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Positron emission tomography findings in heavy users of MDMA

Sir—In the report by U McCann and colleagues (Oct 31, p 1433),[1] the average therapeutic dose of (±)3,4-methylenedioxymethamphetamine (MDMA) in MDMA-assisted psychotherapy was 125 mg, usually given only once or twice. The participants in this study had taken more than 200 doses of MDMA within 4–5 years, at 386 mg per dose, with a range of 70 to 400 uses in that time.

The fact that these participants have taken the drug at such high doses and frequency must be considered. There may be a compulsive component to their behaviour, that could be reflected by serotonergic abnormalities on their scans from positron emission tomography (PET) with the radioligand carbon-11-labelled McN-5652. Another assumption is that some of the participants used MDMA in a rave setting, where crowding and overheating are likely, which have been shown to affect the neurotoxic effects of MDMA in laboratory animals.[2] A third assumption in these heavy users is their likely exposure to other drugs[3] such as amphetamine.

Also at issue is McCann and colleagues' interpretation of their data. They equate a 22% loss in the number of serotonin-reuptake sites with brain damage. However, why is this loss not seen as an adaptive response to chronic exposure of a serotonergic agonist/releaser? How do we reconcile this PET data with the knowledge that many antidepressants functionally reduce the number of reuptake sites or the expression of its mRNA?[4,5]

Many potent medicines have toxic doses, but this effect should not discount the potential use of MDMA in psychotherapy. G Ricaurte himself has yet to publish the results of a study he did in which monkeys were given single oral doses of MDMA every 2 weeks, which failed to yield any adverse effects. Perhaps the next group of participants recruited for imaging should be individuals who have undergone MDMA-assisted psychotherapy at the recommended dosage and frequency.

Worldwide illicit use of MDMA warrants a more thorough understanding of this drug. Most importantly, the limited study by McCann and colleagues should not prevent further research into its use as a psychiatric medicine. Their findings do not justify a high estimate of the risk of a therapeutic dose.

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Authors' reply

Sir—We thank Julie Holland for her comments, since they afford us an opportunity to address some of the misconceptions about MDMA-induced serotonin (5-HT) neurotoxicity and its detection by PET. Holland posits that compulsive behaviour rather than MDMA use might be responsible for the reductions in serotin (5-HT) transporter density. To our knowledge, there is no evidence that obsessive compulsive disorder is associated with reductions in 5-HT transporter density. Moreover, we excluded participants with this disorder and other psychiatric disorders linked to 5-HT to avoid the type of potential confound that Holland postulates.

We agree that overheating associated with raves may exacerbate the neurotoxic effects of MDMA, although evidence to substantiate this view is not available for human beings. Although most of our participants had also used other recreational drugs, MDMA was their drug of choice. Contrary to Holland's assertion, amphetamine has never been shown to damage brain 5-HT neurons, even at high doses.

It is not clear where Holland obtains the value of 22% loss of 5-HT transporters. However, it is important to recognise that the sensitivity of PET for the detection of 5-HT transporter loss is unknown. Findings in our laboratory indicate that PET imaging with ^{11}C McN-5652 tends to underestimate the magnitude of reductions in 5-HT transporter density by about 50%.

With regard to "functional reductions" in 5-HT transporters, 5-HT transporter density is not reduced 2 weeks after chronic administration of selective serotonin reuptake inhibitors.[1] Direct 5-HT agonists are not known to reduce 5-HT transporter density. It is erroneous to equate reductions in mRNA expression with reductions in 5-HT transporter protein content.

Holland's major point seems to be that she believes that MDMA has potential psychotherapeutic value, and that MDMA is safe when used in lower, less frequent doses. Unfortunately, despite claims of MDMA's therapeutic potential for more than 20 years, no controlled study has validated this contention. The study in monkeys that she refers to, where no evidence of neurotoxic injury was found, involved drug dosage of MDMA that were below those proposed for psychotherapeutic settings (once equivalent human doses are calculated with appropriate interspecies dose scaling methods). As to the safety of typically used doses, single doses of MDMD that produce lasting 5-HT deficits in rodents and non-human primates overlap with the equivalent doses used by humans.[2,3]

Therapists interested in using psycholytics as adjuncts to psychotherapy would be better served by efforts to develop a non-neurotoxic medication, one with a wide margin of safety and low potential for abuse. Efforts to minimise the dangers of MDMA's are ill-advised at a time when the data on neurotoxic effects is compelling and the recreational use of MDMA by many young people is on the rise.

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Fatal MDMA intoxication

Sir—J A Henry and I R Hill (Nov 28, p 1751)[1] report a fatal interaction between ritonavir and 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy"). MDMA plasma concentrations measured in their patient largely exceeded those expected after ingestion of 180 mg MDMA. They argue that concomitant treatment with ritonavir could be responsible for a metabolic interaction between both drugs, leading to toxic concentrations of MDMA, and that CYP2D6 (a polymorphic isoenzyme of cytochrome P450) would be involved in such interaction.[2] Ritonavir is mainly a CYP3A substrate and secondarily a CYP2D6 and CYP2C9 substrate. Clinical interactions reported until now with CYP2D6 substrates seem less relevant than those associated with CYP3A.[3]

As the investigators mention, three factors should be taken into account: the patient had an impaired liver function because of alcoholism; treatment with ritonavir was started 2 weeks before the accident; and his status as an extensive or poor metaboliser for CYP2D6 substrates was unknown. All three factors would have determined a metabolic impairment of drugs clearance. On the other hand, the patient gave a history of having taken two tablets of ecstasy (about 140 mg) with little effect, and as soon as a further half tablet was ingested, he experienced the initial symptoms of MDMA intoxication.

We would like to propose a non-linear pharmacokinetics of MDMA as another explanation for this case of fatal MDMA intoxication. In the context of a series of clinical studies in 14 healthy volunteers with experience in the recreational use of MDMA, in which different doses of MDMA were tested to select the most adequate for further pharmacological studies of the drug,[4] an unexpected phenomenon was observed. The following doses were tested: 50 mg (n=2), 75 mg (n=8), 100 mg (n=2), 125 mg (n=8), and 150 mg (n=2). MDMA plasma and urinary concentrations were measured in all the participants.[5] All participants were phenotyped as extensive metabolisers by means of dextromethorphan as a probe drug for CYP2D6 activity. A preliminary analysis of MDMA area under the plasma concentration versus time curve (AUC_{0-24h}) and peak plasma concentrations (C_{max}) suggested a non-linearity in the pharmacokinetics of MDMA. Although there was a factor of 3 in the range of doses given (50–150 mg), AUC_{0-24h} and C_{max} increased by a factor of 10 and 6, respectively:

MDMA dose (mg)	$AUC_{0-24\,h}$ (ng mL^{-1} h^{1})	C_{max} (ng/mL)
50	457 (505)	51 (45)
75	1332 (646)	126 (38)
100	2057 (283)	190 (20)
125	2624 (573)	229 (46)
150	5439 (411)	465 (122)

Data are mean (SD).

The lack of linearity of MDMA pharmacokinetics implies that fairly small increases in the dose of MDMA ingested could lead to disproportionate increases in MDMA plasma concentrations and, consequently, with an increased risk for MDMA acute intoxication. In addition to drug to drug interactions and the individual's metabolic status, which Henry and Hill mention, a possible phenomenon of non-linear pharmacokinetics could be another factor that may explain the high plasma concentrations of MDMA.

This study was supported by grants FIS 97/1198, CIRIT (1997SGR00077), ISCIII 97/4344 and Plan Nacional sobre Drogas, Madrid

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Sir—Entactogens represents a class of psychoactive synthetic compounds abused as recreational designer drugs, for example MDMA, methylene-dioxyethylamphetamine (MDE), or 3,4-methylenedioxyamphetamine (MDA). Originally these drugs were regarded as being "safe", but an increasing number of severe adverse effects and even deaths have been reported, such as the report by J A Henry and I R Hill.[1] Additionally, several cases of MDMA-induced hepatic damage requiring subsequent liver transplantation have been described.[2,3]

The responsible underlying mechanism is still unclear. One possible explanation is that deficiency in cytochrome P4502D6 (CYP2D6) expression could be a genetic factor that predisposes to an increased risk of MDMA-related toxic effects due to an accumulation of MDMA or MDMA-related drugs. In-vitro studies have shown that demethylenation of MDMA, MDA, and MDE is a major metabolic pathway catalysed by the CYP2D6 enzyme.[4] This enzyme exhibits a genetic polymorphism with 7–10% of white people expressing no functional enzyme (poor metaboliser).[5]

To assess this question for the first time three patients admitted for MDMA-related hepatotoxicity were genotyped for CYP2D6 alleles, which allows a correct prediction of the poor metabolisers phenotyped in more than 99% of white people.[5] Two of these patients, whose case histories were published in 1997, had MDMA-induced fulminant hepatic failure and subsequent liver transplantation. Both patients had regularly taken MDMA on weekends for several months without any side-effects. After a further intake of MDMA, they developed fulminant hepatic failure: the histopathology revealed massive liver necrosis.[2,3] Screening for hepatic viruses was negative.

The third patient, a 17-year-old woman had recurrent periods of massive right-upper quadrant abdominal pain and jaundice. The laboratory findings revealed only raised concentrations of liver enzymes; serological tests for hepatitis A, B, and C virus, cytomegalovirus, Epstein-Barr virus, and antinuclear, antimito-chondrial and smooth-muscle antibodies were negative. Other causes of jaundice could be ruled out. A liver biopsy specimen showed toxic hepatitis characterised by lobular disarray with swollen hepatocytes, centrolobular necrosis with activated Kupffer cells, and a large amount of ceroid pigment surrounded by infiltrates of inflammatory cells,