RAVE DRUG (ECSTASY) AND SELECTIVE SEROTONIN 
REUPTAKE INHIBITOR ANTI-DEPRESSANTS

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ABSTRACT

3, 4 Methylenedioxymethamphetamine (MDMA) also known as Ecstasy is a common 
recreational drug of abuse and reports of abuse of tricyclic antidepressants are also known. We 
report two cases of misuse of selective serotonin re-uptake inhibitors (SSRIs) antidepressants in 
combination with Ecstasy and their beneficial subjective effects experienced by misusers. We 
hypothesise the probable underlying pharmacological reasons and recommend its use in the treatment 
of neurotoxic effects of MDMA.

Key words : MDMA, antidepressant, SSRI's, treatment potential

3, 4 Methylenedioxymethamphetamine (MDMA). Ecstasy, a synthetic analogue of 
amphetamine and mescaline, is a commonly 
used recreational drug of abuse and has recently 
been the focus of tremendous controversy. It has 
received wide publicity in the popular press and 
medical journals (Lancet, 1996) and a wide range 
of psychopathology ranging from panic attacks, 
depression to psychotic depression has been 
reported (McGuire et al., 1994). Concerns about 
the abuse potential of any centrally active or 
mood altering drugs are not new (Sheppard, 1970). There have been reports of abuse of 
amitriptyline in combination with methadone 
(Cohen et al., 1978, Cantor, 1979) and recently 
dothiepin misuse has also been reported' (Dorman et al., 1995) and the patients who 
misuse dothiepin report euphoria and sedation 
with complex visual and auditory hallucinations. 
Experiences are pleasant and seem to occur in 
cloured consciousness.

Reports from some of our patients suggest 
that selective serotonin re-uptake inhibitor 
antidepressants combined with MDMA is 
becoming popular with people who go to 
metropolitan clubs and raves. We are told good 
quality MDMA is becoming harder to find and so 
users are resorting to drug combinations to 
 enhance its effects, such as MDMA combined 
with ketamine, an anaesthetic agent, and with 
fluoxetine (Singh, 1995).

Here we report two cases of misuse of 
SSRI antidepressants, fluoxetine and sertraline 
in combination with MDMA.

Case 1: Mr. A, a 45 year old ex-dancer 
suffering from HIV infection and no past 
psychiatric illness was receiving treatment for a 
mild depressive illness and was on fluoxetine 
20 mg daily. Occasionally he used to go to discos 
and he used to take MDMA. He noticed that the 
days he took Ecstasy, within an hour he felt a 
rush and enough energy to dance for 2 to 3 
hours'. He also felt that by combining fluoxetine 
this effect was prolonged by a further two hours 
and there was an absence of hangover effects 
and 'the comedown was easier'.

Case 2 : Mr. B, a 24 year old unemployed 
man suffering from HIV infection with no past 
history of psychiatric illness was prescribed 
sertaline 50 mg daily by a physician apparently 
for mild depressive illness. He had extensive 
experience with Ecstasy before using it in
A.N. SINGH & J. CATALAN

combination with sertraline. Typically he would ingest 50 mg of sertraline before taking Ecstasy and his subjective experience was almost identical to that of the first case. He also experienced initially a rush, prolonged effect, easier comedown following a high and it stopped 'comedown depression' and absence of hangover effects.

DISCUSSION

The cerebral cortex in many mammals is innervated by two morphologically distinct classes of 5-HT axon terminals, fine and beaded one. These two types of axon have different regional and laminar distribution and are differentially sensitive to neurotoxic effects of certain amphetamine derivatives, which includes Ecstasy. Administration of Ecstasy to various animals has been shown to cause long term destruction of serotonergic axons and axon terminals in the brain (Green & Goodwin, 1995). The fine axons are much more sensitive to neurotoxic effects than the beaded axons, and the loss of fine axons lasts for months, whereas the beaded axons remain unaffected following neurotoxic drug treatment (Mamounas et al., 1991). An individual using Ecstasy utilise doses approaching those shown to be neurotoxic in non-human primats and indeed a 26% decrease in 5-hydroxy indoleacetic acid in cerebral spinal fluid was found in Ecstasy users (Ricaurte et al., 1990).

Green & Goodwin (1995) stated that Ecstasy can cause neurotoxicity to those serotonergic systems of the brain in human being, however, this has been questioned (Saunders, 1996). There is no doubt the misuse of Ecstasy produces neuropsychiatric complications (Macguire et al., 1994). In addition to effecting serotonergic system it has also been observed that Ecstasy reduces CSF, HVA (homovanillic acid) particularly in women (McCann et al., 1994), a finding that is in keeping with the observation that at high doses, Ecstasy can damage dopaminergic as well as serotonergic neurons (Commins et al., 1987) and a recent crosssectional association study, suggested evidence for specific serotonergic neurotoxicity of MDMA in humans, using serotonin transporters legend [123] β-CIT (Semple et al., 1999).

In the laboratory, SSRIs block MDMA induced serotonin release and they also block MDMA neurotoxicity and it has also been reported that fluoxetine does not block MDMAs reinforcing subjective effect (McCann & Ricaurte, 1993).

The two cases described here also suggest that the selective serotonin reuptake inhibitors, fluoxetine and sertraline, at doses that interact with the serotonin uptake sites in human does not block the subjective effects of MDMA and also that Ecstasy psycho-active effects may be separate from its neurotoxic actions.

Cytochrome P450 2D6 has been implicated at the main enzyme involved in Ecstasy metabolism and the SSRIs, fluoxetine and sertraline are important inhibitors of this enzyme, suggesting that they could increase blood levels of Ecstasy and thus enhance its effect. What is not known is whether single doses of these SSRIs are sufficient to inhibit the enzyme. It would be interesting if someone could measure the rate of metabolism of Ecstasy, with and without single doses of SSRIs. Potential functional consequences of Ecstasy induced brain 5-HT neurotoxic lesions are not yet clear. If true, the health implications of this finding could be serious. Evidence is now mounting that Ecstasy can cause serotonergic, dopaminergic and other abnormality in the neurotransmitter system and the effect of such a loss of "serotonergic/dopaminergic reserve" in later life is difficult to predict but could be clinically significant and these neurotransmitter systems are thought to be involved in the aetiology of various common psychiatric illnesses such as depression and schizophrenia. Our patients subjective experience suggest that SSRIs may be useful in limiting the adverse effects of Ecstasy as it appears to be mitigating the neurotoxic effects of MDMA. Theoretically atypical neuroleptics which blocks 5-HT and
RAVE DRUG (ECSTASY) & SSRI ANTI-DEPRESSANTS

dopamine may also be useful. A larger scale controlled study is overdue.

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