

## Viewpoint

## MDMA (Ecstasy) neurotoxicity: assessing and communicating the risks

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MDMA (3,4-methylenedioxyamphetamine) is an amphetamine analogue that produces euphoric and stimulant effects and a feeling of closeness towards others.<sup>1,2</sup> For more than a decade, MDMA (colloquially known as “Ecstasy” or “E”) has been widely used by young adults as a dance-party drug.

The usual recreational oral dose is 1–2 tablets (each containing about 60–120 mg of MDMA) a standard oral dose of 0.75–4.00 mg per kg in 60–80 kg people. MDMA is typically used once fortnightly or less because tolerance to the effects of MDMA develops rapidly. More frequent use requires larger doses to achieve the desired effects, but this increases the prevalence of unpleasant side-effects.<sup>3</sup>

A number of deaths have occurred as a result of malignant hyperthermia or idiosyncratic reactions to the drug, but these have been rare.<sup>4</sup> MDMA is perceived by many users to be a safe drug.<sup>1</sup> Few report the craving associated with opiates or cocaine<sup>3</sup> and most MDMA users are aware of only mild and transient disruptions of functioning.<sup>3,5</sup> The perceived safety of MDMA is at odds with animal evidence of MDMA neurotoxicity, an increasing prevalence of hazardous patterns of use among recreational MDMA users, and emerging evidence of neurotoxicity among heavier MDMA users.

### MDMA neurotoxicity in primates

MDMA administration in rodents and non-human primates produces large and possibly permanent damage to axons and axon terminal fibres containing 5-hydroxytryptamine (5-HT, serotonin). Long-term reductions in the density of 5-HT axons are most evident in the cortex, hippocampus, and striatum.<sup>6,7</sup> Other markers of brain 5-HT function, including the density of 5-HT uptake sites and the concentration of the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA), are similarly reduced. The mechanism underlying this neurotoxicity has not yet been determined, although a role for MDMA-induced hyperthermia and free-radical formation is likely.<sup>8</sup> Decreases in the density of brain 5-HT axons have been seen in squirrel monkeys more than 7 years after MDMA administration.<sup>6</sup> Some regrowth of axons occurs, but this is abnormal and incomplete.<sup>6,7,9</sup>

Most of these animal studies have administered 5 mg per kg of MDMA twice daily for four consecutive days, which is much higher and more frequent dosing than is

typical in human users. Moreover, in animal studies MDMA is often injected subcutaneously, which in monkeys is two to three times more neurotoxic than the oral route preferred by human users.<sup>10</sup> Because of these differences in dose and route of administration, proponents of recreational MDMA use have argued that this animal evidence has little relevance to human users.<sup>2</sup> This ignores the well-established principles of interspecies dosage scaling which indicate that larger animals are more susceptible to the toxic effects of a given dose of a drug than smaller animals.<sup>11</sup> In the case of MDMA, primates are more susceptible to MDMA neurotoxicity than rats,<sup>7</sup> which in turn are more susceptible than mice.<sup>12</sup>

### Changing patterns of MDMA use

Surveys suggest that a substantial minority of recreational MDMA users use the drug in a way that increases the risk of 5-HT neurotoxicity. First, one in six of a sample of 329 Australian users had injected MDMA at some time.<sup>13</sup> Second, 42% had used MDMA for 48 h or more at least once in the past 6 months.<sup>13</sup> Third, the intake of multiple tablets in a single-use episode may be increasing.<sup>3,13</sup> Finally, MDMA is often used in environments that are hot and crowded with limited access to drinking water, increasing the risk of hyperthermia, which exacerbates MDMA neurotoxicity in rats.<sup>14</sup>

### Evidence of 5-HT neurotoxicity in MDMA users

Suggestive evidence of neurotoxicity in human MDMA users has emerged during the past decade (table). Decreased concentrations of 5-HIAA in the cerebrospinal fluid of MDMA users have been noted in several studies.<sup>15–19</sup> Studies measuring the prolactin response to an L-tryptophan, M-chlorophenylpiperazine, or D-fenfluramine challenge in MDMA users have for the most part suggested a blunted neuroendocrine response to serotonergic agonists.<sup>15,20–23</sup>

Two brain-imaging studies have provided more compelling evidence of MDMA neurotoxicity.<sup>24,25</sup> McCann and colleagues<sup>24</sup> reported reduced binding of the radioligand (<sup>11</sup>C) (–) McN-5652 in several brain regions in MDMA users, indicating a reduced density of 5-HT uptake sites. The same research group showed reductions in axon densities in baboons at necropsy with similarly decreased (<sup>11</sup>C) (–) McN-5652 binding following neurotoxic doses of MDMA.<sup>9</sup>

Critics have argued that low 5-HT function may be a cause rather than an effect of MDMA use because low concentrations of 5-HT have been linked to impulsivity and sensation seeking in humans.<sup>26</sup> It is therefore notable that Semple and colleagues<sup>25</sup> have shown a decreased density of 5-HT uptake sites in the brains of heavy MDMA users compared with controls who were well

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Assay	Number in MDMA group	Usual dose (mg)	Number of times used	Frequency of use (per month)	Duration of use (years)	Drug free pre-test (weeks)	Results (%)	
<b>Brain imaging studies</b>								
McCann et al <sup>24</sup>	PET	14	386 (NA)	228 (NA)	6 (NA)	4-6 (NA)	19 (NA)	Decreased
Semple et al <sup>25</sup>	SPECT	10	..	672(647)	..	>1	2-6 (1-1)	Decreased
<b>Cerebrospinal-fluid analysis</b>								
Peroutka et al <sup>16</sup>	CSF 5-HIAA	5	161 (40)*	18 (12)*	..	<1-6	>6	-13 (p>0-05)
Ricaurte et al <sup>19</sup>	CSF 5-HIAA	33	125 (44)	52 (45)	0-78 (0-41)	3-5 (1-9)	16-7 (23-3)	-26 (p<0-05)
McCann et al <sup>15</sup>	CSF 5-HIAA	30	170 (82)	94-4 (90-6)	4-2 (4-8)	5-0 (3-0)	17-9 (24-7)	-32 (p<0-05)
McCann et al <sup>17</sup>	CSF 5-HIAA	22	272 (188)	215 (155)	5-7 (2-8)	4-5 (3-3)	13-9 (30-5)	-26 (p<0-05)
Bolla et al <sup>18</sup>	CSF 5-HIAA	24	158 (NA)†	60 (NA)†	2 (NA)†	4-8 (NA)†	4 (NA)†	-28 (p<0-02)
<b>Prolactin response to 5-HT agonists</b>								
Price et al <sup>23</sup>	L-tryptophan challenge	9	135 (44)	..	1-9 (1-7)	5-1 (2-3)	9-4 (7-1)	-46 (p>0-05)
McCann et al <sup>15</sup>	L-tryptophan challenge	30	170 (82)	94-4 (90-6)	4-2 (4-8)	5-0 (3-0)	17-9 (24-7)	+ 48 (p>0-05)
Gerra et al <sup>22</sup>	D-fenfluramine challenge	15	106 (91)	62-7 (34-2)	4-7 (2-7)	1-2 (0-7)	3-0 NA	-100 (p<0-001)
Gerra et al <sup>22</sup>	D-fenfluramine challenge	15	106 (91)	69-3 (38-0)	4-7 (2-7)	1-3 (0-8)	52-0 NA	-83 (p<0-05)
McCann et al <sup>20</sup>	M-chlorophenylpiperazine	25	319 (280)	196 (24)	5 (1-0)	5-0 (3)	14-0 (29)	Decreased (p=0-024)‡

Data are mean (SD) unless indicated.

\*Estimated from table data or graph.†Data are median values. ‡Area under the curve data. Results column for CSF studies indicates % difference in 5-HIAA concentrations comparing MDMA users and controls. Results column for prolactin studies indicates % difference (relative to baseline) in the peak prolactin response to a 5-HT agonist in MDMA users and controls. 5-HIAA=5-hydroxyindoleacetic acid. PET=Positron Emission Tomography. SPECT=Single Photon Emission Computed Tomography. NA=not available.

### Studies showing 5-HT neurotoxicity in MDMA users

matched for alcohol, tobacco, and cannabis use. Regional differences in 5-HT transporter density were far fewer in this study than in the study of McCann and colleagues, possibly because the radioligand used by Semple and colleagues had higher non-specific binding.

Two studies have suggested other alterations in the brains of MDMA users. One reported a reduction in brain glucose metabolism in the left hippocampus of users, but this was the only significant difference seen in 14 brain regions assessed.<sup>17</sup> The other study showed correlations between extent of MDMA use and indices of electroencephalogram (EEG) power and coherence.<sup>28</sup> The EEG patterns of the heavier MDMA users were similar to those seen with ageing and dementia.

### Possible functional correlates of 5-HT neurotoxicity

If MDMA does damage 5-HT systems in humans, what functional consequences should we expect? Initial studies suggested only moderate behavioural or cognitive deficits in laboratory animals given neurotoxic doses of MDMA.<sup>29</sup> Some research suggesting 5-HT neurotoxicity in human MDMA users has also found an absence of symptoms.<sup>19,30</sup> Nonetheless, there have been many case reports of neuropsychiatric sequelae after MDMA use,<sup>4,31</sup> and an increasing number of controlled studies suggest cognitive, behavioural, and emotional problems in MDMA users.

**Impulsivity**—Soubrie<sup>32</sup> has suggested that 5-HT may have a central role in behavioural inhibition. Rats with 5-HT damage are impulsive, insensitive to punishment, and hyperactive in the face of novelty. Human beings with low concentrations of 5-HIAA in cerebrospinal fluid have exhibited violent, impulsive, alcoholic, and criminal behaviour.<sup>32</sup> One report has shown that MDMA users are more impulsive than matched polydrug-using controls on a laboratory behavioural measure<sup>33</sup> but there are also contradictory results.<sup>15</sup>

**Depression**—Depressed patients and successful suicides show various abnormal indices of 5-HT function.<sup>34</sup> At least two studies have now documented a transient depression of mood in the days following MDMA use.<sup>5,35</sup> This depression seems to have lifted by 1 week after MDMA use. Such a pattern of mood change is consistent with MDMA's short-term effects on the concentrations of brain 5-HT.<sup>35</sup> A more persistent lowering of mood is

suggested by the high prevalence of depressive symptoms in a sample of Australian MDMA users.<sup>13</sup> The prevalence of irritability, depression, and sleep disturbances was related to frequency of MDMA use, reported dose of MDMA, binge use of MDMA, and the number of other drugs used to manage the after-effects of MDMA use.<sup>13</sup> These results are consistent with other findings from Italy.<sup>31</sup>

**Cognitive dysfunction**—Serotonergic damage may adversely affect memory and higher cognitive function. The hippocampal formation receives a dense 5-HT innervation that may be particularly vulnerable to MDMA's neurotoxic effects.<sup>6</sup> One study found profound deficits in working memory in rats exposed to high doses of MDMA.<sup>36</sup>

Data now also indicate an acute disruptive effect of MDMA on short-term memory in human beings,<sup>5,30</sup> as well as a longer term impairment in memory and cognition.<sup>5,17,18,30,37</sup> Both verbal<sup>3,30</sup> and visual<sup>18</sup> memory impairments have been noted in long-term users tested in the drug-free state. One study that shows memory deficits in MDMA users compared with a control group of polydrug users who have not used MDMA is particularly compelling.<sup>37</sup> Deficits have also been seen in tests of logical reasoning and serial addition.<sup>5,17,18,30,37</sup>

### Implications for research

Only a prospective study of 5-HT function in MDMA-naïve individuals that are randomly assigned to MDMA or placebo conditions could definitively show that recreational MDMA use was neurotoxic in human beings. For ethical, political, and legal reasons such a study is unlikely to ever be done. Instead, we have to rely upon evidence from observational studies of recreational MDMA users. These need to include large samples of a broad range of MDMA users to assess the link between MDMA use and indicators of neurotoxicity. The use of appropriately matched control groups is critical in such studies. It is important to find out whether suggestive evidence of neurotoxic effects in the heavy MDMA users tested to date also occur in less frequent users. Some have argued that even a single moderate oral dose of MDMA may be neurotoxic in human beings,<sup>38</sup> although this claim is controversial<sup>39</sup> and difficult to verify on the basis of current evidence. Future studies should specifically address this important issue.

Other emerging diseases associated with long-term MDMA use also need to be better described. These include: cardiac dysfunction,<sup>40</sup> eating disorders,<sup>31</sup> thermoregulatory deficits,<sup>41</sup> sleep abnormalities,<sup>42</sup> and congenital defects in babies exposed to MDMA in utero.<sup>43</sup> Verification of a reported risk of clinical depression and suicide in MDMA users is a priority. MDMA users with memory dysfunction should be studied prospectively to find out whether dysfunction resolves with abstinence or increases with age. PET and other imaging studies might be combined with neuropsychological assessment to study links between decreases in 5-HT uptake sites in specific brain regions and memory loss.

An opportunity should be taken to investigate the human neurotoxicity of fenetylline (fenfluramine) and dexfenetylline (dexfenfluramine), both of which were recently withdrawn from the market. These drugs cause 5-HT neurotoxicity in laboratory animals that is very similar to that seen with MDMA.<sup>44</sup> More than 50 million people have been prescribed these drugs worldwide, so studies of possible functional deficits in these people may help to define the risks of MDMA use.

There are also anecdotal reports that some MDMA users are combining MDMA with selective serotonin reuptake inhibitor (SSRI) drugs such as fluoxetine to dampen the dysphoria experienced after MDMA use.<sup>1</sup> Fluoxetine, when administered before or soon after MDMA, provides some protection against neurotoxicity in animals<sup>12</sup> but there are also concerns that it could potentiate acute toxic effects of the MDMA in susceptible individuals.<sup>4</sup> The interaction between SSRIs and MDMA and between MDMA and other widely used illicit drugs should be more thoroughly investigated.<sup>45</sup>

### Implications for health education

The consistency of the clinical, epidemiological, and neurological studies reviewed strongly suggests that MDMA can produce neurotoxic effects in some recreational users. Those individuals who are at greatest risk are those who use two or more street doses of MDMA at a time, those who use the drug fortnightly or more frequently, those who inject MDMA, and those who use MDMA for 24 h or more.

Current and potential users of MDMA need to be told about these risks by education delivered by peers in the dance-party milieu and through the media used by members of this subculture (eg, videos and the internet). Peer-based education of injecting drug users about the risks of infectious disease from equipment sharing, in combination with needle and syringe programmes, has substantially changed risk behaviour in this population.<sup>46</sup> A similar approach may also be successful among MDMA users who are better educated and less socially disadvantaged than injecting drug users.<sup>3,13,45</sup>

A non-alarmist and accurate portrayal of the evidence is required if it is to receive the support of influential individuals in the MDMA-using subculture. Such an education campaign should acknowledge uncertainties about the risks of occasional use of "low" doses of MDMA while emphasising the risks that heavier and more frequent MDMA users probably face. It could also include suggestions on how to minimise any neurotoxic effects (such as avoidance of hyperthermia)<sup>14</sup> and the risks of bingeing and injecting MDMA should be highlighted. Finally, MDMA users need to be warned that neurotoxic effects may occur in the absence of subjectively noticeable symptoms.

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