4 THE ENIGMA OF ECSTASY

IMPLICATIONS FOR YOUTH AND SOCIETY

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A sensationalized topic of discourse during the past two decades has been use of the drug known popularly as "ecstasy." Regaled by some as "penicillin for the soul" and condemned by others as a dangerous brain toxin, ecstasy is an object of intense interest and extensive experimentation by large sections of the youth population. Lurid media coverage has contributed to widespread confusion regarding the genuine level of risk and putative safety parameters. Unfortunately, the drug's illicit status and centerpiece role in lavishly funded War on Drugs research has raised serious questions regarding the scientific ethics and credibility of some government-sponsored investigations. Whether ecstasy turns out to cause the severe central nervous system degeneration concluded in high-profile studies or these grave prognostications have been exaggerated and misleading, the health and well-being of millions of (mostly young) users may be hanging in the balance.

HISTORY

Ecstasy is the name given in the early 1980s to the still-legal drug 3,4-methylenedioxymethamphetamine, or MDMA, by entrepreneurs involved in its early marketing. MDMA is a phenethylamine originally discovered shortly before World War I, by German pharmaceutical researchers at Merck, as a byproduct in the preparation of a styptic compound (Shulgin and Shulgin, 1991; Holland, 2001). The chemical structure of MDMA has similarities to both the classic hallucinogen mescaline and to methamphetamine. Its analogs in nature include nutmeg and the sassafras plant.

Formal investigations with MDMA did not commence until the early 1950s, when animal experimentation was conducted by researchers

working on the top secret MK-ULTRA military intelligence program designed to explore the range of various proposed psychochemical brainwashing agents. Human experimentation with MDMA was put on hold, however, after studies with its phenethylamine analog and metabolite MDA (3,4-methylenedioxyampehtamine) accidentally caused the overdose death of an army volunteer subject (Shulgin, 1986, 1990).

In the mid-1970s, a distinguished San Francisco pharmacology professor named Alexander Shulgin was introduced to MDMA by a graduate student who claimed that his use of the drug had ameliorated a chronic stuttering condition. Intrigued by the report, Shulgin synthesized MDMA and took it himself. Describing the experience as "an easily controlled altered state of consciousness with emotional and sensual overtones, and with little hallucinatory effect" (Shulgin and Nichols, 1978, p. 77), Shulgin suggested that the compound be explored for its potential as an adjunctive treatment for psychotherapy.

From the 1950s until the early 1970s, a variety of hallucinogens were examined for potential efficacy in the treatment of psychiatric disorders. But with the advent of the late 1960s counterculture and its appropriation and identification with what were popularly known as psychedelics, formal research was actively discouraged (Grinspoon and Bakalar, 1979; Grob, 1998, 2002a). Almost three decades would pass before the political storms had sufficiently dissipated that sanctioned medical investigations into the treatment potential of hallucinogens and related compounds could be resumed.

By the early 1980s, MDMA had established a quiet niche as an adjunct and amplifier of the psychotherapeutic process, particularly among mental health professionals on the West Coast. Compared with the prototype hallucinogen used in research investigations in the 1950s and 1960s, LSD (lysergic acid diethylamide), MDMA was considered by early practitioners to be relatively mild, easily controlled, and short acting. It was also observed to enhance the capacity for introspection and to facilitate articulation of underlying feelings. A seemingly unique element of the MDMA experience that was thought to be particularly valuable for psychotherapy was its observed proclivity to induce empathogenic states (Adamson and Metzner, 1988). Empathy—the capacity to deeply and intuitively understand the conditions of others—is recognized as a higher order mental function, and the capacity for empathic rapport is considered to be one of the strongest predictive factors for psychotherapy outcome.

Drawing on lessons learned from prior work with psychedelics, clinicians understood that the optimal utilization of MDMA required a paradigm shift from conventional psychopharmacologic treatment (Grinspoon and Bakalar, 1986). Whereas medication treatment in psychiatry generally involves daily drug administration for weeks, months, or even years, in this novel treatment model, the active agent might be utilized only once or twice in the context of ongoing psychotherapy. Critical to this model were the mental set of the patient and the environmental setting where the experience was facilitated, so both were carefully controlled (Bakalar and Grinspoon, 1990).

Applications for MDMA treatment were similar to clinical conditions that had demonstrated surprising responsivity to interventions with classic hallucinogens until their politicization and eventual banishment from the therapeutic armamentarium years before. Of particular interest to psychiatric researchers were patients with disorders generally considered to be nonresponsive to conventional treatment models. Such refractory conditions included alcohol and drug abuse, chronic posttraumatic stress disorder, and the physical pain and emotional distress commonly associated with end-stage medical illness. As was the case with the classic hallucinogens decades earlier, MDMA treatment was often observed to facilitate a surprising degree of recovery in resistant patient populations (Greer and Tolbert, 1986; Riedlinger and Riedlinger, 1994).

Unfortunately, before formal, methodologically sound research protocols could be implemented, the use of MDMA had evolved in new and politically provocative directions. By the mid-1980s, the national media were reporting the spread of MDMA, now called ecstasy, to the recreational youth drug scene. Particularly in the state of Texas, there were heated calls for government intervention to stem the rapid popularization of the drug. Spurred on by Senator Lloyd Bentsen, who had been aroused by his Texas constituents, the U.S. Drug Enforcement Administration (DEA) in 1985 called for public hearings to determine the scheduling of what was still a legal drug. And on July 1, 1985, the DEA placed MDMA in an emergency Schedule I category. By definition, Schedule I is reserved for drugs that are deemed to have a high potential for abuse, have no currently accepted medical use, and lack accepted safety for use, under medical supervision.

From June to October 1985, the DEA held hearings in several cities across the United States and heard testimony from law enforcement personnel, health officials, MDMA psychotherapists, and patients who claimed to have strongly benefited from MDMA treatment. On May

22, 1986, the presiding DEA administrative law judge, Francis Young, ruled that MDMA did not fit the criteria for Schedule I placement and recommended that it be assigned Schedule III status, with formal research being encouraged to establish potential efficacy and parameters for safe use. Dismayed by this decision, however, the chief DEA administrator, John Lawn, overruled his own administrative law judge and ordered that MDMA remain a Schedule I drug. A subsequent appeal brought forward by Lester Grinspoon, a psychiatrist on the faculty of the Harvard Medical School, briefly removed MDMA from Schedule I placement from December 1987 to March 1988. With court rejection of the appeal, however, MDMA was returned to Schedule I placement, where it remains to this day (Lawn, 1986; Young, 1986).

In the wake of the DEA scheduling hearings, the national media woke up to the new and titillating story of MDMA, now known as ecstasy. As coverage sensationalizing the use of ecstasy grew and spread across the United States and Europe, a new phenomenon called "raves" emerged. These were occasions on which large numbers of youth, often in the hundreds or even thousands, would take ecstasy and gather to dance long into the night to the beat of "club" or "techno" music. Far from discouraging the use of what was now an illegal drug, the DEA hearings appeared to have encouraged the widespread dissemination of MDMA for recreational purposes. Alarmed by stories of unorthodox psychotherapy and provoked by evidence that the drug had established a recreational niche in the Texas club scene, the authorities felt compelled to crack down. In the process of subjecting MDMA to the most highly controlled legal restrictions and penalties, however, recreational ecstasy became one of the most out-of-control drug phenomena to occur in modern history. As a result, we have not only had to contend with the serious public health implications of millions of people experimenting with the drug, often in high risk contexts, but we have also failed to properly explore the therapeutic potentials and safety parameters of what a psychotherapist colleague had once described to Alexander Shulgin as "this penicillin for the soul" (Shulgin and Shulgin, 1991).

CHANGING PATTERNS OF USE

Worldwide, the use of ecstasy has been most prominent in the United Kingdom. By the late 1980s the use of ecstasy at dance clubs had

attracted the attention of British tourists on the Spanish resort island of Ibiza. With the export of the rave phenomenon to the United Kingdom, use of ecstasy soared. Between 1990 and 1995, use increased by over 4000% in the United Kingdom, with estimates of between 500,000 to 1,000,000 young people taking the drug every weekend. Surveys indicate that approximately one-third of all youth there have tried ecstasy, leading some commentators to describe the emergence of the rave scene as the largest youth cultural phenomenon in British history (Saunders, 1993; Saunders and Doblin, 1996; Sylvester, 1995; Sharkey, 1996; Collin, 1998).

In the United States, use of ecstasy has ebbed and flowed depending on availability of the drug. In the late 1980s, wildly exaggerated estimates of youth use of the drug were promoted in prestigious medical journals, most particularly a report in the *New England Journal of Medicine* declaring that 39% of Stanford University students had tried ecstasy (Peroutka, 1987). On subsequent inquiry, however, it was noted that the context of the study was the Stanford Student Union on several weekend evenings, where surveys were distributed by attractive young research assistants (D. J. McKenna, personal communication, May 2, 1989, with written corroboration August 29, 2004). A more methodologically sound study of students at Tulane University in the early 1990s did ascertain that 24% of students there had experimented with the drug (Cuomo, Dyment, and Gammino, 1994).

During the late 1990s use of ecstasy in the United States increased significantly, presumably because of large supplies of the drug smuggled into the United States from Europe and the Middle East. Several highly publicized legal seizures of vast quantities of ecstasy traced the origin of the drug supply to criminal operations in Holland and Israel. During the final few years of the 20th century, the use of ecstasy among high school students more than doubled, peaking in 2001 with 12% of high school seniors acknowledging having tried the drug (National Institute on Drug Abuse, 2002). With media coverage sensationalizing this rapid surge of use among young people, law enforcement efforts to cut off both foreign and domestic supplies of the drug increased. Whereas in 1998 U.S. Customs confiscated 750,000 tablets of ecstasy, by the year 2000, 9,300,000 tablets were seized (U.S. Customs Service, 2000), demonstrating the rapidly increased proliferation of the drug on the U.S. illicit drug market. Federal sentencing guidelines for large quantities of the drug were stiffened in 2001, when the U.S. Sentencing Commission increased the punishment for possession of 800 pills (200

grams) of ecstasy from 15 months' incarceration to 5 years, and for 8000 pills (2000 grams), from 3 years to 10 years (U.S. Sentencing Commission, 2001; Rosenbaum, 2002).

As use of ecstasy in the United States and around the world has escalated, another troubling phenomenon has emerged within the recreational youth drug scene. Over the last decade and a half, as manufacture and marketing of the drug have shifted from idealistic proponents of the beneficial effects of MDMA to being controlled by criminal gang enterprises intent on maximizing profits, the quality of the drug has undergone steady deterioration. Whereas in the 1980s and early 1990s virtually all ecstasy was MDMA, by the late 1990s, an astounding degree of drug substitution had arisen (Shewan, Delgarno, and King, 1996; Wolff et al., 1996; Ramsey, Partridge, and Byron, 1999; Sferios, 1999; Inciyan, 2000). Many recent surveys have indicated that more than 50% of pills marketed as ecstasy are actually drugs other than MDMA. These drug substitutes include methamphetamine, cocaine, opiates, LSD, phencyclidine (PCP), ketamine, dextramethorphan (DXM), gammahydroxybutyrate (GHB), and paramethoxyamphetamine (PMA). In particular, PMA, an extremely potent amphetamine, has been associated with several high-profile deaths initially attributed to ecstasy use (Kraner, McCoy, and Evans, 2001; Martin, 2001).

Early proponents of MDMA as an empathy-generating, heart-opening catalyst for psychospiritual transformation advocated limited use (echoing the popular philosopher Alan Watts's admonition decades before, regarding hallucinogens, that "when you get the message, you can hang up the phone"; Watts, 1962, pp. 25–26). But observers of the youth rave scene in recent years have been struck by the increasing degree of frequent and high-dose ecstasy use along with polydrug ingestion, in which a variety of different drugs are consumed in close succession, both knowingly and because of ecstasy drug substitution. In particular, methamphetamine, a stimulant with serious addictive and deleterious central nervous system effects, has assumed increasing prominence as a dance drug catalyst (Collin, 1998). Inevitably, such escalating and excessive use patterns have kindled concerns regarding the short- and long-term risks to the health and safety of participants in the youth ecstasy scene.

ADVERSE HEALTH EFFECTS

With the escalating ecstasy use patterns evident in youth, it was inevitable that increasing cases of serious adverse effects would be reported.

In the United States, the evidence of ecstasy use in screened emergency room patients skyrocketed from a few hundred in the mid-1990s to more than 5000 in 2001 (Drug Abuse Warning Network, DAWN, 2003). It is important, however, that many of these recorded histories also involved concomitant use of other drugs and alcohol. Consequently, to attribute the adverse outcomes of these polydrug ingestion cases to ecstasy or MDMA alone is highly misleading. Indeed, data supplied by DAWN (2003) for 2001 show that only 14% of emergency room patients in whom MDMA was detected had not used other drugs, whereas 86% of the emergency room admission involved polydrug ingestion, including 48% with comorbid alcohol use and 29% with cocaine use.

When assessing the level of public health risk from ecstasy, it is also necessary to place in perspective the relative dangers of other commonly abused drugs, including those that have remained legal and socially sanctioned. U.S. data for the year 2000 reveal that 60 deaths nationwide were associated with ecstasy use (approximately 2 in 100,000 users), whereas 50,000 deaths were attributed to alcohol use (50 per 100,000 users) and 400,000 to tobacco use (400 per 100,000 users; DAWN, 2003). A slightly higher proportional level of risk for ecstasy use has been reported in the United Kingdom, where 36 ecstasy deaths were reported in 2000, compared with 104,000 tobacco-related deaths (McKenna, 2002). Nevertheless, and in spite of the relatively low number of ecstasy-related fatalities, these deaths remain personal and collective tragedies, particularly given that many of these fatalities may have been prevented if basic harm reduction strategies had been implemented.

The most frequent cause of death associated with MDMA ingestion is malignant hyperthermia, in which core body temperature overheats to catastrophic levels in individuals who appear to have idiosyncratic vulnerabilities in central nervous system temperature regulation. When body temperature escalates to the range of 105 to 106 degrees Fahrenheit, a potentially fatal condition of excessive blood clotting called disseminated intravascular coagulation (DIC) occurs, which leads to muscle breakdown (rhabdomyolysis), acute kidney and liver failure, seizures, and death. Most of these hyperthermia deaths have occurred at dance clubs, where individuals engage in prolonged exercise (dancing) in crowded facilities with poor ventilation, high ambient temperatures, and limited access to fluids and rooms for resting (Henry, Jeffreys, and Dawling, 1992). One tragic example occurred in England in the early 1990s when a young person died on each of two on consecutive

weekends in the same club, from malignant overheating. Investigation revealed that the establishment's owners, in order to increase profits, had cut off the water supply to the restrooms, and instead were selling glasses of water at the bar for the price of a beer (Matthews and Jones, 1992). Clearly, with proper education of patrons and a higher ethical standard for club proprietors, such deaths should be preventable. As a case in point, in the late 1990s, public health authorities in Holland (a country with drug policies quite different from those of the United States and most other European nations) established strict rules regulating ambient temperature, proper ventilation, easy access to fluids, and government-supervised, high-quality drug testing. Consequently, in the years following implementation of this comprehensive harm reduction policy, morbidity associated with ecstasy use was significantly reduced and mortality virtually eliminated. Instead of the standard "just say no" (or face the consequences) policy, Dutch authorities have emphasized a practical and effective approach to providing young people with valuable information and conditions designed to reduce the common dangers associated with recreational drug use.

A related phenomenon associated with fatalities secondary to ecstasy use, though far less frequent, is water intoxication, of which several cases have been reported. In these events, individuals have apparently consumed excessive quantities of water while not exercising, leading to catastrophic degrees of water retention, dilutional hyonatremia, seizures, and death. It is interesting that, in the handful of reported cases, all of the victims have been young women. The explanation for this phenomenon appears to be the effects of MDMA on vasopressin, or antidiuretic hormone (ADH). British medical researchers Henry, Fallon, and Kieman (1998), in an important investigation, demonstrated that controlled laboratory administration of MDMA significantly increases central vasopressin secretion in women subjects, but not in men. The implications of these case reports is that ecstasy use associated with compulsive and excessive water consumption by vulnerable individuals may be as dangerous as neglecting to replace fluids when engaging in prolonged vigorous exercise in hot and crowded environments. Thus, it is clear that if safe parameters of use do exist, as early proponents of the MDMA therapeutic model suggested, they tend to unravel when use of the drug occurs in the recreational drug scene.

Another reported potential adverse outcome of MDMA is liver damage. Several cases of apparent hepatotoxicity in individuals with histories of recent ecstasy ingestion have highlighted this concern. While

most of the reports were of individuals who also abused alcohol and/or other drugs, not all were. Given the increasingly poor quality of black-market manufactured ecstasy, the risk for idiosyncratic reactions—particularly in individuals with prior hepatic injury—remains of concern (Henry et al., 1992; Dykhuizen, Brunt, and Atkinson, 1995).

Underlying medical vulnerability has also been a critical factor in a series of individuals with reported cardiovascular autonomic dysregulation, cardiomyopathy, and mitral valve prolapse (Dowling, McDonaugh, and Bost, 1987; Nichols, Davis, and Corrigan, 1990; Lester, Baggott, and Welm, 2000). Deaths have occurred, albeit low in number, in individuals who had apparently not been aware of any preexisting cardiac problems. As has unfortunately been the case in young athletes who appear to be in good condition yet experience sudden cardiac arrest after exercise, MDMA intoxication has been implicated in several fatalities.

PHARMACOKINETICS

An additional important factor to appreciate is that MDMA possesses nonlinear pharmacokinetics, which means that as dosages are augmented, the capacity for drug metabolism and clearance is exhausted, causing plasma levels of MDMA to increase exponentially (Mas, Farré, and de la Torre, 1999). Of considerable concern, and relevant to the recreational drug scene where young ravers often take excessive dosages, is that the higher the plasma level of MDMA, the greater the potential for elevation of blood pressure. Unfortunately, the common self-dosing patterns observed in recreational users often leads those most vulnerable to a heightened risk for inducing hypertensive crises, cardiac malfunction, and cerebrovascular accidents.

Another concern about the uncontrolled use of recreational MDMA has been the potential risks of dangerous interactions between MDMA and prescription drugs. MDMA is metabolized primarily by the cytochrome P450 hepatic systems CYP2D6 and CYP3A4 (de la Torre, Farré, and Ortuño, 2000). MDMA may influence or be influenced by other drugs metabolized by the same cytochrome P450 isozymes. Drugs also possessing prominent 2D6 metabolism, including the selective serotonin reuptake inhibitor (SSRI) antidepressants fluoxetine (Prozac) and paroxetine (Paxil) as well as the illicit drug cocaine, inhibit MDMA

metabolism in the human liver (Ramamoorthy, Ai-Ming, and Suh, 2002), thus posing the risk of impaired degradation and protracted exposure to high levels of MDMA. A life-threatening interaction was also reported in one case of an HIV-positive young man's between treatment regimen of protease inhibitors ritonavir (Norvir) and saquinavir (Fortovase)—potent inhibitors of both CYP3A4 and CYP2S6—and his recreational MDMA (Harrington, Woodward, and Hooton, 1999).

PSYCHIATRIC SEQUELAE

As was the case with hallucinogen users during the 1960s, ecstasy has been associated with a variety of psychiatric disturbances, including panic disorder (Pallanti and Mazzi, 1992), paranoid psychoses (McGuire and Fahy, 1991) and depression (MacInness, Handley, and Harding, 2001). The lessons learned from counterculture casualties decades ago are as applicable today, including the question of which users are most at risk for developing serious emotional sequelae. Individuals with evidence of prior psychiatric disorders, and those with strong family histories for mental health problems, constitute a particularly vulnerable group. And of greatest concern are those young people who develop frequent ecstasy use patterns, often in combination with use of other drugs and/or alcohol. This combination of past psychiatric disorders, positive family histories, and frequent polydrug and ecstasy use are often critical contributory factors when MDMA ingestion precipitates adverse mental health outcomes.

NEUROTOXICITY CONTROVERSIES

More than any other issue, the concern over MDMA's potential to induce brain damage has been a focal point of an often acrimonious debate that has broken out in both the scientific and public arenas. For almost 20 years, the question of neurotoxicity has dominated investigations exploring the range of effects attributed to MDMA. With heavily promoted concerns that "even one dose can cause permanent brain damage," it has proved virtually impossible to examine the suggested

therapeutic benefits of the drug. Since the well-publicized announcement in 1985, during the MDMA scheduling hearings, that rats given massive doses of an analog, MDA, had sustained extensive changes to their serotonergic neurotransmitter systems, research designed to elaborate the extent of brain damage caused by MDMA in animals and humans has received virtually all of the generous government funding allocated to study the drug. Unfortunately, the intrusion of political agendas upon research has created a crisis of scientific ethics and credibility, as well as having obfuscated the genuine effects of MDMA.

There is no doubt that MDMA, when frequently administered to laboratory animals in large amounts, causes noticeable alterations in the central nervous system, particularly in regard to the serotonergic neurotransmitter system (McKenna and Peroutka, 1990). A critical biochemical determinant of emotions and behavior, serotonin plays a role in a variety of conditions including affective disorders, aging, anxiety disorders, developmental disorders, eating disorders, obsessive-compulsive disorder, pain sensitivity, posttraumatic stress disorder, schizophrenia, sexual disorders, and substance abuse. If the proponents of the MDMA neurotoxicity theory are correct and the drug actually has a damaging effect on brain structure and function, then users would likely incur serious clinical deterioration. Indeed, given the enormous numbers of young people who have experimented with MDMA, the implications clearly are that society is in serious jeopardy of a looming catastrophic public health crisis. The question of whether MDMA does actually damage the brain, however, is the object of growing controversy and is far from settled (Grob, 2000, 2002b).

Much of the evidence in support of MDMA neurotoxicity has been the result of research conducted using small laboratory animals in which a variety of acute and reversible effects have been noted. Short-term reductions of serotonin and its metabolites have been consistently observed, with gradual recovery back to baseline levels. Marked variations in extent of change have been noted in different species, with nonhuman primates showing more sensitivity to the drug than rats and mice. A salient feature of the so-called neurotoxicity phenomenon has been histopathological evidence of axonal degeneration in serotonin-containing neurons. Of significance, however, is that what occurs is a distal axotomy, with proximal regeneration and complete sparing of the cell body (Molliver et al., 1990; Baumgarten and Zimmermann, 1992).

A number of controversies have colored the debate over MDMA neurotoxicity. Proponents of the hypothesis that MDMA causes brain damage have utilized the concept of interspecies scaling, that the larger the animal the greater the sensitivity to suggested neurotoxicity. For example, monkeys are more sensitive to MDMA's effects on the brain than rats (Chappell and Mordenti, 1991). This theory, however, entirely ignores interspecies differences in pharmacokinetics and metabolite ratios. A case in point is that with fenfluramine, which induces virtually identical effects to MDMA on the serotoninergic neurotransmitter system, humans metabolize the drug much differently than do squirrel monkeys, and are actually far closer in pharmacokinetic profile to smaller species like rats (Caccia et al., 1982; Johnson and Nichols, 1990; Marchant et al., 1992). Fenfluramine is consequently of far greater potential toxicity to the squirrel monkey than it is to either the rat or the human. Given the relative chemical similarities between fenfluramine and MDMA, neurotoxicity in the human central nervous system is likely of less concern than in the squirrel monkey, the opposite of what has been concluded from incorporating the theory of interspecies scaling without metabolic and pharmacokinetic considerations.

A puzzling absence in the case for neurotoxicity has been the lack of clear evidence of injurious functional effects in animal behavior investigations. With laboratory animals receiving high-dose, frequent regimens of MDMA, the expectation has been that animal corollaries of human neurologic and psychiatric conditions would be easily demonstrated. There has been a surprising paucity, however, of reports of deleterious animal behaviors induced by MDMA (Slikker et al., 1989). Given the extensive involvement of serotonin systems in central nervous system function, the lack of expected findings has confounded expectations.

Another challenge to the assumption that MDMA is a dangerous brain toxin comes from neurotoxicological investigations that have failed to identify standard neurotoxicity markers (e.g., astrogliosis) in MDMA-treated animals. Known neurotoxins—including bilirubin, cadmium, tri-methyl tin, the dopamanergic neurotoxin MPTP, and the classic serotonergic neurotoxins para-chloroampehtamine (PCA) and 5,7-dihydroxytryptamne (5,7-DHT)—predictably induce a proliferation of enlarged astroglial cells. This classic evidence of neuronal destruction is absent with MDMA (O'Callaghan, 1993; O'Callaghan and Miller, 1995). This and other research has raised the consideration that rather than neurotoxicity's being the consequence of MDMA's effects, the

mechanism of neuromodulation may occur, whereby protein synthesis inhibition functions as a natural extension of the pharmacological activity of compounds.

Human research has focused on suggested cognitive deterioration induced by MDMA (Bolla, McCann, and Ricaurte, 1998; McCann et al., 1999) along with brain imaging investigations that have purportedly mapped the extent of structural destruction (McCann et al., 1998). Serious methodological flaws, deceptive data analyses, and misleading conclusions have plagued much of this work (Grob, 2000, 2002b; Grob and Poland, 2004). Subjects in many of these studies tend to be poorly matched with controls and have often proved to be polydrug abusers, though the extent of their drug use is often camouflaged. Concerns have also been raised, particularly in high-profile investigations, about questionable statistical manipulations, including lumping controls with subjects having lesser cumulative use histories and comparing them to the higher use group without published acknowledgment (Nelson, 1999).

One particularly problematic study involved the use of the L-tryptophan challenge test, an indirect marker of serotonin, in a group of subjects who had histories of self-administering MDMA (Price et al., 1989). The published and heavily promoted results were that the MDMA subjects' serial prolactin measurements (taken after receiving the intravenous L-tryptophan challenge) suggested damage to the serotonin neurotransmitter system. What was not mentioned in the published article, however, was that the subjects had been recruited from a larger group of MDMA-using research subjects who had previously received lumbar punctures for measurement of the major metabolite of serotonin, 5-hydroxyindoleacetic acid (5-HIAA). Subjects for the L-tryptophan challenge study were selected on the basis of their having had 5-HIAA measures at the low end of the curve, thus clearly biasing the results (R. Doblin, personal communication, Sept. 1990). To make matters worse, these same subjects were also administered a battery of neuropsycholgocial tests and were found to have evidence of cognitive impairment caused by MDMA use (Krystal et al., 1992). What was not adequately identified in the published presentation, however, were the conditions under which the subjects were evaluated. The day before testing, subjects were transported by airplane from California (where they lived and where the CSF 5-HIAA study had been conducted) to the East Coast (where the L-tryptophan study was occurring). A consequence of this would naturally be some degree of jet lag during

their participation in the study, a circumstance not present in the non-MDMA-using controls. Another confounding factor that would have affected cognitive performance was that, several hours before being tested, the MDMA subjects had been administered intravenous L-tryptophan, a sedating drug. This study's serious methodological flaws and deceptive reporting have become emblematic of the concerns over scientific ethics and credibility that have arisen from this research program.

A particularly alluring research focus that has garnered provocative media attention has been brain imaging studies of subjects who reported positive histories for MDMA use. Unfortunately, many of these studies have also suffered from methodological deficiencies, particularly in regard to their use of poorly matched controls and questionable statistical design. One particularly high-profile study (McCann et al., 1998) was published in October, 1998, to sensationalized headlines trumpeting proof that definitive evidence had been discovered by using PET scans to identify MDMA-induced brain damage. No substance abuse histories were reported in the published article, however, and on closer inspection it was also apparent that selected subjects had had excessive use histories clearly indicative of serious drug dependence (Erowid, 1998). Furthermore, subsequent investigation revealed that the researchers had used questionable statistical analysis techniques, including logarithmic compression of data, to exaggerate positive findings. Other technical criticisms leveled at this study include criticism of the use of a radioligand, [llC](-)McNeil-5652, considered insufficiently specific for serotonin receptors, which also had not been assessed for test-retest variability by the investigators (Kuikka and Ahonen, 1999; Buck et al., 2000). With the alarming degree of bias employed in many of these research programs, it is apparent that the question of whether serotonin neurotoxicity is caused by MDMA still awaits an answer (Kish, 2002). Hopefully, the future will see more rigorous and objective research investigations addressing these important issues, unencumbered by preconceived biases and political agendas.

One final chapter in the MDMA neurotoxicity saga has recently played out in the press. In September, 2002, the prestigious journal *Science* published a report by an influential research team based at Johns Hopkins, declaring that they had found evidence of severe dopamine damage associated with lethal consequences in monkeys injected with MDMA (Ricaurte et al., 2002). The implications of such findings, as the investigators declared to the media, were that MDMA users

were now presumed to be at serious risk for developing Parkinson's disease, a devastating neurodegenerative condition caused by injury to the dopaminergic neurotransmitter system. This entirely new and unexpected "proof" of MDMA's ravaging effects on the brain were eagerly disseminated by the world press. But, one year following its original publication, the authors were forced to print a retraction in *Science*, revealing that what the monkeys had actually been administered was not MDMA but rather methamphetamine, a compound known to have profound effects on dopamine systems (Ricaurte et al., 2003). Whereas the investigators blamed the company from whom they had purchased their drugs (RTI, a North Carolina–based company under contract to the National Institute of Drug Abuse to provide Schedule I drugs for research) for mislabeling drug vials, the company vehemently denied that the fault was theirs. Whether this drug switching was attributable to an innocent labeling error or was in fact outright scientific fraud may never be known. But what is painfully apparent when reviewing this study in the context of the past 15 years of this research program is a consistent pattern of misrepresenting and obfuscating much of the purported evidence for the MDMA neurotoxicity case. Consequently, and in spite of the expenditure of many tens of millions of research dollars, we still do not know the long-term central nervous system implications to millions of persons who have taken the drug.

CONCLUSION

A quarter of a century ago, the drug MDMA was suggested to have therapeutic potential when used under optimal conditions. Because of the rapid emergence of a youth subculture that employed MDMA as an intoxicant and social lubricant, however, formal evaluation of its possible role as an adjunctive treatment for individuals with psychiatric disorders has proved extremely difficult. With the use of ecstasy escalating and occurring in high-risk contexts, particularly among youth, medical and psychiatric dangers have become increasingly apparent. Nevertheless, it is clear that vigorous, proactive, harm reduction efforts (as modeled by Dutch public health authorities) may be of great value in risk prevention and limiting the extent of serious adverse health events. The potential for MDMA to induce serious long-term central nervous system injury, however, is a matter that remains far from

settled. In spite of extensive and high-profile efforts to resolve the debate and declare irrefutable evidence that MDMA causes brain damage, serious concerns have been raised questioning scientific ethics and credibility.

When MDMA was placed on Schedule I status by the DEA in the mid-1980s, the primary justifications were to prevent further illicit spread to the youth recreational drug markets and to protect prospective users from self-inflicting serious brain injury. Twenty years later, it is apparent that making the drug illegal has not stopped its rapid spread, particularly to vulnerable populations. What is clear is that, until recently, efforts to formally evaluate the potential safety and efficacy of the MDMA treatment model have been consistently frustrated. Shortly after the retraction (Ricaurte et al., 2003) of the Ricaurte et al. (2002) *Science* paper and the consequent media attention to what was recognized as a serious research scandal, a pilot investigation (in Charleston, South Carolina) of MDMA in the treatment of chronic posttraumatic stress disorder received full regulatory approval. It is to be hoped that further efforts to objectively and honestly investigate the full range of effects of MDMA will be successful. By adhering to strict standards of scientific ethics and by being insulated from political pressures and agendas, it should be possible to finally establish the full range of potential risks and benefits. Only in this way will it be possible to address the serious public health concerns that have been raised, as well as to investigate the potential of developing an entirely new and novel psychiatric treatment.

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