MDMA: Its History and Pharmacology

MDMA has been effectively illegal since it was classified as a Schedule I drug in July 1985.

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Better known as Ecstasy, (±)3,4-methylenedioxymethamphetamine (MDMA) has been known as Adam, XTC, and just plain X. A synthetic amphetamine analog with stimulant properties, it appears to exert unique psychological effects in humans, which discriminates it from chemically related substances.[1,2] MDMA has been effectively illegal since it was classified as a Schedule I drug in July 1985. In spite of its illegal status, its recreational use has skyrocketed in the past several years.[3] This rise in usage has been particularly prevalent among adolescents and has been inextricably linked with the increasingly popular raves, all-night dance marathon parties that have gained recent media attention. MDMA use at raves is rampant, as found in preliminary data gathered by the authors.

This rise in use is cause for concern and perhaps alarm. MDMA has been convincingly demonstrated to damage brain serotonin neurons in experimental animals.[4] The question of whether the compound is neurotoxic in humans is as yet unanswered. Given the rapid rise of use of MDMA and the unresolved questions of its toxicity, an understanding of the compound's history, psychological and physiological effects, and its present use in novel settings is vital, as psychiatrists are increasingly likely to encounter patients who have used MDMA.

The compound's appeal rests principally on its psychological effect, a dramatic and consistent ability to induce in the user a profound feeling of attachment and connection. The compound is perhaps misnamed. The Los Angeles dealer who coined the term *Ecstasy* wanted to call the drug *Empathy*, "but who would know what that means?"[5]

HISTORY

MDMA was first patented in 1914, by Merck in Darmstadt, Germany.[6] MDMA was not, as is sometimes thought, initially intended as an appetite suppressant, but was originally developed as a parent compound. The historical record concerning the compound then falls temporarily silent; if any early experimentation with MDMA occurred, documentation has been lost. The United States Army experimented with the compound during the 1950s. This material was declassified and became available to the general public in the early 1970s. These findings consist primarily of a number of LD-50 determinations for a variety of laboratory animals.

MDMA was first used by humans in the late 1960s. It was discovered by free-thinking pop aficionados (New Age seekers), people who liked its properties of inducing feelings of well-being and connection.[7] Introduction to clinical psychotherapy practice occurred on the West Coast of the United States in the begin-

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TABLE 1
Subjective Effects of MDMA (Plateau Phase)

Altered time perception
Increased ability to interact with others
Decreased defensiveness
Changes in visual perception
Increased awareness of emotions
Decreased aggression
Speech changes
Decreased obsessiveness
Decreased restlessness
Decreased impulsivity

Adapted from Leister M, Grob C, Bravo G, Walsh R.[21]

TABLE 2
Adverse Effects of the Use of MDMA

Decreased desire to perform mental or physical tasks
Decreased appetite
Trismus
Bruxism
Decreased libido
Inability to complete the sexual response cycle
Increased restlessness
Increased anxiety
Decreased ability to perform mental or physical tasks
Depressed mood
Nystagmus
Motor tics
Headaches

Adapted from Leister M, Grob C, Bravo G, Walsh R.[21]

ning of 1976, with the East Coast following suit six months later.[6] Given MDMA's capacity to induce feelings of warmth and openness, a number of practitioners and researchers interested in insight-oriented psychotherapy believed it would be an ideal agent to enhance the therapeutic process. Before the compound was made illegal in 1985, it was used extensively for this purpose.[8]

MDMA was also popular, as it is today, with young people. For this group, the drug's capacity to induce feelings of connection, as well as a psychomotor agitation that can be pleasurably relieved by dancing, make it an ideal party drug. In spite of widespread usage during the early 1980s (at least 30,000 tablets being produced per month in 1984, for example), the drug did not attract much attention from the media. It continued to be used by ever-increasing numbers of party-goers, New Age seekers, and psychotherapists.

The drug's popular use was changed by events in Texas. Until 1985, the drug was not scheduled and its use was thus unregulated, but legal. A distribution network in Texas began an aggressive marketing campaign and, for a time, it was available over the counter at bars, at convenience stores, and even through a toll-free number (D. Harlow, personal communication). This widespread use attracted the attention of Texas Senator Lloyd Bentsen. He petitioned the Food and Drug Administration and the compound was placed on Schedule I on an emergency basis as of July 1, 1985.

There was originally a series of three hearings scheduled to determine MDMA's permanent status. DEA officials were reportedly surprised that a substantial number of people, including therapists and clergymen, came out in support of a less restrictive categorization. The administrative judge recommended that the compound be placed on Schedule III. The compound's possible neurotoxicity, combined with concern about illicit drug use in general, resulted in MDMA's permanent placement on Schedule I.

PHYSIOLOGIC EFFECTS

MDMA is usually ingested orally; other methods of administration are reportedly less efficacious. The usual single dose is 100 to 150 mg. The initial effects begin about 20 to 40 minutes after ingestion and are experienced as a sudden, amphetamine-like "rush." Nausea, usually mild but sometimes severe enough to cause vomiting, often accompanies this initial feeling.

The plateau stage (Table 1) of the drug lasts between three and four hours. The principal desired effect, according to most users, is a profound feeling of relatedness to the rest of the world. In addition, people on the drug have mild psychomotor restlessness. Other side effects that are commonly experienced are bruxism, trismus, anorexia, diaphoresis, and hot flashes.[9] Although the desire for sex may increase, the ability to achieve orgasm for men and arousal for women is greatly diminished[9] (Table 2). It has thus been termed a sensual, not a sexual, drug.

After-effects may be quite pronounced, sometimes lasting 24 hours or more. The most dramatic "hangover" effect is a sometimes profound anhedonia. In addition, users of MDMA can experience lethargy, anorexia, and decreased motivation, which can sometimes last for days (Table 3).

MECHANISM OF ACTION

MDMA's primary mechanism of action is as an indirect serotonergic agonist.[10] In ad-

dition, it has affinities for a number of other neurotransmitter binding sites. MDMA is a "messy drug," affecting serotonin and dopamine-containing neurons as well as a host of other neurotransmitter systems.[11] MDMA is taken up by the cell through a fluoxetine-sensitive carrier mechanism, effects the release of serotonin stores, and then blocks reuptake. It also inhibits the synthesis of new serotonin, although this does not impact on the molecule's immediate physiologic effects. The drug's various effects of anorexia, psychomotor agitation, difficulty in completing the human sexual response cycle, and profound feeling of empathy can all be explained as actions precipitated by the flooding of the serotonin system.[12]

Because of the physiologic mechanism of the compound, the patterns of usage are unusual. Escalating usage is uncommon.[13] Because the drug depletes serotonin stores, subsequent doses are increasingly less effective and are accompanied by an elevation of side effects rather than an increase in the desired effect. People who use the drug quickly discover this and adjust their usage patterns. In addition, many users who are at first enamored of the drug subsequently lose interest, usually citing the substantial side effects. There is an adage about Ecstasy that captures this phenomenon, "Freshmen love it, Sophomores like it, Juniors are ambivalent, and Seniors are afraid of it."[14] Those who continue to use the drug over longer periods of time usually tend to use the drug only periodically.

In the summer of 1992 a number of deaths, as many as 15, were connected with the use of Ecstasy in England at drug-associated dance parties known as raves.[15] These deaths appear to be similar in certain features to both the serotonin (5-HT) syndrome and the neuroleptic malignant syndrome. Raves are held in sometimes hot, crowded conditions. During that summer, some of the clubs turned off their water supplies in an effort to maximize profits by selling bottled water. Hot, sweaty conditions, the physical exertion, and the dehydration caused by decreased intake may have contributed to the deaths when combined with the drug's effects. Since the English government has mandated an open water supply at all clubs, the deaths have apparently stopped (J. Beck, personal communication).

The drug's neurotoxicity is the most important question about its use. In experimental animals, the ingestion of MDMA causes a decrease in the serum and spinal fluid levels of 5-HIAA in a dose-dependent fashion[6] and damages brain serotonin neuronal axons.[4] While the doses necessary to cause permanent damage to most of the rodent species is many times that normally ingested by humans,[6] in nonhuman primates, the neurotoxic dose approximates the recreational one taken by humans.[4] While there is a paucity of data on human subjects, the doses taken by humans may have permanent sequelae.

TABLE 3
Short-Term Sequelae of MDMA Use (<1 Week)

Decreased sleep
Decreased appetite
Increased sensitivity to emotions
Decreased ability to perform mental or physical tasks
Decreased desire to perform mental or physical tasks
Increased ability to interact with or be open with others
Fatigue
Decreased aggression
Decreased fear
Depressed mood
Decreased obsessiveness
Increased restlessness
Altered perception of time
Decreased anxiety
Decreased libido

Adapted from Leister M, Grob C, Bravo G, Walsh R.[21]

There have been recent reports of individuals with lasting neuropsychiatric disturbance after MDMA use.[16-18] However, the prevalence of this is unclear. In all of 1984, when the drug was legal, fewer than 10 of 99,000 registered visits to United States emergency rooms involved MDMA.[19] The substantial acute side-effects that limit use may also limit the number of permanent casualties. In addition, the impact of serotonergic damage is not clear since some animal data suggest that even significant destruction of serotonin neurons has little functional impact.[20] What this means for humans is, however, an entirely different question and the risks of MDMA must be taken seriously. While in general it seems not advisable to use the drug, individuals with affective illness appear especially at risk.

RECENT DEVELOPMENTS AND THE RAVE PHENOMENON

In recent years, the drug's popularity has been inextricably linked with the rise of the rave phenomenon. Raves are all-night dance marathon parties popular in England since the late 1980s, which have found their way to the United States and the rest of the world. At least one major television network has referred to them as "the next big thing" (CBS, *48*

Hours, "LSD: Return Trip," February 1993).

At raves, groups of young people (typically in their teens) dance to rapid, lyricless electronically synthesized music ("techno"). These events traditionally take place in unregulated and unlicensed locations such as stadiums and football fields, but the venues have become increasingly mainstream. A drug that makes its users feel closer to those around them, heightens their sensory perception, and induces psychomotor restlessness relieved by dancing is seen by teenagers and young adults as the perfect match for this venue. The large numbers who use MDMA at raves (up to 70%, according to McDowell's preliminary data) demonstrate how widespread this combination has become.

MDMA's high price, usually $25 per tablet, a price that has remained remarkably stable over the past 10 years, deters more widespread use and makes the use of the much-cheaper LSD and amphetamines more compelling. Indeed, this is a phenomenon that has been noted in England. As raves have become longer and longer and the need to stay up all night greater, methamphetamine has become more popular. MDMA, while the drug of choice at raves, is probably not the most common. Young people initiated into the world of raves with MDMA quickly use other drugs as well, most commonly LSD, mushrooms, and marijuana.

What have been promoted as peaceful, enjoyable places where young people could dance and achieve a cultural identity appear to have become havens of drug use. For a teenager, MDMA costs a great deal of money. Given the burgeoning popularity of MDMA, the cost to society could prove to be considerably more.

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