Response to Ricaurte et al. 2003 (reply to Mithoefer et al. 2003)
By Mithoefer, Jerome and Doblin

BACKGROUND AND SUMMARY

On June 6, 2003, Science published an exchange of letters about MDMA neurotoxicity between Mithoefer and colleagues (Mithoefer et al. 2003) and Ricaurte and colleagues (Ricaurte et al. 2003). Since Science doesn't publish replies to letters, we (Mithoefer, Jerome and Doblin, all members of the MAPS MDMA/PTSD research team) have chosen to continue the debate by writing this response to the Ricaurte et al. letter.

These letters represent the latest exchange in an argument that began in 1985 when Ricaurte's data about MDA neurotoxicity in rats was cited by the DEA as justification for the emergency scheduling of MDMA, which criminalized both the recreational and the therapeutic use of MDMA. Though the DEA's emergency scheduling was later found by the Courts to be invalid (the Attorney General had failed to subdelegate emergency scheduling power to the DEA), and after two years of hearings the DEA Administrative Law Judge recommended that MDMA be placed in Schedule III to permit its medical use, both medical and non-medical use of MDMA remain illegal. MAPS' MDMA/PTSD protocol represents the first and only FDA-approved study of the therapeutic use of MDMA in the 18 years since MDMA was criminalized.

The Mithoefer letter critiqued the MDMA risk assessment in a Ricaurte et al. paper, previously published in Science (Ricaurte et al. 2002). In that paper, Ricaurte et al. reported on dopamine function in squirrel monkeys and baboons injected with repeated doses of MDMA and raised the alarm that "even individuals who use MDMA on one occasion may be at risk for substantial brain injury if they use two or three sequential doses, hours apart, as is often the case in recreational settings." Ricaurte concluded that "humans who use repeated doses of MDMA over several hours are at high risk…for developing Parkinsonism and other neuropsychiatric diseases…"(Ricaurte et al. 2002).

The Mithoefer letter ended with the following sentence, "We hope the theoretical risks suggested by this study are not inappropriately generalized to clinical MDMA research, which has been conducted without evidence of toxicity (including no detectable changes in serotonin transporter or memory)." Ricaurte et al. concluded their reply with the following statement, also about the therapeutic use of MDMA, "Although we understand that Mithoefer and colleagues feel strongly about the potential therapeutic effects of MDMA, we remain of the opinion that there are not sufficient data to conclude that clinical MDMA research can be conducted without running the risk of monoaminergic brain neural injury."

It is telling to note that Ricaurte et al. do not attempt to refute our statement that there is no evidence of neurological or functional toxicity associated with clinical use. Instead, they make a weak claim that is logically impossible to refute, saying that there isn't enough data to conclude that there is no risk associated with the clinical use of MDMA. As they well know, there is never enough data to prove a negative such as the absence of

risk. Nor do we claim that there is no risk, but instead focus on conducting a rational risk assessment followed by a balancing of risks and benefits. What we do claim, in part based on research by Ricaurte et al., is that there are minimal and acceptable risks associated with the oral administration of 125 mg MDMA in a clinical context.

MORTALITY RATE: DISCREPANCIES BETWEEN RICAURTE ET AL. LETTER AND PAPER AND BETWEEN RICAURTE'S PRIMATES AND HUMANS

Ricaurte et al. make a misleading statement in their letter that "one of ten monkeys treated with our sequential dosing regimen of MDMA that we used died of complications related to hyperthermia." This directly contradicts statements made in the original paper that two primates died of hyperthermia. In addition, two more did not receive the third planned injection due to signs of behavioral toxicity. Ricaurte et al. may have treated more monkeys than stated in the paper. However, their letter fails to acknowledge a fatality in the baboons treated in their study. The actual mortality rate is quite important, even given their small sample size, since it calls into question the claim made by Ricaurte et al. in the title of their paper that they administered the equivalent of a "common recreational dose regimen of MDMA."

In their paper, they report that one out of five squirrel monkeys treated with MDMA "developed malignant hyperthermia and died within hours after receiving the last dose of MDMA" while another squirrel monkey "had unstable, tentative gait after the second dose, and therefore was not give the third planned dose." They also report they treated five baboons, and that "again, one of five animals died, this time shortly after receiving only two doses of MDMA. Malignant hyperthermia (up to 41.6 C) was again an important factor. A second baboon appeared unstable after the second dose of MDMA, and therefore received only two of the three planned doses."

Hyperthermia is a well-known complication of ecstasy use (Henry and Rella 2001), but examination of relevant data indicates that is not common. When considering the following statistics, it must be kept in mind that most ecstasy-related ER visits and fatalities result from when ecstasy (often containing other drugs in addition to or instead of MDMA), is taken in combination with other drugs. Calculations from several papers indicate that between 0.01% and 0.029% of all ecstasy exposures result in emergency room visits (Baggott 2002; Baggott et al. 2001). Furthermore, up to 75% of ecstasy-related ER admissions are likely due to mild to moderate complaints, such as feeling anxious or dizzy (Cregg and Tracy 1993; Williams et al. 1998). Ecstasy-associated mortality has been estimated to be between 0.021% and 0.087% in ecstasy users (across multiple episodes) (Baggott 2002). By contrast, 20% of the animals in Ricaurte's studies died after just one episode, and up to 40% experienced severe adverse effects (though percentages may be lower if in fact more animals were treated than originally reported). The greater frequency of hyperthermia and fatalities reported by Ricaurte and colleagues suggests that the dose regimen used is not equivalent to doses commonly employed by human users.

DATA SHOWING HEAVY MDMA USE HAS NO EFFECT ON DOPAMINE

Ricaurte et al dismiss the three studies we cited that showed no dopaminergic reductions in heavy MDMA users by claming that, "if "binge" users were not included or were insufficiently represented, DA markers [including the dopamine transporter (DAT)] would not be expected to differ significantly from those in controls." What constitutes "binge use" is left undefined.

One of the studies we cited (Kish et al. 2000) was an autopsy study of a polydrug user (reportedly used MDMA, cocaine and heroin) who died from an unspecified drug overdose at age 26. He is reported to have consumed MDMA on over 300 occasions, and "from age 23-26, he would use the drug [MDMA] four to five nights a week, at rave clubs. This usually included a three-day weekend binge at which 6 to 8 tablets of MDMA would be ingested." Based on estimates of ecstasy tablet content (Baggott et al. 2000; Cole et al. 2003), this individual may have regularly consumed between 420 and 560 mg per session, or 6 to 8 mg/kg, and dosage could have been as high as 840 mg per session. While there were signs of serotonin neurotoxicity in this case, there was no evidence of dopamine toxicity. If this case does not qualify as a "binge user," then contrary to Ricaurte's earlier claims, "binge users" cannot be all that common. And if this doesn't qualify as binge use, what does?

In the second study that we cited (Reneman et al. 2002), dopamine transporter densities in 29 Ecstasy users, who averaged 324 tablets with an average use of 1.7 (+-0.7) tablets per occasion, were no different than controls. A separate group of 9 Ecstasy users who averaged 358 tablets with an average use of 2.3 (+-0.7) per occasion, who also used amphetamine an average of 47.5 times in the previous year with an average use of 410 mg each occasion, did show about 12% lower striatal dopamine densities as compared to Ecstasy users who did not use amphetamine. Reneman et al. suggest that "while sole ecstasy use does not decrease striatal DA transporter densities in human beings, the combined use of amphetamine and ecstasy may be associated with reduced striatal DA transporter densities."

Participants in the third study we cited (Semple et al. 1999) had consumed an average of 672 (+-647) tablets (range 50-1800). While the average number of tablets per occasion was not reported, it is likely to be rather high considering that the average age was 25.5 years (+-4.4 years). Again, SPECT revealed no evidence of lower dopaminergic transporter densities.

An examination of these studies suggests that whatever "binge use" may be, as defined by Ricaurte et al., it is not frequently practiced by ecstasy users. If this use pattern occurs often, how can it be that the heavy users in the studies above showed no reductions in dopamine?

Most importantly, these studies involve subjects who self-administered substantially higher and more frequent doses of Ecstasy than will be administered in any clinical research settings. Certainly, the clinical use of MDMA does not qualify as binge use. Therefore, according to Ricaurte et al.'s own risk assessment, after the use of MDMA in a

clinical non-binge context, the "DA markers [including the dopamine transporter (DAT)] would not be expected to differ significantly from those in controls."

CLINICAL USE OF MDMA WITHOUT SEROTONIN REDUCTION

Ricaurte et al. dismiss as unpublished and then ignore the data that we cited showing no serotonin transporter reductions in MDMA-naïve subjects after the administration of up to two doses of 1.5 to 1.7 mg/kg MDMA (Vollenweider et al. 2001; 2000). This data deserves more than a mere dismissal, as this is the only study ever conducted in which PET was performed before and after the administration of MDMA in a clinical setting. Vollenweider et al. are a highly regarded and prolific team with numerous MDMA-related publications and are preparing for publication a paper on the PET research described above, along with more recent findings of no changes in neurocognitive performance after one or two administrations of MDMA (Ludewig et al. 2003).

Since we submitted our letter to Science, the largest ever PET study of recreational users of Ecstasy was published (N=117) (Buchert et al. 2003), as was a separate paper reporting on neurocognitive and mood tests conducted in the same subjects (N=120) (Thomasius et al. 2003). These studies lend further support to our conclusion that subjects face minimal risk from the two doses of pure MDMA to be administered in our study. Current users of MDMA, who had on average consumed 827 tablets of Ecstasy, had serotonin transporter levels in a few brain regions that were between 4% and 6% lower than controls, an amount unlikely to be clinically significant. Serotonin transporter levels in former Ecstasy users, who averaged 799 tablets of Ecstasy, were the same as controls, suggesting recovery over time. Current MDMA users scored the same as controls on neurocognitive and mood tests. Surprisingly, former users scored somewhat lower than controls on some neurocognitive tests, though not on mood tests, suggesting that memory findings in some Ecstasy users result from factors other than serotonin levels.

While MDMA is clearly not risk-free, these studies in Ecstasy users suggest that two moderate doses of pure MDMA administered in a clinical context are not likely to produce significant reductions in serotonin or any adverse neurocognitive consequences.

INTERSPECIES SCALING

Ricaurte and colleagues express concern about our noting their failure to follow rules of interspecies scaling in their dosage regimen. We never claimed that Ricaurte and colleagues used interspecies scaling in the relevant study, as can be seen by reading the text to the letter. We mentioned it only because in previous papers and correspondence (e.g. Ricaurte et al. 2000; McCann and Ricaurte 2001), the authors have insisted on extrapolating findings from non-human studies to humans via interspecies scaling. If interspecies scaling is as reliable as they claim, then why did the authors forego it in this study? Furthermore, the very title of their paper shows an implicit use of interspecies scaling in that they claim that they have administered the equivalent of a "common recreational dose regimen of MDMA."

MDMA TOXICITY IN MICE

Ricaurte and colleagues state that we "ignore" findings of MDMA-induced dopamine toxicity in mice. Given the limited space allotted to our letter, we saw no reason to refer to this well-known fact. Yet there is no reason to assume that the MDMA-associated dopamine neurotoxicity in mice bears any relation to Ricaurte's findings, particularly since equivalent or nearly equivalent doses provoke only serotonin, but not dopamine, neurotoxicity in rats. Recent studies suggest that the process leading to MDMA neurotoxicity in mice differs from that in rats (Colado et al. 2001; Sanchez et al. 2003). Dopamine neurotoxicity in mice after MDMA sheds no light on dopamine neurotoxicity in humans except to indicate the importance of interspecies differences. It could just as easily be said that similar, and as yet undiscovered, differences in primates explain the appearance of dopamine toxicity in some primates, but not in others.

ROUTE OF ADMINISTRATION: ORAL V. SUBCUTANEOUS INJECTION

The authors contend that route of administration does not greatly affect degree of toxicity seen after MDMA, and the literature largely supports their contention (Finnegan et al. 1988; Kleven et al. 1989; Ricaurte et al. 1988; Slikker et al. 1988). However, only one of the studies cited by Ricaurte et al. was in squirrel monkeys, one of the two primate species used in their recent publication, and none were in baboons, the other primate species they used. While Ricaurte et al. report in their letter that the difference between oral and subcutaneous injection in squirrel monkeys varied by brain region, they summarized these differences quantitatively in their abstract stating, "Orally administered MDMA was approximately one-half as effective [at reducing serotonin] as subcutaneous administered drug."

HUMAN SPINAL TAP STUDIES

Referring to studies in rabbits and humans, Ricaurte and colleagues argue that reduced homovanillic acid (HVA) in cerebrospinal fluid (CSF) is not a good marker of dopamine function, and research failing to find lower HVA in ecstasy users cannot be used in a case against dopamine toxicity in humans (Loeffler et al. 1995; Parkinson Study Group 1995). It should be noted that the study cited above in humans was of people with Parkinson's disease and did not employ any direct measures of dopamine function, only behavioral measures of disease progression. Ricaurte and colleagues may be correct in their assertions, but the fact remains that studies conducted by Ricaurte that assessed CSF levels of dopamine metabolites still failed to find reduced levels in ecstasy users. At the time these studies were conducted, Ricaurte considered the gathering of CSF measures to be worth the pain to the subjects. While it is gratifying to see scientific progress result in the abandonment of methods previously thought relevant, this calls for a degree of humility in evaluating the reliability of currently cutting-edge methods, the flaws of which remain to be discovered. This is particularly relevant since prior PET studies conducted by Ricaurte, Vollenweider and Buchert's teams all used a ligand that is now considered to generate unreliable data in the cortex.

METHAMPHETAMINE AND PARKINSON'S

Counter to our assertions of little or no association between methamphetamine use and reduced dopamine transporter or movement disorders, Ricaurte and colleagues claim that studies exist that demonstrate reduced dopamine transporter and signs of movement disorders in methamphetamine users. However, the studies cited by Ricaurte and colleagues offer mixed support for their claims. Their own study (McCann et al. 1998) found that dopamine transporter levels in methamphetamine users were not significantly different from those in people with early-onset Parkinson's disease. Setting aside the possibility that early-onset Parkinson's disease is not identical to the more common form of Parkinson's disease, it is thus surprising that no motor problems are described in the methamphetamine-using group. The study by Volkow and colleagues cited in Ricaurte's letter (Volkow et al. 2001) assessed dopamine D2 receptor density in methamphetamine users, and not dopamine transporter sites, finding lower levels in methamphetamine users. Volkow and colleagues did compare dopamine transporter levels in a sample of five methamphetamine users, and measured fine and gross motor skills. This study found an increase in markers of dopamine transporter binding in abstinent methamphetamine users, and improvement on one motor task, but not another. Their research findings failed to demonstrate a direct link between changes in dopamine transporter binding and motor task performance in abstinent users, and call into question findings of irreversible reduction in dopamine transporter after methamphetamine use. However, despite focusing on studies assessing dopamine transporter, Ricaurte and colleagues did not refer to this study. The third study cited (Sekine et al. 2001) found lower dopamine transporter in methamphetamine users but did not measure motor performance. The only study examining motor task performance was not cited by the authors. At the very least, Ricaurte and colleagues are overstating the case for an association between reduced dopamine transporter in methamphetamine users and long-lasting impairments in motor task performance. This suggests that even if reduced dopamine transporter were found in ecstasy users, such findings cannot serve as evidence of greater risk for developing Parkinson's disease. Furthermore, methamphetamine is currently an FDA-approved medicine marketed for the treatment of obesity and attention deficit disorder, and is prescribed on a daily basis. The risks of MDMA administered several times in the context of clinical research are likely to be substantially lower than the daily administration of methamphetamine.

CONCLUSION

Ricaurte et al. do not dispute our statement that there is no evidence that the clinical use of MDMA is associated with neurotoxicity or functional consequences. Instead, they assert a weak claim that is logically impossible to refute, saying that there isn't enough data to conclude that there is no risk associated with the clinical use of MDMA. We do not claim that there is no risk, but instead focus on conducting a rational risk assessment followed by a balancing of risks and benefits. What we do claim, based in part on research by Ricaurte et al., is that there are minimal and acceptable risks associated with the oral administration of 125 mg of pure MDMA in a clinical context.

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