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# Are psychedelic drug treatments seeing a comeback in psychiatry?

After a hiatus of nearly 40 years, psychedelic drugs (or hallucinogens) are being increasingly researched as possible adjuncts to psychotherapy for treatment-resistant anxiety disorders and addictions. This research offers an exciting future for this class of drugs whose image has been tarnished by recreational use since the 1960s. Through cautious and evidence-based studies, these medications could be finding their way back to where they began their lives: as valid and effective tools for clinical medicine and neuroscientific research.

Psychedelic drugs, such as D-lysergic acid diethylamide-25 (LSD), 3,4,5-trimethoxybenzeneethanamine (mescaline), O-phosphoryl-4-hydroxy-N,N-dimethyltryptamine (psilocybin), 3,4-methylenedioxymethamphetamine (MDMA) and dimethyltryptamine (DMT), occur in abundance throughout the natural world and have been used by humankind for thousands of years.

In some cultures these substances are important tools for spiritual experiences, while in others they are labelled as dangerous drugs of abuse. What is less well known by many psychiatrists is the historic role they played in psychiatry for a brief interval and that there is currently a growing international explosion of research into developing them again as clinical tools.

## Defining psychedelic drugs

Many psychiatrists will define psychedelics as drugs that cause an acute confusional state, producing profound alterations in consciousness and inducing perceptual distortions as part of an organic, toxic psychosis. From a cross-cultural perspective, the psychedelic drugs may be defined as spiritual tools, used in the form of plants and fungi by many non-Western cultures as part of their religious ceremonies.

For many lay people, the psychedelic drugs are little more than illegal and dangerous drugs of abuse – considered to be addictive compounds, not to be distinguished from cocaine and heroin, which are understood to be wholly negative – the cause of an individual, if not society's, destruction.

However, two contemporary definitions for psychedelic drugs include the following:

- These drugs can be developed as useful and safe medical treatments – used as adjuncts to psychotherapy to alleviate the symptoms and modify the course of many treatment-resistant mental illnesses
- They can be developed as vital research tools with which to better our understanding of the brain and the nature of consciousness.<sup>1</sup>

## Ancient uses of psychedelic drugs

Psychedelic plants have been used by non-Western cultures as spiritual tools for thousands of years. They have shaped the course of many established religions and continue to be used throughout the world as part of religious ceremonies for many cultures.<sup>2</sup> Examples include the legendary 'soma', appearing throughout Sanskrit texts forming the basis of the Hindu religion. Of the 1200 texts of the Rig Vedas, some 100 describe the mystery substance soma. The active component of soma was possibly the hallucinogenic *Amanita Muscaria* (Fly Agaric) mushroom.

In ancient Greece, as part of the Eleusinian Mystery Rites, there was the 2000-year-old practice of worshipping the Goddess Demeter through ingestion of a drink made from Paspali grass, inadvertently impregnated with ergot – the active component of which is a close relative of LSD. During the secret ceremony, the initiates, who included Plato and Cicero, described their experience of seeing and communicating with the Goddess herself.

## History of psychedelics in medicine

After the discovery of the psychotropic effects of LSD in the 1940s by the Swiss Chemist Albert Hofmann,<sup>3</sup> there followed a short period of clinical use within psychiatry. Psychiatrists and psychotherapists found that LSD had the ability to allow a deeper access to repressed memories and an improved relationship between patient and therapist. The 'classical' psychedelics such as LSD and psilocybin were studied throughout the 1950s and 1960s, and thousands of case reports of their use exist.<sup>4</sup> The number of adverse incidents was low<sup>5</sup> and doctors developed progressively more sophisticated methods for achieving the most comfortable and productive psychedelic sessions. Their techniques were often informed by Eastern tradition – with elements of meditation and chanted verses in a relaxing, facilitative environment.<sup>6</sup> However, despite these numerous reports, by modern research standards the studies of the 50s and 60s have little more than anecdotal value as they usually lacked

**Studies currently underway (Phase II)**

- MDMA-assisted psychotherapy to treat resistant PTSD: Underway in the USA by Dr Michael Mithoeffer<sup>25</sup>
- MDMA-assisted psychotherapy to treat resistant PTSD: Underway in Switzerland by Dr Peter Oehen<sup>26</sup>
- Psilocybin-assisted psychotherapy to treat the anxiety and pain associated with terminal cancer: Underway in the USA by Dr Charles Grob<sup>27</sup>
- LSD-assisted psychotherapy to treat the anxiety and pain associated with end-stage cancer: Underway in Switzerland by Dr Peter Gasser<sup>28</sup>
- Ibogaine-assisted psychotherapy to treat opiate addiction: Follow-up and review of previous therapy in Canada underway by Leah Martin and Sandra Karpetas<sup>29</sup>

**Studies currently under planning and awaiting full approval**

- Psilocybin-assisted psychotherapy to treat the anxiety and pain associated with end-stage cancer: Underway in USA by Dr Roland Griffiths<sup>30</sup>
- MDMA-assisted psychotherapy to treat the pain and anxiety associated with end-stage cancer: Planned by Dr John Halpern in the USA<sup>31</sup>
- Using (sub-psychedelic doses of) LSD and psilocybin to treat cluster headaches: Study planned by Dr Andrew Sewell in the USA<sup>32</sup>

**Studies that have been completed**

- Psilocybin-assisted psychotherapy to treat obsessive-compulsive disorder<sup>33</sup>
- Ketamine-assisted psychotherapy to treat alcohol dependence<sup>34</sup>
- Ketamine-assisted psychotherapy to treat heroin dependence<sup>35</sup>
- Psilocybin as an agent to induce a mystical-type experience<sup>36</sup>
- Physiology and dose studies with dimethyltryptamine (DMT) in humans<sup>37</sup>

**Table 1.** Psychedelic drug trials currently underway, planned and completed

control groups and follow-up and were subject to selection bias.<sup>7</sup>

With the leaking of LSD from the scientific community into widespread public use, medical research ended virtually overnight, as doctors, in the face of a massive press bias against LSD, were forced to distance themselves from the drug.<sup>8</sup> Many psychedelic therapists, having found their work with LSD promising, were disheartened by the prohibition, and by the mid-70s their work was virtually extinct. On giving up their work with LSD some psychiatrists went on to develop alternative non-drug-assisted transpersonal psychotherapy methods and some went on to work with the little known, still legal at the time, drug MDMA.

**Is MDMA the future for psychedelic research?**

MDMA is the synthetic psychoactive drug better known as the street drug 'ecstasy'. The MDMA experience has several features that make it well suited to assist psychotherapy. Sometimes referred to as an 'empathogen' or 'entactogen', MDMA promotes relaxation, facilitates a loosening of the ego and encourages an increased thoughtfulness and contemplativeness.<sup>9</sup> These effects can produce a state of improved insight and aid a greater exploration of otherwise painful repressed memories, by 'inhibiting the subjective fear response to an emotional threat'.<sup>10</sup> This makes MDMA

a particularly useful drug for patients with post-traumatic stress disorder (PTSD)<sup>11</sup> or for patients experiencing anxiety associated with the process of dying in cases of terminal cancer.<sup>12</sup>

There are also well-recognised effects on the relationship between the patient and the therapist. These stem from MDMA's ability to increase levels of understanding and empathy.<sup>13</sup> The warmth and feelings of empathy that are experienced under MDMA allow users to approach previously difficult intimate relationship conflicts in a new light, and account for the utilisation of MDMA as an agent to assist in couples' therapy in the USA in the early 1980s.<sup>14</sup>

Crucially, the MDMA experience is almost always pleasurable and manageable. It is far less perceptually distorting than that of the classical psychedelics. MDMA, strictly speaking an 'empathogen' rather than a psychedelic drug, is less intense and shorter acting than LSD (two to five hours compared to LSD's 8 to 12 hours). It offers a similar therapeutic potential for lowering a patient's defences and aiding the psychotherapeutic process.<sup>15</sup> Altogether this makes MDMA a much more attractive tool for psychotherapy than LSD.<sup>16</sup> Since the 1970s, MDMA psychotherapy has seen an emerging underground use by analysts and there are now a number of trials underway throughout the world using MDMA and other psychedelic drugs.

### **Safety profile of the psychedelic drugs when used clinically**

The 'classical psychedelics' (psilocybin, LSD, mescaline) have a remarkably safe physical profile relative to other psychoactive compounds. There are no recorded deaths from any direct toxic effects of these drugs – even in overdose.

Psychological safety concerns include the risk of anxiety episodes or triggering psychosis in vulnerable individuals. As reported in several reviews, transient anxiety or depression after taking LSD have been reported in many cases. These cases typically resolve spontaneously with supportive care.<sup>17</sup> There are reports of prolonged psychiatric symptoms after LSD use, but this response remains rare. In one survey of 5000 people to whom LSD or mescaline had been administered in therapeutic and research settings, adverse psychiatric reactions lasting more than 48 hours, including psychosis, were reported in 0.08 per cent of research volunteers and 0.18 per cent of psychiatric patients.<sup>18</sup>

Another condition occasionally attributed to hallucinogenic drugs is hallucinogen persistent perception disorder (HPPD), sometimes wrongly referred to as 'flashbacks'. HPPD involves changes in visual perception long after the acute intoxication with the drug is over. To date, there are no studies reporting the prevalence of HPPD in the general population, but examination of reports and estimates of use of LSD and other hallucinogens in the USA suggest that HPPD is rare.<sup>19</sup> By excluding high-risk groups, and ensuring careful attention is paid to set and setting (*ie* the context of the psychedelic experience) during human psychedelic drug research, these risks can be reduced to a minimum.

The psychedelic drugs are rarely described as addictive. This has been demonstrated by both epidemiological evidence (in which users becoming dependent on psychedelic drugs is very rare) and animal studies (in which laboratory animals do not readily self-administer themselves with psychedelic drugs to anything like the extent they do with drugs such as cocaine and alcohol).<sup>20</sup> Extrapolated to humans, this suggests a very low dependence potential. There still exists concern around the risk of long-term neurotoxicity with MDMA, although in recent years this has been challenged by contemporary neurobiological and neuroimaging evidence.<sup>21</sup> And a recent influential *Lancet* paper<sup>22</sup> suggested that the health risks of LSD and MDMA, even when abused recreationally, have been greatly exaggerated. The study classified these substances a long way down the table of harm, well below alcohol and cigarettes in terms of physical, psychological and dependence risk potential.

Crucially, regarding the safety profile of psychedelic drugs, whatever risks may exist for recreational users

of these drugs, Phase I studies have consistently demonstrated that moderate amounts of substances such as LSD, psilocybin and MDMA can be administered relatively safely in the context of medically monitored clinical trials.<sup>9,23,24</sup>

### Current research

The double-blind placebo controlled trials outlined in Table 1 have all been many years (some literally decades) in their planning because of the complex ethical and political issues involved with this sort of research.

As the studies currently underway are still in the Phase II pilot stage, no published results are available yet. However, details of preceding Phase I studies and publicly-viewable protocols are available on the Internet (see References). Further details of all these planned, ongoing and completed studies can be found at the websites for the Multidisciplinary Association for Psychedelic Studies (MAPS: [www.maps.org](http://www.maps.org)) and Heffter Research Institute ([www.heffter.org](http://www.heffter.org)).

### Current state of the psychedelic community

There is an interesting shift going on within the psychedelic medical research community. The community is striving for acceptance – not just within mainstream medicine but also from a distrustful general public. By distancing itself from the pseudo-scientific image of the past and increasingly aligning itself with respected organisations that are embracing prominent medical and neuroscientific professionals of the day, the psychedelic community itself is well aware of the need to adopt a more measured approach if it is to progress. Whilst at this year's World Psychedelic Forum in Basel, Switzerland – a multidisciplinary event in which scientists from all fields come together every two years to discuss psychedelic drugs – one journalist described the atmosphere to me as being like that of the Labour Party conferences of the early nineties!

So the future looks bright for the research potential of psychedelic drugs. This subject offers a valuable chance to integrate the sometimes divergent subjects of psychiatry and psychotherapy, making it an exciting time to be on the leading edge of research in both fields. But we should not get too carried away. This time round we must avoid the messianic passion of the 1960s and exercise caution and restraint if we are to truly develop these fascinating substances as prescription medicines for the future.

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### References

1. Sessa B. Is it time to revisit the role of psychedelic drugs in enhancing human creativity? *J Psychopharmacol* 2008; In Press.
2. Schultes E, Hofmann A, Ratsch C. *Plants of the Gods*. Rochester, Vermont: Healing Arts Press 1998;pp9-19.
3. Hoffman A. *LSD: My Problem Child*. McGraw-Hill Book Company 1980;pp35-52.
4. Grinspoon L, Bakalar B. Therapeutic uses. In: *Psychedelic Drugs Reconsidered*. New York: The Lindsmith Center, 1997;pp192-237.
5. Malleon N. Acute adverse reactions to LSD in clinical and experimental use in the United Kingdom. *Br J Psychiatry* 1971;118:229-30.
6. Grof S. The principle of LSD psychotherapy. In: *LSD Psychotherapy. Florida: Multidisciplinary Association for Psychedelic Studies*, 2001;pp123-47.
7. Grob C. Psychiatric research with hallucinogens: What have we learned? *The Yearbook for Ethnomedicine and the Study of Consciousness*, Issue 3, 1994.
8. Sessa B. Can psychedelics have a role in psychiatry again? *Br J Psychiatry* 2005;186:457-8.
9. Vollenweider FX, Gamma A, Liechti M, et al. Psychological and cardiovascular effects and short-term sequelae of MDMA ('ecstasy') in MDMA naive healthy volunteers. *Neuropsychopharmacology* 1998;19:241-51.
10. Greer GR, Tolbert R. A method of conducting therapeutic sessions with MDMA. *J Psychoactive Drugs* 1998;30(4):371-9.
11. Bouso JC. Using MDMA in the treatment of post-traumatic stress disorder. In: *Ecstasy: The Complete Guide*. Julie Holland, ed. Vermont, Rochester: Park Street Press, 2001;pp248-61.
12. Greer G, Tolbert R. The therapeutic use of MDMA. In: *Ecstasy: The Clinical, Pharmacological and Neurotoxicological Effects of the Drug MDMA*. SJ Peroutka, ed. Holland: Kluwer, 1990.
13. Cami J, Farre M, Mas M, et al. Human pharmacology of 3,4-methylenedioxyamphetamine ('ecstasy'): psychomotor performance and subjective effects. *J Clin Psychopharmacol* 2000;20:455-66.
14. Greer GR, Tolbert R. Subjective reports of the effects of MDMA in a clinical setting. *J Psychoactive Drugs* 1986;18(4):319-27.
15. Holland J. The Legal Status of MDMA around the World. In: *Ecstasy: A Complete Guide*. Julie Holland, ed. 2001. Vermont: Park Street Press, 2001;Chapter 10.
16. Sessa B. Is there a role for MDMA-assisted psychotherapy in the UK? *J Psychopharmacol* 2007;21(2):220-4.
17. Strassman RJ. Human hallucinogenic drug research: regulatory, clinical, and scientific issues. *NIDA Res Monogr* 1994;146:92-123.
18. Cohen S. Lysergic acid diethylamide: side effects and complications. *J Nervous and Mental Disorders* 1960;130:30-40.
19. Halpern J, Pope H. Hallucinogen persisting perception disorder: what do we know after 50 years? *Drug Alcohol Depend* 2003;69(2):109-19.
20. Fantegrossi WE, Woods JH, Winmger G. Transient reinforcing effects of phenylisopropylamine and indoalkylamine hallucinogens in rhesus monkeys. *Behavioural Pharmacol* 2004;15:149-57.
21. Vollenweider FX, Gucker P, Schönabächer R, et al. Effects of MDMA on 5-HT uptake sites using PET and [<sup>11</sup>C]-McN5652 in humans. Data presented at the 2000 conference of the German Society for Psychiatry, Psychotherapy and Neuromedicine.
22. Nutt DJ, Blakemore C, et al. The Development of a rational scale to assess the harm of drugs of potential misuse. *Lancet* 2007;369:1047-53.
23. Nichols DE. Hallucinogens. *Pharmacol Ther* 2004;101(2):131-81.
24. Halser F, Grimberg U, Benz, et al. Acute psychological and physiological effects of psilocybin in healthy humans: A double blind, placebo-controlled dose-effect study. *Psychopharmacology* 2004;172:145-56.
25. Protocol at: [www.maps.org/research/mdma/ptsd\\_study/protocol/protocol051606.pdf](http://www.maps.org/research/mdma/ptsd_study/protocol/protocol051606.pdf)
26. Protocol available at: [www.maps.org/mdma/swissptsd/protocol011806.pdf](http://www.maps.org/mdma/swissptsd/protocol011806.pdf)
27. Protocol available at: [www.canceranxietystudy.org](http://www.canceranxietystudy.org)
28. Protocol at: [www.maps.org/research/lsd/swisslsd/LDA1010707.pdf](http://www.maps.org/research/lsd/swisslsd/LDA1010707.pdf)
29. Protocol available at: [www.maps.org/ibogaine/iboprotocol70706.pdf](http://www.maps.org/ibogaine/iboprotocol70706.pdf)
30. Details can be found at: [www.heffter.org/pages/research.html](http://www.heffter.org/pages/research.html)
31. Protocol at: [www.maps.org/research/mdma/canceranxiety/irb-protocol/](http://www.maps.org/research/mdma/canceranxiety/irb-protocol/)
32. Details can be found at: [www.clusterbusters.org](http://www.clusterbusters.org)
33. Moreno FA, Wiegand CB, Taitano EK, et al. Safety, tolerability and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. *J Clin Psychiatry* 2006;67:1735-40.
34. Krupitsky EM, Grinenko AY. Ketamine psychedelic therapy (KPT): A Review of the Results of Ten Years of Research. *J Psychoactive Drugs* 1997;29(2):165-83.
35. Krupitsky EM, Burakof AM, Dunaevsky IV, et al. Single versus repeated sessions of ketamine-assisted psychotherapy for people with heroin dependence. *J Psychoactive Drugs* 2007;39(1):13-9.
36. Griffiths RR, Richards WA, McCann U, et al. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. *Psychopharmacology* (online edition): July 11, 2006.
37. Strassman R. *DMT: The Spirit Molecule*. Rochester, Vermont: Park Street Press, 2001;pp89-98.