

Commentary

The MDMA-Neurotoxicity Controversy: Implications for Clinical Research with Novel Psychoactive Drugs

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During the mid-1980s, a debate arose over the suitability of a unique psychoactive compound, 3, 4-methylenedioxymethamphetamine (MDMA), as an adjunct to psychotherapy. Proponents of MDMA-facilitated treatment reported it to be a relatively mild, easily controlled, and short-acting drug that enhanced the capacity within the psychotherapy setting for introspection and empathy, noticeably reducing depression and anxiety, yet without distracting alterations in perception, sense of self, or body image (Grinspoon and Bakalar, 1986). Treatment outcome, often of cases refractory to conventional therapies, was reported to be highly impressive (Greer and Tolbert, 1990). Results from subsequent legal MDMA psychotherapy research in Switzerland support these early claims of MDMA's therapeutic utility.

However, in the United States, before rigorous methodological designs could be applied within controlled clinical research settings, the Drug Enforcement Administration ruled to deny the availability of MDMA for medical use. This decision was influenced not only by media reports sensationalizing its use in the population, but by laboratory studies reporting serotonergic neurotoxicity in animals. Subsequent investigations were also directed at evaluating neurotoxicity in humans previously exposed to MDMA. Unfortunately, these efforts have, on careful examination, often contained flaws in methodology as well as interpretation.

One frequently cited study has claimed to have found "central serotonergic dysfunction" in individuals with past use of MDMA who were administered L-tryptophan challenge tests (Price et al., 1989). We have discussed elsewhere (Grob et al., 1990) that methodological flaws, including lack of baseline measures as well as inadequate screening for other psychotropic drugs that affect serotonergic function, raise questions regarding the significance of these findings. This study also failed to mention that their nine subjects who were preselected were among those with the lowest cerebrospinal fluid

5-hydroxyindoleacetic acid levels from a larger group of 34 heavy MDMA users (Doblin, personal communication), producing a sample with a clear bias for producing results indicative of central serotonergic dysfunction.

Since 1985, when reports first surfaced of serotonergic neurotoxicity in laboratory animals administered large amounts of MDMA, expectations grew that a flood of patients with damaged serotonergic neurotransmitter systems would surface. Such anticipation was in large part fueled by confusion of MDMA with the opiate analogue 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP; Beck, 1990), which had been demonstrated earlier in the decade to cause severe and irreparable damage to the dopaminergic system. However, the degree to which clinical cases of MDMA-presumed damage to serotonergic function have been reported has been surprisingly limited, and confounded by associated variables. McCann and Ricaurte (1991) recently reported on two cases of depression following self-administration of MDMA. Given the degree of premorbid psychopathology and prior polysubstance abuse of these subjects, direct "evidence" linking MDMA to clinically manifest serotonergic deficit syndromes remains uncertain. Another clinical case report (Whitaker-Azmitia and Aronson, 1989) associating MDMA use with two transient anxiety episodes may not have given sufficient attention to the highly adverse setting for the experiences (the New York City subway system). Although MDMA is by no means an innocuous drug, particularly when used by vulnerable and unprepared individuals in uncontrolled settings, clinical evidence to date examining the degree of risk pertinent to the low dose, highly controlled therapeutic MDMA treatment model remains limited. In support of this, legal MDMA psychotherapy research has been under way in Switzerland since 1988 without reports of adverse neuropsychiatric sequelae.

Concern has also been raised over what has been called MDMA's substantial abuse liability. Although cases do exist of compulsive self-administration of MDMA, such persistent use patterns appear to be "ex-

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tremely rare" (Peroutka, 1989). The only National Institute of Drug Abuse-funded study into the human use of MDMA, as well as three other studies of nonmedical MDMA use, one in the United States and one each in the Netherlands and Australia, provide additional evidence suggestive of a relatively low abuse potential (Beck et al., 1989; Korf et al., 1991; Siegel, 1986; Solowij and Lee, 1991). In fact, MDMA appears to be rather unique among the so-called recreational drugs, in that most individuals who have taken the drug report a relative disinclination, rather than a craving, to take the drug repeatedly. Reports of abuse have been particularly uncommon among those who have used MDMA for therapeutic or spiritual purposes (Beck, 1990; Watson and Beck, 1991).

Further elucidation of the term neurotoxicity as it applies to the serotonergic system is also necessary. Evidence showing actual regeneration of neuronal terminals presumed permanently destroyed by massive amounts of MDMA in laboratory animals (Battaglia et al., 1987) needs to be considered. New findings examining the effect of the highly potent serotonergic neurotoxin 5,7-dihydroxytryptamine may also be relevant. 5,7-Dihydroxytryptamine appears to reactivate dormant developmental signals in the brain which encourage sprouting of serotonergic fibers as well as stimulation of an astrocytic growth factor. To activate these mechanisms, which are postulated to have a role in healthy regeneration and treatment of the aged brain, serotonergic neurons must first be "damaged or blocked" (Azmitia and Whitaker-Azmitia, 1991). Such findings indicate that conclusions about the meaning of MDMA-induced "neurotoxicity" are premature.

Should MDMA be the subject of clinical research? The recreational use of MDMA, as well as initial concerns about structural and functional brain damage, has up to now prevented clinical investigators from gathering data in humans about MDMA's risk to benefit ratio. We believe that a thorough yet dispassionate review of the existing data suggests that the experimental

use of MDMA in humans can be justified. It is necessary to draw a clear distinction between uncontrolled use of MDMA for nontherapeutic purposes and proposals for sanctioned application of MDMA in treatment settings, particularly for cases refractory to conventional therapies. We must now begin to ask open-minded questions that may potentially yield new and innovative treatment modalities, even if such approaches include novel psychoactive drugs such as MDMA.

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