Short Communication

A CLINICAL CROSSROADS FOR MDMA

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Abstract—Clinical studies of MDMA have been hindered by the fear of harming participants through MDMA-induced neurotoxicity. However, experimental animal studies and brain imaging studies of recreational Ecstasy users have not evidenced that a therapeutic dose of MDMA would be sufficient to cause long-term serotonergic deficits. Furthermore, the issue of potential neurotoxicity may not be as important as it first seems since certain chemicals have been shown to protect against MDMA-induced neurotoxicity. Although clinical studies conducted thus far have been promising, more research into the effects of MDMA administration in humans is needed before solid conclusions can be made in respect to the possibility of safely using MDMA as an adjunct to therapy. Finally, a clear distinction should be maintained between the recreational and clinical use of MDMA

Keywords—clinical, Ecstas, MDMA, neurotoxicity, serotonin

Prospective clinical studies of MDMA, where the purity and dose of the MDMA used is controlled within a group of subjects that can be monitored before, during, and after the experiment, are just beginning to appear. One issue that has plagued the progress of these studies is the question of whether the dose of MDMA required to induce a therapeutic state of mind (a dosage of approximately 1.7 mg/kg) could possibly cause neurotoxic damage in participants (Vollenweider, Jones & Baggott 2001). However, since animal studies have shown that certain chemicals can protect against MDMA's neurotoxic effects, such as selective serotonin reuptake inhibitors (SSRIs) or ketanserin, this issue may not be as prominent as it first appears to be (Nash, Meltzer & Gudelsky 1990; Schmidt 1987). Therefore, while the issue of whether a therapeutic dose of MDMA can cause neurotoxicity is still of importance, the greater issue may be if there are chemicals that can belay neurotoxic concerns altogether without canceling the positive behavioral aspects of clinical MDMA use.

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MDMA NEUROTOXICITY IN MONKEYS VERSUS CLINICAL USE IN HUMANS

The effects of MDMA administration in monkeys are likely to closely model the effects of MDMA use in humans, so it is relevant to assess studies in monkeys that used doses close to that of a clinical dose of MDMA. Ricaurte and colleagues (1988), measuring two weeks after administration, observed 5-HT deficits in six different brain regions in monkeys that were orally administered 5 mg/kg of MDMA twice daily for four days; the reductions ranged from about 30% to 60%. Although not as severe in its effect, a single oral dose of 5 mg/kg still lessened 5-HT content in the hypothalamus and thalamus, with reductions of about 15% and 20% respectively. However, since this study used a dose three times greater than that used in a clinical setting, it may not serve as an accurate basis for comparison. Taking the dosage a step down, Insel and colleagues (1989) failed to find any significant reductions in 5-HT uptake sites in monkeys that were injected with 2.5 mg/kg of MDMA twice daily for four days. While it could be argued that humans are likely to be more greatly affected by MDMA's neurotoxic effects at the doses used in monkeys, it is still notable that multiple and frequent injections of MDMA at a dose of 2.5 mg/kg were not sufficient to cause neurotoxicity, especially in light of the determination that the oral route of administration attenuates MDMA neurotoxicity by about 30% to 70% (Ricaurte et al. 1988). Based on these results, it seems that greater doses of MDMA than those clinically administered to humans on an occasional basis would be necessary to induce neurotoxicity, although a precise margin of safety for MDMA use is still unknown.

RECREATIONAL ECSTASY USE VERSUS CLINICAL USE IN HUMANS

Recent brain imaging studies of recreational Ecstasy users that reported differences in serotonin transporter (SERT) binding might be useful in attempting to answer the question of whether the clinical use of MDMA is likely to cause neurotoxicity. Several studies have found significantly less SERT binding in frequent Ecstasy users in comparison to Ecstasy-naive controls. Most of these studies have revealed modest regional brain differences in SERT binding, ranging from approximately 5% to 15%(Buchert et al. 2004, 2003; Thomasius et al. 2003; Reneman et al.

2001a, b; Semple et al. 1999). However, a few of these studies have revealed more drastic differences, ranging from approximately 10% to 70% (McCann et al. 2005, 1998). Importantly though, differences in SERT binding found thus far have been in users who had on average taken Ecstasy at high levels (typically more than one pill per occasion, with a maximum dose of several pills) on a frequent basis (usually a few times per month or more) over extended periods of time (a mean duration of three or more years). Given the dose-dependent relationship of MDMA-induced neurotoxicity in experimental animal studies, it would not be surprising if ingesting multiple doses of Ecstasy frequently over a long period of time actually did destroy 5-HT axons in the human brain. Furthermore, certain factors may serve to increase the risk of 5-HT neurotoxicity in recreational Ecstasy users, including the use of MDMA in combination with other drugs such as amphetamine (Cole & Sumnall 2003), a high ambient temperature while under the influence of MDMA (Colado et al. 1999), and the concomitant use of other neurotoxic drugs such as methamphetamine (Ricaurte, Schuster & Seiden 1980). In contrast to recreational Ecstasy use, the clinical use of MDMA involves the occasional ingestion of single doses in a controlled setting. Therefore, the results of brain imaging studies of frequent Ecstasy users may not be particularly relevant to the use of MDMA as a therapeutic adjunct. Additionally, differences in SERT binding have not been found in moderate Ecstasy users or in Ecstasy users who had abstained from use for 20 weeks or longer (Buchert et al. 2004, 2003; Thomasius et al. 2003; Reneman et al. 2001a, b). Thus far, the results of brain imaging studies do not evidence that the careful and controlled use of MDMA in a clinical setting would be sufficient to cause long-term serotonergic decline.

RECENT STUDIES OF MDMA USE IN A CLINICAL SETTING

Vollenweider and colleagues (1998) conducted a double-blind study in which healthy volunteers who had never been exposed to MDMA were compared to control participants given placebos. Psychological measures of participants orally administered 1.7 mg/kg of MDMA showed significant increases in scores of thoughtfulness-contemplativeness, positive mood, and self-confidence. These measures also failed to indicate significant changes in delusional thought content, hallucinatory experiences, or loss of thought control. No serious side effects or complications were noted, and common adverse side effects, such as jaw clenching, loss of appetite, and impaired balance, were not seen as problematic. Participants administered MDMA subjectively reported greater acknowledgement of emotions, a heightened sense of closeness to others, and an increase of verbal openness. In conclusion, the authors stated that the findings of this study support the notion that MDMA is a unique psychotropic, quite distinct from the classic hallucinogens and stimulants.

Liechti and colleagues (2000a) conducted a similar study that looked at the psychological effects of participants given an SSRI (citalopram) previous to an oral dose of 1.5 mg/kg of MDMA. The authors noticed that although the subjective effects of MDMA were reduced by citalopram pretreatment, they were extended over a longer period of time, evoking a change in the mean duration from three hours to five hours. They also commented that citalopram binds with the highest affinity to 5-HT uptake sites of all the SSRIs currently available, a fact that could mean other SSRIs may interfere less with MDMA's psychoactive effects. However, since citalopram was effective at reducing MDMA's psychological effects by about 60% and did not completely block them, the authors concluded that MDMA's effects on the 5-HT uptake site must only be part of its course of action in eliciting behavioral responses. Liechti and colleagues hypothesized that postsynaptic 5-HT sites and dopamine receptors probably play some role in its behavioral effects. Surprisingly, the authors did not mention the possibility of halting neurotoxicity through the administration of an SSRI as late as three hours after MDMA administration (Schmidt 1987). Although administration of an SSRI previous to that of MDMA has been shown to interfere with MDMA's psychological effects, the administration of an SSRI as late as three hours after MDMA administration could allow MDMA to induce its full psychological effects while at the same time not allowing MDMA to induce its neurotoxic effects.

In another similar study, Liechti and colleagues (2000b) studied the effects of pretreatment with ketanserin, a 5-HT_2 antagonist, on participants orally administered 1.5 mg/kg of MDMA. Interestingly, ketanserin had little or no effect on the positive behavioral changes induced by MDMA. At the same time, it significantly reduced emotional excitation, alterations in perception, and the number of adverse side effects reported by participants. Since antagonism of 5-HT_2 receptors by ketanserin significantly reduced hallucinogen-like experiences in participants, the authors concluded that these perceptual changes are probably mediated in part by these receptors. Also, in light of the fact that ketanserin has been shown to protect against MDMA-induced neurotoxicity (Nash, Meltzer & Gudelsky 1990), its additional ability to reduce the negative effects associated with MDMA use makes it a prime candidate for ensuring the safe use of MDMA in a clinical setting.

Liechti, Gamma and Vollenweider (2001) employed an experimental design much like the previous studies when they observed gender differences in participants given oral doses of MDMA ranging from 1.35-1.8 mg/kg. The mean duration of an MDMA experience in this study was 3 1/2 hours. The researchers' primary finding was that MDMA's subjective effects seemed to be greater in women than in

men. The authors commented that this was in accord with retrospective studies of Ecstasy users that suggested that MDMA-induced neurotoxicity may be more pronounced in women than in men, even when accounting for differences in weight.

CONCLUSION

Thus far, clinical studies of MDMA have been promising. Positron emission tomography (PET) of participants who had taken a single oral dose of MDMA revealed no significant changes in their SERT binding (Vollenweider, Jones & Baggott 2001). Positive measures of behavior have shown increases after MDMA administration, while negative measures of behavior and negative side effects have been minimal. In addition, chemicals known to protect against MDMA neurotoxicity present the possibility of the safe use of MDMA as a therapeutic adjunct, regardless of what dosage of MDMA is likely to cause neurotoxicity in humans.

Few individuals would be willing to dispute that the recreational use of Ecstasy can lead to harm, and in rare cases, even to death. However, those mental health professionals interested in the therapeutic use of MDMA will continue to fight for a fair proving ground. On this note, it is important that a clear distinction be maintained between the recreational and clinical use of MDMA. Although relevant studies seem to indicate that the clinical use of MDMA would not cause neurotoxicity, more prospective research into the effects of MDMA administration in humans is needed before firm conclusions can be made. Finally, the potential to stifle neurotoxic concerns altogether, possibly through pretreatment with ketanserin or through the administration of an SSRI as late as three hours after MDMA administration, needs to be addressed more thoroughly.

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