CORRESPONDENCE

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Effects of MDMA (ecstasy) use and abstention on serotonin neurons

Sir—There is need for ecstasy users, the general public, and diverse governmental agencies involved in drug use policy to obtain accurate information on the risks of 3, 4-methylenedioxymethamphetamine (MDMA or ecstasy). The study of Liesbeth Reneman and colleagues (Dec 1, p 1864),[1] and previously, McCann and colleagues' report,[2] have been highly quoted by the media on the toxic effects of ecstasy to the human brain. Unfortunately, these studies are sufficiently flawed in terms of methods and presentation of data to make a clear and simple conclusion impossible.

Reneman and colleagues and McCann and colleagues use radioligands, which bind to the serotonin transporter (SERT), with differences in brain-binding concentrations representing differences in concentration of serotonin neurons. Unfortunately, whether SERT was ever reliably measured is uncertain. Thus, in McCann and colleagues' study, binding data in normal participants were so scattered that the researchers needed to logarithmically transform the data. Since this wide scatter of SERT values cannot correlate with any known index of serotonin neuron integrity, their data cannot be viewed as reliable (no test-retest data were provided) or valid.

Reneman and colleagues selected for study a radioligand, 123-labelled-iodine 2β-carbomethoxy-3β-4-iodophenyl ([^{123}I]β-CIT), which is not selective for SERT. [^{123}I]β-CIT binding to areas of high SERT density in living human brain is displaced only by about 50% by a selective serotonin transporter blocker,[3] which suggests that much of the binding is to non-SERT transporters. At best, the sum of norepinephrine, dopamine, and serotonin transporters are slightly decreased (women only) in these non-striatal brain areas.

I agree with McCann and colleagues' later conclusion[4] about measurement in areas of low SERT density, that there is little evidence that [^{123}I]β-CIT can accurately measure specific binding to cortical SERT sites—two-thirds of the brain areas investigated by Reneman and colleagues. Perhaps it would have been better to have waited for the development of a SERT radioligand which is not subject to these validity problems.

To be informed on the risks of ecstasy, the reader needs to know the extent to which ecstasy might be toxic to human brain (ie, 9 *vs* 90% neuronal loss). It is extraordinary that two reports on ecstasy toxic effects can have omitted or not stated clearly (only log values provided[2]) the actual percentage reduction of SERT in the different brain areas. Finally, Reneman and colleagues do not acknowledge the striking discrepancy between their data and those of McCann and colleagues for loss of neurons.

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1 Reneman L, Booij J, de Bruin K, et al. Effects of dose, sex, and long-term abstention from use on toxic effects of MDMA (ecstasy) on brain serotonin neurons. *Lancet* 2001; **358:** 1864–69.

2 McCann UD, Szabo Z, Scheffel U, Dannals RF, Ricaurte GA. Positron emission tomographic evidence of toxic effect of MDMA ("Ecstasy") on brain serotonin neurons in human beings. *Lancet* 1998; **352:** 1433–37.

3 Pirker W, Asenbaum S, Kasper S, et al. β-CIT SPECT demonstrates blockade of 5HT-uptake sites by citalopram in the human brain in vivo. *J Neural Transm* 1995; **100:** 247–56.

4 McCann UD, Ricaurte GA, Molliver ME. "Ecstasy" and serotonin neurotoxicity: new findings raise more questions. *Arch Gen Psychiatry* 2001; **58:** 907–08.

Sir—Liesbeth Reneman and colleagues[1] report that the prevalence of current depression among MDMA users does not differ from controls with significantly lower serotonin neurochemical states on single-photon emission computed tomography in MDMA users. This finding contrasts with the well established low serotonin theory of depression. There are several possible explanations for this contrast.

First, the recruitment process could have excluded MDMA users with severe current psychiatric morbidity. The investigators do not comment on rates of psychiatric disorder other than depression, yet psychosis and a range of affective disorders are common in MDMA users.[2] If such disorders were absent, selective recruitment could also be responsible.

Second, Reneman and colleagues screened for psychiatric morbidity with the composite international diagnostic interview but do not specify how depression was diagnosed. If they adopted a high diagnostic threshold for the depression syndrome, they could have underestimated morbidity by excluding partial depressive syndromes.

Finally, assuming that psychiatric morbidity has not gone undetected, tested participants might have the short *SS* allele of the serotonin transporter, making them resistant to developing low-serotonin-related psychiatric symptoms and syndromes,[3] or alternatively, the low serotonin neurochemical state was compensated by other neurotransmitter systems, including norepinephrine, dopamine, or glutamate. In support of the latter view, we note that heavy MDMA users were more likely to have been recent users of cocaine or amphetamine.

Reneman and colleagues' findings have implications for the treatment of MDMA-related depression. We suggest clinical trials with norepinephrine reuptake inhibitors such as reboxetine in the treatment of MDMA-related depression, since this neurotransmitter system remains intact compared with the destroyed serotonin system. Furthermore, the selective serotonin-reuptake inhibitor, citalopram,[4] and dopamine-2-receptor blocker antipsychotic drug, haloperidol[5] only partly improve MDMA-related psychopathology.

Reneman and colleagues highlight that parieto-occipital and occipital cortical serotonin transporter are selectively decreased by MDMA. Why this mechanism arises or what the clinical importance is are unclear. One possible explanation is that these areas have high reserves of serotonin transporter that are not functional but were detected by neuroimaging technology. The types of such polymorphism of serotonin transporter need to be investigated.

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1 Reneman L, Boon J, Bruin K et al. Effects of dose, sex, and long-term abstention from use on toxic effects of MDMA (ecstacy) on brain serotonin neurons. *Lancet* 2001; **358:** 1864-69.

2 Parrot AC, Milani R, Parmar R. Recreational ecstasy/MDMA and other drug users from the UK and Italy: psychiatric symptoms and psychobiological problems. *Psychopharmacology* 2001; **159:** 77–82.
3 Whale R, Quested DJ, Laver D. Serotonin (5-HTTT) promoter transporter genotype may influence the prolactin response to clornipramine *Psychopharmacology* 2000; **150:** 120–22.
4 Liechti ME, Vollewneider FX. The serotonin reuptake inhibitor citalopram reduces acute cardiovascular and vegetative effect of' MDMA/ecstasy in healthy volunteers. *J Psychopharmacol* 2000; **14:** 269–74,
5 Liechti ME, Vollenweider FX. Acute psychological and physiological effects of' MDMA/ecstasy after haloperidol treatment in healthy humans. *Eur Neuropsychopharmacol* 2000; **10:** 289–95.

Sir—Liesbeth Reneman and colleagues[1] describe possible sex differences in MDMA's long-term effects in serotonin neurons. Binding ratios of [^{123}I]β-CIT, a radioligand that binds with high affinity to serotonin transporters, were significantly lower in female, but not in male, heavy (≥50 tablets) MDMA users than in controls. Binding ratios were significantly higher in female ex-MDMA users than in female heavy users. No neurotoxic effects were seen in male users. However, I think, as do George Ricaurte and Una McCann in their accompanying Dec 1 Commentary,[2] that these results should be interpreted with care.

I think that it is important to consider that, as reported by Sherlock and colleagues,[3] MDMA doses in tablets sold as ecstasy can vary 70-fold. On the contrary, other ecstasy tablets contain no MDMA at all, but various other substances.[4]

Reneman and colleagues' recruitment of participants at the same venues might lessen the possibility of diversifying MDMA doses per tablet. However, MDMA users could have acquired tablets from different suppliers, and doses in tablets sold by the same source might vary. Subjective drug histories of the participants were registered. However, the only objective drug analysis made was a single urine drug screening. And, since participants in the study were asked to abstain from use of all psychoactive drugs for at least 3 weeks before the study, a positive drug screen served as an exclusion criterion.

Thus, although self-reporting of the number of tablets consumed might have been accurate, a possible explanation for the lack of neurotoxic effects in men might be that male participants had only consumed tablets containing very small MDMA doses, or no MDMA at all.

In future studies, analysis of MDMA doses in ecstasy tablet samples acquired from the venue at which participants are recruited might be useful, or asking participants to bring tablets from their own supply for analysis.

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1 Reneman L, Booij J, de Bruin K, et al. Effects of dose, sex, and long-term abstention from use on toxic effects of MDMA (ecstasy) on brain serotonin neurons. *Lancet* 2001; **358:** 1864–69.
2 Ricaurte GA, McCann UD. Assessing long-term effects of MDMA (Ecstasy). *Lancet* 2001; **358:** 1831–32.
3 Sherlock K, Wolff K, Hay AW, Conner M. Analysis of illicit ecstasy tablets: implications for clinical management in the accident and emergency department. *J Accid Emerg Med* 1999; **16:** 194–97.
4 Giroud C, Augsburger M, Sadeghipour F, Varesio E, Veutheu JL, Rivier L. Ecstasy: the status in French-speaking Switzerland—composition of seized drugs, analysis of biological specimens and short review of its pharmacological action and toxicity. *Schweiz Rundsch Med Prax* 1997; **86:** 510–23.

Authors' reply

Sir—In response to Stephen Kish, [^{123}I]β-CIT, a non-selective radioligand, binds with high affinity to 5-HT and dopamine transporters. However, neither dopamine nor norepinephrine blockers displace [^{123}I]β-CIT binding in the hypothalamus and midbrain region, whereas 5-HT transporter blockers do.[1] In animals, cortical [^{123}I]β-CIT binding can be displaced by 5-HT transporter blockers, but this has not yet been studied in human beings.[1]

In many animal studies, MDMA affects only 5-HT and not dopamine or norepinephrine neurons. Since MDMA users and controls in our study had similar striatal [^{123}I]β-CIT binding ratios,[2] our data probably reflect loss of 5-HT and not dopamine transporters. We initially included percentage changes, but changed to 95% CI differences, as suggested in statistical peer review.

P M Haddad and colleagues discuss the importance of depression. The association between reduced 5-HT transporter densities and depression might be affected by postsynaptic 5-HT_2 receptors, location in the brain, or both. The adverse effects of MDMA use on mood have not been clearly shown and seem to contradict each other.[3] To avoid potential confounders to outcome measures, we did not exclude participants for the presence of psychiatric disorders. We screened for psychiatric morbidity DSM-IV criteria and the composite international diagnostic interview. The diagnostic threshold of DSM-IV major depression is generally judged low with this interview. However, the presence of affective (depression), anxiety, and eating disorders, psychoses, or a combination of these was not related to former ecstasy use.

Concerning the short *SS* allele of the 5-HT transporter polymorphism (5-HTTLPR): genotype distribution in the MDMA users (*LL* 17 [31%]; *LS* 29 [54%]; *SS* eight [15%]) was in good accordance with 5-HTTLPR genotype distribution in healthy white European people;[4] controls and MDMA users did not differ in genotype distribution. Therefore the *SS* allele probably did not make MDMA users more resistant to developing psychiatric morbidity.

Women were not exposed to higher doses of MDMA by mg/kg, as Elisabeth Ratzenböck suggests. We showed in the report's table 2 that men had a higher exposure on a tablet/kg base (average seven tablets/kg), and dismissed this as a possible explanation for our findings. We do not agree that the content of MDMA in tablets taken by female users should be higher than in those taken by male users.

The participants in this report overlap substantially with those in a report published in the *Archives of General Psychiatry*.[5] In that report, we focused on the relation between 5-HT transporter density and verbal memory in 13 MDMA-naïve controls, 16 ex-MDMA users, and 22 heavy MDMA users. In the present report we used almost the same group of controls (n=15, memory data missing in two), almost the same group of heavy MDMA users (n=23, memory data missing in one), and exactly the same group of ex-MDMA users (n=16). However, we added a group of moderate MDMA users (n=15) to allow us to study the dose-response relation between MDMA exposure and 5-HT transporter density, and the possibility of sex differences in the vulnerability to the neurotoxic effects of MDMA. We will inform the editor of the *Archives of General Psychiatry* of the above overlap and the fact that in addition to 5-HT transporter density and neuropsychological parameters, dopamine transporter densities and 5-HTTLPR genotypes were assessed in these participants. A report with data on the dopamine transporter density has been published,[2] and one with data on the 5-HTTLPR is currently under review of the same participants. Both papers state explicitly that we reported on different issues in the same individuals in earlier papers.

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