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J Psychopharmacol 2007; 21; 787
DOI: 10.1177/0269881107084738

Psychopharm

Journal of Psychopharmacology
21(8) (2007) 787–791

ISSN 0269-8811
SAGE Publications
Los Angeles, London,
New Delhi and Singapore
10.1177/0269881107084738

MDMA, politics and medical research: Have we thrown the baby out with the bathwater?

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Introduction

3,4-Methylenedioxymethlyamphetamine (MDMA) has penetrated extensively into our culture in the last thirty years. It started life in medicine when adopted as a clinical tool by psychotherapists on the West Coast of America who used it as an alternative to the then banned LSD for facilitating interactions in couples' therapy. From the therapist's couch the drug leaked into public use, with a growing recreational use that eventually lead to its prohibition in the mid-eighties. As with LSD, the medical research on MDMA then stopped but its recreational use continued to grow especially in relation to the rave or party scenes so that by the nineties the drug was becoming demonized by politicians and parents alike.

Although the politicians raved against the drug with a similar ferocity to those writhing on the dance floors, the doctors and pharmacologists argued among themselves about the short, medium and long-term dangers of MDMA. In the background, meanwhile, MDMA as a therapeutic tool disappeared from view. Exactly as with LSD before it, the drug had now drifted so far from its clinical origin for this to become forgotten.

But are we missing something important by allowing the political agenda to hijack MDMA from science and medicine? Has the politicians' single-minded demonization of all recreational drugs as 'Of No Medical Use' resulted in MDMA becoming an innocent bystander caught in the crossfire of the War on Drugs? After all, MDMA is not the first such drug that has been treated this way. Its prohibition as a class A schedule 1 drug in the UK severely restricts researching the compound on humans and illustrates a profound phenomenon that pervades the field of medical research: that current political restrictions on medical research threatens to undermine our scientific goals of objectivity and the search for evidence-based clinical excellence. In this paper we look at some of the features that make MDMA a potentially useful medical and research tool and asks that these be explored in a dispassionate manner – without the political agenda influencing the scientific argument.

MDMA, serotonin, mood and the tryptophan depletion test

As a psychotropic drug, MDMA has a remarkable and relatively rare characteristic – that of marked psychological consistency of effect. When administered to healthy humans under medical supervision, MDMA is able to induce a mental state that is usually pleasurable to almost every user, almost every time. Few other psychotropic drugs have this ability (except perhaps, the opiates, which will be mentioned later). While there is some anecdotal evidence that the intensity of the user's initial experiences with MDMA diminishes quantitatively with prolonged use (Shulgin, 1986), the qualitative experience remains reliably consistent. This consistency, together with our knowledge that MDMA acts as potent indirect serotonin agonist, tells us a lot about the role of serotonin in mood states.

An important theoretical research tool, used by psychopharmacologists to understand the role of serotonin, is the tryptophan depletion challenge test (reviewed Hood *et al.*, 2005). By restricting brain access of this essential amino acid, and thereby reducing the synthesis of serotonin, tryptophan depletion can induce low mood in depressed patients and some predisposed healthy controls. It also reverses the efficacy of SSRI drugs in subjects taking them for depressive and anxiety disorders (Bell *et al.*, 2005). These studies provide powerful support for the serotonin hypothesis of depression and, more specifically, for the role of serotonin in mood. The tryptophan depletion test is well-established as a therapeutic tool, with over 50 studies demonstrating its efficacy.

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Despite this clear body of evidence that depleting serotonin is associated with the induction of depression there is **NO** comparable data on the effects of increasing 5HT on mood – a strong unidirectional bias that needs explanation!

Effects and pharmacology of MDMA

Given the pharmacodynamics of MDMA – the release of 5HT and probably also, though to a lesser extent, dopamine and noradrenaline (Johnson *et al.*, 1986; Steele *et al.*, 1987) – it is perhaps, not surprising that acute MDMA use elevates mood and gives strong feelings of well-being. This would suggest there is a very real role for developing this or related drugs as a treatment for depressive disorder or at least as a test of the theory that increasing 5HT directly relates to improvement in depression MDMA has some well-recognized psychological characteristics. It has been demonstrated to consistently increase levels of understanding, closeness and empathy (Liester *et al.*, 1992; Cami *et al.*, 2000; Sumnall *et al.*, 2006), to encourage an increased thoughtfulness and contemplativeness (Vollenweider *et al.*, 1998a) and to aid a greater exploration of otherwise painful repressed memories, by 'inhibiting the subjective fear response to an emotional threat' (Greer and Tolbert, 1986).

These characteristics suggest MDMA could be a useful clinical tool for assisting psychotherapy (Sessa, 2007). But above and beyond these effects that could be useful in *psychotherapy*, what about its use purely as a potent serotonin agonist to explore in more detail the role of 5HT in brain function? One issue that would need careful consideration is the possibility that after the initial rise in synaptic serotonin there is a subsequent depletion in total brain levels of 5HT (Reneman *et al.*, 2002). This may explain the period of adverse neuropsychological phenomena – including low mood, irritability, anxiety, aggressiveness and difficulty concentrating – found for a day or so after ecstasy use.

MDMA's legal status

Despite promising anecdotal research in the USA in the 1980s that suggested therapeutic potential for MDMA (Greer and Tolbert, 1986) the scheduling, in 1986, of it and all chemically related drugs has left this subject relatively unstudied for over 20 years.

At the time the DEA were considering the prohibition of MDMA, they invited comments from those psychotherapists who were championing the medical use of the drug. Very few studies had been done at that point, and they were by their own admission merely anecdotal in quality. However, the results had been promising and in their conclusions they called for further controlled studies to look at the subject more closely. But in a chicken-and-egg situation, the DEA justified the prohibition of MDMA on the basis that 'it was felt that the studies lacked the appropriate methodological design necessary to ascertain the reliability of the observations' (http://www.maps.org/dea-mdma/pdf/0196.PDF). An appeal against the DEA's decision overturned the scheduling for just one year, before it was re-scheduled again. This time the judge over-seeing the case recommended that MDMA be placed in Schedule 3, to allow for further medical research into the potential therapeutic uses for MDMA. But this recommendation was ignored by the DEA and the drug was placed permanently in Schedule 1 (Iverson, 2006). There followed an intense blocking of further research into the compound and there remains a significant lacuna in this area of understanding to this day.

In the UK, MDMA together with other related ring-substituted amphetamines have been illegal since 1977, when added to the 1971 Misuse of Drugs Act as class A drugs. There have been a few studies on it since then but all relate with its potential toxicity (Henry).

What happens when depressed people take MDMA?

Because of the gap in our knowledge about therapeutic applications for MDMA, this question cannot be answered with confidence. The theoretical potential of using MDMA as potent serotonin-enhancer to treat depression has been postulated by Riedlinger and Montagne (2001). But there is very little empirical clinical information regarding the effects of MDMA on depressed patients. There exist numerous anecdotal reports of the expected transient rise in mood during recreational use of MDMA by depressed people – we have seen several examples in our tertiary mood disorders clinic – but this is often followed by a return of the previous depressed mood and occasionally associated with unpleasant psychological and physiological 'hangover' effects. Because of these negative effects there is little evidence – anecdotal or otherwise – of depressed people carrying out long-term self-medication with MDMA. The existence of a hangover associated with MDMA is well-documented by recreational users of ecstasy. Among ecstasy users this hangover effect (sometimes called the mid week blues or 'Blue Wednesday'), may last for between one and seven days and might be further exacerbated by the adverse environmental circumstances in which recreational ecstasy is often consumed (i.e., at night with consequent sleep deprivation, with excessive physical exertion and often together with other psychoactive drugs). However, some studies also suggest that even when MDMA is given in pure form in the laboratory situation or therapeutic circumstances the hangover syndrome also occurs (Liecheti, 2001; Greer and Tolbert, 1986).

Parrot's comprehensive review of the evidence for and against the development of MDMA as a psychotherapeutic agent (2007) summarizes that for the majority of cases the acute MDMA experience has a positive effect on mood, but that the subsequent 'recovery period'/hangover effect often includes significant lowering of mood that may count against it's effectiveness as a therapeutic agent – especially for vulnerable individuals. Parrot emphasizes the importance of further research to more accurately assess those properties of the acute set and setting that may be contributing to a more positive or negative experience and how these factors might be interacting with the recovery period to establish the over-all risk:benefit ratio of using the drug clinically. Above all, Parrott is also asking that further research might address the relative gap in knowledge about how the neurochemical effects of MDMA might

explain its observed qualities at relieving psychiatric distress, as the current theories tend to describe only psychodynamic models.

Several studies have highlighted the association between MDMA users and mental illness. An epidemiological study by Lieb *et al.* (2002) demonstrated that among a population of young ecstasy users, there were significantly higher rates for almost all DSM-IV mental disorders compared with nonusers. However, examination of the temporal patterns of ecstasy use revealed that in the majority of cases the mental disorders occurred before the users' first experience with ecstasy. Lieb *et al.* concluded that care should be taken in cross-sectional studies in interpreting mental disorder signs merely as a consequence of ecstasy use. Similarly, another recent prospective study by Huizink *et al.* (2006) demonstrated high levels of depression and anxiety among a cohort of young adults who were regular users of ecstasy. Huizink's study clearly demonstrated that this population of ecstasy users showed significant symptoms of depression and anxiety as children and adolescents, *before* ever taking ecstasy. These studies suggest that some users may take ecstasy as self-medication against pre-existing depression.

Safety and risks of taking MDMA

The debate about the possible dangers of MDMA has had a lot of exposure in both the popular and scientific press in the last 20 years and is well-documented elsewhere (Sessa, 2007). However, in the UK to date, only approximately 20 deaths per year since 1990 have been attributed to ecstasy (ONS, 2002). These high-profile deaths have also involved other drugs, often including heavy alcohol use, impure samples of ecstasy or excess water consumption. Even so, this figure is still remarkably small, given that there are at least 100 million tablets distributed in the UK each year (NCIS, 2001). In contrast, annually there are around 7 000 alcohol-related deaths and 106 000 tobacco-related deaths (ONS, 2002, 2003).

Some studies suggest heavy, recreational ecstasy use may be linked to a transient and reversible neurotoxicity (Molliver *et al.*, 1990), particularly when the drug is taken frequently and in high doses (Ricaurte *et al.*, 1985). However, physiological studies involving limited, infrequent and moderate doses of MDMA (as it is used in the psychotherapeutic setting) demonstrate that the drug has no lasting neuropsychological effects (Halpern *et al.*, 2004) and no evidence of neurotoxicity (Ludewig *et al.*, 2003). So scientific studies describing the dangers of taking ecstasy recreationally refer to doses or patterns of use that are irrelevant to the clinical usage of MDMA for psychotherapy (Grob, 2002). A simple analogy would be to imagine doctors from the Royal College of Surgeons or Anesthetists being denied access to prescribe, or even *research*, the opiate drugs for clinical use because of the existence of recreational heroin abuse. Opiates are vital parts of these doctors' formulary, and while they are undeniably abused in society, they are also essential clinical tools when used safely by clinicians. MDMA (which is incidentally considerably less toxic than the opiates, when used either clinically or recreationally) may have the potential to be an equally important tool for psychiatry.

Is there a place for a trial that examines the possible role for MDMA in treating depression?

There are already several trials underway worldwide exploring MDMA as an adjunct to psychotherapy. Studies include using MDMA to treat post-traumatic stress disorder (PTSD) and to aid psychotherapy for the anxiety associated with end-stage cancer (Sessa, 2007). That these trials are underway at all illustrates a general acceptance within the medical community that when used in moderate doses in controlled circumstances, the clinical applications for MDMA are justified.

However, above and beyond using MDMA as psychotherapeutic tool, could it be possible that it has a role as a potent serotonin agonist in treating depression? With much smaller dosages than those being used recreationally (which tend to use 120 mg plus), could MDMA, if taken repeatedly and at much lower doses (say 10–25 mg) have a gradual, beneficial effect on mood? Perhaps, a trial that proposed administering 'subpsychedelic' doses of MDMA, on a regular basis, to patients with clinical depression might be of benefit? One might expect the drug to have similar effects to the SSRI drugs, but because one need not wait for serotonin levels to build up slowly through inhibiting re-uptake of the neurotransmitter, one might propose the mood-enhancing effects of low-dose MDMA might be noticed much quicker than with an SSRI drug. And perhaps, if taken in such low doses there would not be such a dramatic rebound serotonin depletion causing a significant hangover effect? The possibility of using MDMA to lift mood early and then transfer to an SSRI of other anti-depressant to continue longer term might be considered.

One particular area where this rapid onset may be of use clinically is in circumstances where mood elevation is required quickly for emergency reasons and there is no time to wait for up to six weeks for the anti-depressant effects of traditional drugs. In these situations the current treatment is electro-convulsive therapy (ECT). In this scenario could MDMA be used instead of ECT?

All these questions make for an interesting proposal that there may be a much larger role for MDMA in clinical medicine than just as an adjunct to psychotherapy. However, with the current drug laws standing as they are, any researcher interested in this field still has significant barriers to overcome before proposing any such projects. Moreover, the controlled status of such compounds in most western countries deters pharma companies from even exploring this arena, as they fear that any novel compound with action like MDMA would necessarily be subject to similar legal controls. These would probably hamper its being studied therapeutically and would limit its use and acceptability, even if it were to be shown to have efficacy and to be safer than MDMA in terms of abuse liability, hangover and neurotoxicity.

Socio-political agenda on drugs has a deleterious effect on medical research

Clinicians, the police, pharmacologists and the general public alike are increasingly questioning the current drug laws. A recent major

multidisciplinary review in The Lancet seriously challenged the current prohibition laws and declared the present system to be not based on scientific foundations (Nutt *et al.*, 2007). The authors propose that the current system of classification in the UK (in which controlled drugs are classified in classes A, B and C) does not always accurately reflect the true physical harm, risk of dependence and social harm of controlled drugs. They used Delphic Analysis to more accurately classify twenty potential drugs of abuse – including legal drugs such as alcohol and tobacco – into a hierarchy. This form of analysis utilizes a lengthy and broad discussion by experts in multiple fields using principles of evidence-based medicine to more precisely assess the drug's potential for harm. The results suggest there is no significant correlation between the current Misuse of Drugs Act and the harm rating elicited by this analytical method. While some drugs currently classified as the most harmful (Class A) also scored highly in the Lancet study (e.g., Heroin and Cocaine), other drugs that are currently Class A, such as ecstasy and LSD scored very low in the harm rating. And conversely, some of the legal drugs (alcohol, tobacco and benzodiazepines) scored highly. A system that allows for drugs such as alcohol and nicotine to be freely available while drugs with less damaging pharmacological profiles are criminalized is bound to give off the wrong message to the public.

The Lancet paper demonstrates that our current methods for assessing harm are not based on the most accurate medical or social evidence. Indeed, it is often on parameters other than evidenced-based medical criteria that drugs are prohibited in the first place. It is well-recognized, for instance, that racist socio-political factors influenced the prohibition of cannabis in the 1930s in the USA (Bonnie *et al.*, 1999). Frank statements of racism aligned cannabis use with the migrant Mexican population in the USA in the 1930s and then again with the black jazz musicians in the 1950s.

In the 1960s a similar association between psychedelic drug use and the undesirable left-wing politics that challenged the authorities over foreign policy in Vietnam was often quoted in debates that lead to the eventual prohibition of LSD in 1966 (Lee and Shalin, 1992). Research on these drugs has been extremely limited since their prohibition.

Conclusion

The development of MDMA as a tool to assist psychotherapy is now well underway, but perhaps, the next stage of exploring the drug's potential lies in proposing a study that investigates it's role as a potent serotonin agonist to rapidly elevate mood. However, a study such as this remains extremely difficult to put forward given the continuing prohibition. Should such studies prove successful they could offer a novel approach to the treatment of depression although the current laws mitigate against pharma following up such findings with new drugs with the same actions. This situation is bad for science and bad for patients and quite illogical. We must not let MDMA research be hijacked by politics, as has happened with LSD. MDMA is a medical tool and it deserves to remain within medicine.

The 'War On Drugs' waged by successive governments against all substances with abuse potential threatens to strangle our advancement of knowledge about how these substances might be used safely and effectively to treat patients with unremitting mental illnesses. We do not seek to condone the recreational use of potentially dangerous compounds, but rather to view the subject with a scientific objectivity that the political agenda is often seen to be lacking. Such an approach is essential if we are to provide the most effective and targeted social policies around prohibition and, crucially, the best evidenced treatments for our patients.

Declaration of Interests

None

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