

Curbside Consult

Does recreational ecstasy use cause long-term cognitive problems?

The recreational drug ecstasy, also known as “XTC” or “E,” Adam, Clarity, or Essence, is widely used by young people throughout the United States and Western Europe. The drug is an amphetamine derivative, with the pharmacologic name 3,4-methylenedioxymethamphetamine (MDMA). Its popularity has been enhanced by its close association with particular forms of music and dance venues and, despite well-publicized cases of MDMA-associated death, by the widely held belief that it is a “safe” drug. Indeed, many users and social commentators believe that with better management, the negative consequences of MDMA use can be avoided.¹ This belief is based on the false premise that the danger associated with MDMA lies exclusively with poor control of environmental temperature and “bad” or adulterated drug. The latter risk, it is believed, would be eliminated by better quality control as a result of legalizing the drug. A review of the scientific literature, however, paints a very different picture of this drug, which is far from benign.

ANIMAL STUDIES

Evidence of neurotoxicity

Numerous animal studies have yielded clear evidence of potent neurotoxic effects of MDMA that are specific to central serotonergic (5-HT) systems.² Given the important role that 5-HT plays in regulating emotion, memory, sleep, pain, and higher order cognitive processes, it is possible that MDMA might cause a variety of behavioral and cognitive deficiencies, as well as impairing memory. Although the applicability of these results to the human condition has been vigorously contested, clinical observations are sufficient to raise legitimate concern over the negative consequences of exposure to MDMA in humans.

The evidence that MDMA is toxic to central serotonergic nerve terminals was derived from experiments in several different species, including rats² and a variety of subhuman primates.^{3,4} The latter group appears to be

up to 4 times more susceptible to MDMA than are rodents. Although initially it was thought that toxicity required multiple exposure to relatively high doses of MDMA, subsequent studies have shown that a single exposure to a high dose, or several exposures to lower doses, can induce the same profile of toxicity.⁵ More recently, studies in rats showed that even a single exposure can result in some manifestations of neuronal damage⁶; in primates, both the doses and treatment regimens that produce neurotoxic effects overlap with those doses that some humans received when using ecstasy recreationally.⁷

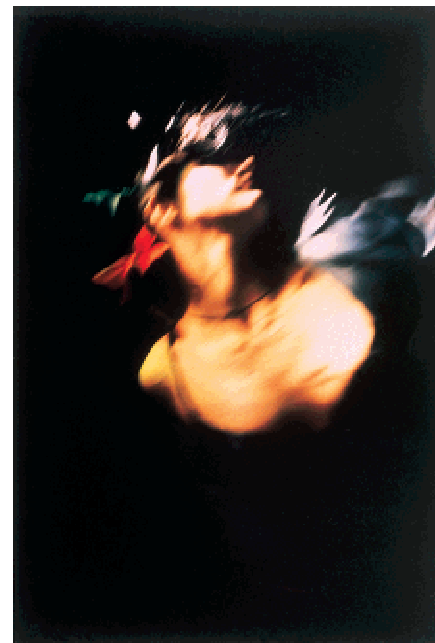
Radiologic and cognitive changes

Despite the loss of a high proportion of 5-hydroxytryptamine (5-HT) terminals throughout the forebrain in animals, functional imaging reveals that the short- to medium-term effects of repeated MDMA treatment are largely limited to alterations in subfields of the hippocampal formation⁸ where changes in glucocorticoid and 5-HT receptor expression are also evident.^{9,10} These same changes in the hippocampus are thought to underlie a range of neuroendocrine, affective, and cognitive dysfunctions associated with clinical depression and normal aging. Although initially it proved difficult to find any cognitive sequelae that correlated with these changes,¹¹ recent animal studies have shown subtle, but lasting, deficits in cognitive behaviors that do correlate with the levels of damage to 5-HT systems in the hippocampus.¹²

HUMAN STUDIES

Evidence of neurotoxicity

Evidence from human studies has accumulated more slowly, but it is becoming apparent that the toxic effect of MDMA on central serotonergic systems found previously in animal studies has a clear parallel in human users of the drug. There is now direct evidence of a lasting decrease in 5-HT uptake sites (a marker for the integrity of 5-HT nerve terminals) in human volunteers with a past history of MDMA abuse.¹³ Moreover, this decrease correlates positively with the extent of their self-reported previous exposure to the drug, and is in keeping with decreases in more general biochemical markers for central



Joseph Orenzif/Trevillion Pictures

Recreational use of ecstasy can affect brain function

serotonergic activity reported elsewhere.¹⁴ Positron emission tomographic (PET) imaging has revealed that the consequences of MDMA toxicity may be even more widespread than predicted from animal experiments. In addition to the hippocampal formation, both the amygdala and areas of neocortex may be affected by MDMA.¹⁵

Cognitive changes in ecstasy users

The manifestations of this neurotoxicity, in terms of altered cerebral function and behavioral change, range from neuroendocrine impairments¹⁶ to deficits in verbal memory and reasoning,¹⁷ short-term memory and semantic recognition,¹⁴ and visual memory.¹⁸ More general indices of intelligence are also adversely affected,¹⁹ but reports of serious long-term psychiatric disorders are still rare, with the possibility that previous exposure to MDMA merely accentuates preexisting negative personality features.²⁰ One particularly worrying feature that has emerged is that chronic psychosis, when manifest in MDMA users, reportedly responds poorly to therapy.²¹

The effects of MDMA on cognitive performance arising directly from drug-induced neurotoxicity may be compounded by indi-

rect effects on the cerebral circulation. As well as providing extensive innervation of fore-brain neuronal systems, there is also evidence that cerebral blood vessels are innervated by the same serotonergic neurons arising from the mesencephalon.²² It should not be surprising then that both acute and chronic treatments with MDMA produce cerebrovascular effects. In rats, the acute effect of MDMA is to produce pronounced focal cerebrovascular hyperemia,²³ which, in anatomic distribution, is directly parallel to the occurrence of MDMA-associated hemorrhagic stroke in humans.²⁴ In contrast, the chronic cerebrovascular effects of MDMA are more subtle under normal physiologic conditions and require the superimposition of physiologic stress before becoming fully apparent.²⁵ It is now evident that MDMA abuse is an important risk factor for cerebrovascular accidents in young people. If these vascular accidents are neurologically silent, however, they may only become apparent at a later date. This effect may parallel the type of cognitive decline seen in patients with multi-infarct dementia.

What should we tell ecstasy users?

Findings from animal studies suggest that long-term cognitive problems are associated with MDMA exposure, and clear parallels are now emerging from clinical experience.

It is important, however, not to overstate the case. The young people most at risk are likely to reject out of hand any "scare stories," since they feel that there have been only a few well-publicized cases of harm from the drug. These numbers are small compared to the numbers of individuals who use MDMA regularly. Studies of the drug can be criticized on the basis that they depend heavily on the quality of self-reported data. The data analysis may also be confounded by failure to report multiple drug use or inaccuracies in the reported duration of drug abstinence immediately prior to the investigation.

Nevertheless, health care professionals should be aware that cognitive disorders, mood disturbances, and increased risk of cerebrovascular accidents are among the possible long-term, negative consequences of MDMA exposure in humans.²⁶⁻²⁸ Although subtle at first, these effects may develop into major deficits over the lifetime of an other-

wise healthy individual. In particular, minor short-term deficits may be exacerbated by interaction with normal aging processes in the brain, or as a result of subsequent exposure to physiologic or psychologic stress. Even if these long-term effects are confined to a sub-population of particularly susceptible individuals, the very scale of current usage—3.4 million young Americans have used the drug at least once—is such that the consequences of MDMA exposure could develop into a major health care problem for the future.

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