

CONTINUED...

users who have been abstinent for a period of a few weeks to a few months - longer-term studies have been planned or are underway - and these have shown that the adverse psychiatric and cognitive changes associated with MDMA use are persistent.

In attempting to answer the question of whether MDMA causes permanent damage to human memory abilities, there is no one study that provides a resounding, definitive yes. To be sure, no study provides any evidence that MDMA is a beneficial drug or even that it is safe when taken in moderation. In fact taking MDMA at any dose carries with it the risk of inducing physiological, psychological, and cognitive damage in vulnerable users. Clearly, there is still room to debate the exact nature of the deficits produced by MDMA use. Nevertheless, based on the results from the overwhelming majority of studies conducted so far, the data show that MDMA can be harmful to human health.

Methodological Issues

As much as the data collected so far largely supports the proposition that MDMA damages the serotonin system in the brain and produces long-lasting behavioral deficits, researchers agree that methodological issues, such as limited sample size and difficulties controlling for the possible influence of other illicit substances, have made it difficult to move beyond generalities and unequivocally prove a cause and effect relationship between MDMA use and specific cognitive or psychological damage in humans.

All of the studies reviewed in this report have relied on self-referred MDMA users, recruited through targeted sampling techniques by advertising for volunteers or through word-of-mouth. This introduces an unknown bias into each study since it is possible that such self-referrers are not representative of MDMA users as a whole. There is also the problem of verifying that what users report as Ecstasy is, in fact, solely MDMA. In addition, it is impossible to verify self-reports of past drug use beyond a certain period of time, making it difficult at best to accurately control for prior drug use.

Since there seem to be few, if any, young people who use MDMA without also abusing other drugs, this will continue to be a confounding factor in future studies. Some investigators have tried to accommodate this problem by using a control group comprising individuals who have never used MDMA but who otherwise have closely matched histories of using other drugs of abuse. This type of control has not been used universally, however, and even when it is, it may be difficult to closely match users and controls for prior drug use, as well as on other demographic details such as educational level and age.

Self-reporting also means that it is not possible to determine

with complete confidence or accuracy how much a person has consumed, either on a particular occasion or over a lifetime of use. This uncertainty arises for two reasons: MDMA content is not constant across all tablets, and user memory of how much and how often a person took MDMA over many years is far from reliable.

Ideally, researchers would like to be able to study MDMA's effects in drug-naïve humans, and indeed, a limited number of groups in Europe have received approval from the appropriate governmental regulatory agencies and institutional review boards to conduct what would essentially be Phase I safety trials with MDMA in a limited number of humans. However, there is little likelihood of studying the effects of MDMA on large numbers of drug-naïve volunteers. An alternative might be to conduct longitudinal, controlled prospective studies, in which current MDMA users and controls of non-MDMA users are followed for many years to observe changes from some defined baseline.

Challenges and Future Directions

Though the data presented at this conference and in the literature support the hypothesis that MDMA produces acute behavioral and physiological effects, there is still more to be determined about factors that precipitate severe acute toxicity. For example, are there predisposing genetic factors that increase the risk for acute toxicity? Is overall health status important? Which organs and systems are the primary targets of MDMA toxicity? Are interactions with other drugs important? Does MDMA use lead to tolerance, withdrawal, and craving?

Because MDMA is not the only drug taken by young adults, there is a need for more characterization of interactions between these substances and a determination of how those drug interactions may influence acute toxicity. Is the practice of "bumping" or taking sequential doses of MDMA particularly dangerous? How do individual genetic factors influence MDMA metabolism and drug interactions?

One critical piece of missing data is the incidence of acute toxicity among MDMA users. Assembling this database will require improved emergency room reporting of MDMA-associated incidents. In addition, data do not yet exist on the number of people seeking treatment for MDMA-related dependence and behavioral or psychological problems.

One of the key concerns raised at the meeting was the lack of longitudinal studies designed to follow MDMA users, both as they continue to use the drug and after they have stopped using it. Such studies may provide important insight into how age and length of use affect MDMA's acute and long-term neurochemical toxicity. In addition, such studies would allow researchers to determine if deficits appear later in life, long after use stops, or if adverse effects diminish over time. Such studies, if designed with regular assessment intervals, might also allow researchers

CONTINUED...