the treatment of substance abuse. Areas of future research should include investigation of lower dose MDMA as a possible antidepressant (as is hinted at by its serotonergic effects in animals), and the use of this compound as an adjunct to the dying process in terminally ill patients. Its lack of disorienting effects, shorter duration of action, and capacity to allow communication to continue between concerned parties, bespeak a possibly greater psychotherapeutic effect than the "LSD-like" compounds. The use of MDMA as an adjunct to meditative practice, as suggested by Hofmann (1983) also could provide interesting information.

As in the case of the more powerful and disruptive psychedelic compounds, clinical wisdom would probably exclude certain individuals from exposure to MDMA, unless they were institutionalized at the time and could be carefully supervised for several days after drug administration and/or resolution of acute adverse sequelae. These would be individuals with overt, or a history of, severe mental illness, primitive character structure, and chronic polydrug abusers. Individuals with a family history of severe psychiatric disorder could be screened with currently available biological "trait" markers, and should be given special consideration (Strassman, 1984).

Heuristically speaking, the continued development of psychoactive compounds with unique subjective effects holds great promise for increasing an understanding of the biology of consciousness.

What, then, to call MDMA? I do not know. But its continued investigation should provide data sufficient to appropriately classify it. Based on its subjective effects (see below), a term like "feeling-enhancer," "empathy-catalyst," or "introspection/insight aid," all may capture part of the experience brought on by this drug. Nichols[6], for example, has suggested the term "entactogen," meaning "to cause a touching within."

The fact that MDMA is apparently becoming an increasingly popular street drug does not define it as a dangerous and useless drug, per se. It does imply that people continue seeking drug-induced experiences. What these people are seeking and what it is they are experiencing is of enormous public health consequence. These issues bespeak the need for research in the area, not the abandonment of

study that scheduling MDMA as a Schedule I or II substance (as is currently being considered by the Drug Enforcement Agency) would force, as occurred with the classic psychedelic drugs in the late 1960's and early 1970's.

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Footnotes:

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TABLE I

Comparison of MDMA and Classic Psychedelic Drugs*

	Psychedelics	MDMA
Neurotransmitter Effects		
Dopamine	?Post synaptic effects	Unknown
Serotonin (5-HT)	Pre- and/or post-synaptic effects	Releases 5-HT
Animal Drug Discrimination	Generalization among "psychedelics"	No generalization to DOM
Duration of Action	Four to twelve hours	Two to four hours
Hallucinations	Occasionally	Not seen
Disorientation	Occasionally	Not seen
Cardiovascular effects	Occasional increase in heart rate, blood pressure	Frequent increase in heart rate, blood pressure
Tolerance to Psychologic Effects	Yes	Yes
"Flashbacks"	Fifteen to seventy-seven percent occurrence	Not seen

*For example, LSD, psilocybin, psilocin, and mescaline