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Contents

- Therapeutic potential of psychedelic agents
- Are conclusions overstated for placebo response?
- Improving assessment and treatment of physical health problems in people with severe mental illness: the case for a shared IT system

Therapeutic potential of psychedelic agents

Amphetamine, methylphenidate, morphine, heroin and ketamine are all drugs that can potentially be used clinically but, whenever we hear the word MDMA, the first thoughts that come to mind are of ecstasy, rave parties and people behaving in an odd manner and experiencing hallucinations, paranoia and disinhibition. Recently, there has been a lot of discussion on the use of MDMA for treatment-resistant post-traumatic stress disorder (PTSD), a psychiatric illness that is very difficult to treat and getting common these days because of all the horrific stuff happening around us. Mithoefer *et al*[1,2] found that 83% of participants receiving MDMA-assisted psychotherapy in a pilot study no longer met the criteria for PTSD, and every patient who received a placebo and then went on to receive MDMA-assisted psychotherapy experienced significant and lasting improvements. We are still in the initial stages, and only a few studies have been done, but the results of these studies are very significant. More research in this area is needed and government needs to contribute by moving MDMA to the list of Schedule 2 drugs so that more research can be done. At the same time, one has to be very careful and vigilant to make these drugs legal for therapeutic use, looking into dependence risk, effects on memory, depression and chances of psychosis. More research is needed especially into possible harms of the drug. It will place more responsibility on clinicians to prescribe and monitor drugs like this. Making these drugs legal is not easy but has happened in the past; otherwise, people with terminal cancer would still be suffering with pain and agony in last days of their life, and people with attention-deficit hyperactivity disorder would be suffering despite being capable of doing everything. Legalising MDMA for therapeutic use is going to be beneficial not only for patients but also for the economy, looking at the resources we use for treatment-resistant PTSD.

1 Mithoefer MC, Wagner MT, Mithoefer AT, Jerome L, Doblin R. The safety and efficacy of ±3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study. *J Psychopharmacol* 2011; **25**: 439–52.

2 Mithoefer MC, Wagner MT, Mithoefer AT, Jerome L, Martin SF, Yazar-Klosinski B, et al. Durability of improvement in post-traumatic stress disorder symptoms and absence of harmful effects or drug dependency after 3,4-methylenedioxymethamphetamine-assisted psychotherapy: a prospective long-term follow-up study. *J Psychopharmacol*, 2013; **27**: 28–39.

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We welcome the renewed interest in the therapeutic potential of psychedelic compounds. In their recent editorial, Sessa & Johnson[1] echo the fervent research climate of psychedelics spanning the 1950s and '60s. They suggest that psychedelics may cause prolonged changes in participants' personalities and attitudes following mystical–spiritual experiences. This unique and exciting potential mechanism of action certainly warrants the current renaissance in psychedelic research, and has important implications for study design and participant selection. As we move towards re-exploring the clinical applications of psychedelics, however, we must appreciate that the phenomenology of the psychedelic experience is likely to depend not only on the drug's pharmacodynamic properties, but also on the makeup of the participant ('set') and the environmental context ('setting') in which the drug is administered.

Recent work suggests that the potential importance of set in the psychedelic experience should not be overlooked. Hallucinogenic compounds act via the serotonergic 5-HT_{2A} receptor to affect experience and behaviour. Genetic and neuroimaging evidence suggests that inter-individual differences in serotonergic neurotransmission relate to personality differences and vulnerability to psychiatric illness.[2] Relatedly, research with hallucinogenic compounds has reported sustained changes in personality traits and behaviour.[3] Moreover, reports from individuals who have taken hallucinogenic compounds suggest that the quality of the experience (whether the 'trip' is good or bad) has some connection to the attitude and particular psychological landscape of the individual.[4] Finally, a closer look at the psychological profile of participants who volunteer for these studies reveals that they may not be representative of the general population, and in particular may be more open to new experiences.[3] Together, these ideas suggest that the effect of a hallucinogenic compound on an individual's experience has complex links with their neurobiological and psychological composition.

The quality of the psychedelic experience is also inextricably linked to the environmental and social setting. In the late 1960s, several studies strove to isolate the action of a drug from external influence, including concomitant therapy.[4] Their efforts generated less promising results than studies that, by design, emphasised the importance of the setting.[5] As an illustrative example, one study found sensory deprivation to be antagonistic to the 'LSD experience'.[6] Consequently, the relationship between the psychedelic experience and the setting must be considered in experimental design. Even a structured test or interview can radically alter the resulting phenomenology.[6]

We propose that a fruitful future research programme investigating the therapeutic potential of psychedelic compounds must take the complex interaction between set and setting into account in its participant recruitment and study design. By acknowledging this association, future research will be in a position to understand the full breadth of the psychedelic experience and its potential clinical applications. Although practically challenging, such a comprehensive approach will allow us to re-examine the perhaps premature assertions of the mid-1970s that psychedelics had no therapeutic applications.[5]

1 Sessa B, Johnson MW. Can psychedelic compounds play a part in drug dependence therapy? *Br J Psychiatry* 2015; **206**: 1–3.

2 Ebstein RP. The molecular genetic architecture of human personality: beyond self-report questionnaires. *Mol Psychiatry* 2006; **11**: 427–45.

3 MacLean KA, Johnson MW, Griffiths RR. Mystical experiences occasioned by the hallucinogen psilocybin lead to increases in the personality domain of openness. *J Psychopharmacol* 2011; **25**: 1453–61.

4 Drugs Forum. *The Psychedelic Crisis: Bad Trip*. 2011 (https://www.drugs-forum.com/forum/showwiki.php?title=The_psychedelic_crisis:_bad_trip).

5 Oram M. Efficacy and enlightenment: LSD psychotherapy and the drug amendments of 1962. *J Hist Med Allied Sci* 2012; **69**: 221–50.

6 Hoffer A, Osmond H. *The Hallucinogens*. Academic Press, 1968.

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Author's reply: MDMA research is a fascinating branch of research medicine that is now really taking off. Dr Pathania refers to the recent work of Mithoefer and colleagues, whose long-term follow-up study showed a sustained absence of PTSD symptoms in 20 patients with treatment-resistant PTSD 4 years after a single course of MDMA-assisted psychotherapy.

In the wake of these pilot studies, MDMA therapy research is now moving into phase 3, with large, multicentre trials beginning within the next 24 months (see www.maps.org/research/mdma for more details). This includes, we hope, a UK-based arm of the project and a planned licensing date for MDMA as a prescription medicine for treatment-resistant PTSD by 2021. These are bold steps indeed. For the large population of patients with PTSD who remain chronically unwell and untreated by traditional methods (almost 50% of all sufferers) this cannot come soon enough.

Drs Nour & Krzanowski provided a thoughtful and stimulating reply to the article I co-authored with Dr Matt Johnson regarding the contemporary development of psychedelic drug-assisted psychotherapy for drug dependence disorders.[1] They are absolutely correct to draw attention to the importance of set and setting. These are essential factors to bear in mind whenever a psychedelic drug is used – either clinically, during research or recreationally; the outcome of a psychedelic experience is highly dependent on the user's mindset and the environmental conditions in which they take the drug.[2] All the research studies Dr Johnson and I mentioned in our review have appropriately paid attention to the concepts of set and setting.

In Dr Johnson's work within the USA with psilocybin, in all the UK-based psychedelic drug studies that I have contributed towards in recent years (with LSD, ketamine and psilocybin), and in our forthcoming UK-based MDMA study, we have been careful to ensure that participants are fully informed about the drugs they are taking, that appropriate safety measures are in place to reassure them and that the studies are conducted in safe, welcoming, relaxed and facilitative environments. These measures are an important active part of the drug experience. It is arguable that much of the bad press psychedelics have received in the decades since their vilification in the late 1960s has arisen as a result of negative psychedelic experiences in the context of poorly managed set and settings. When these factors are diligently managed, the vast majority of psychedelic experiences in most people are positive. The epidemiological work of Dr Teri Krebs, who looked at a very large sample of psychedelic users, illustrates the relative safety and benefit of psychedelic drug use in contemporary times.[3]

1 Sessa B, Johnson MW. Can psychedelic compounds play a part in drug dependence therapy? *Br J Psychiatry* 2015; **206**: 1–3.

2 Sessa B. *The Psychedelic Renaissance: Reassessing the Role of Psychedelic Drugs in the 21st Century Psychiatry and Society*. Muswell Hill Press, 2012: p. 23.

3 Krebs TS, Johansen P. Psychedelics and mental health: a population study. *PLoS One* 2013; **8**: e63972.

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Are conclusions overstated for placebo response?

The implications of Leuchter *et al*'s research[1] not only have potential for our further understanding of placebo responses in clinical trials, but also bring into question the pharmacological advantage of antidepressant medication over placebo in clinical outcomes for depression. Their findings warrant full evaluation so that they can be considered within the context of the wider research base. However, an accurate appraisal is currently limited by a lack of clarity in the methodology presented. We suggest several areas in which further clarification could assist critical appraisal.

First, the use of the Hamilton Rating Scale for Depression (HRSD) as a measure of depression severity warrants discussion. A 2014 literature review failed to find evidence to support its use, describing it as irretrievably flawed. Interestingly, many scale items were not found to sufficiently contribute to the measure of depression severity.[2] Without a valid measure of severity, can we be assured that participants met criteria for at least moderate depressive symptoms at baseline? Any failure to exclude those with milder symptoms could also account for the similar outcomes demonstrated in pill-taking groups. The National Institute for Health and Care Excellence advocate the avoidance of antidepressant prescription in those with less than moderate depressive symptoms, because of the poor risk–benefit ratio.[3]

In terms of the study design, the sample size appears to be smaller than one would anticipate. This is not helped by the significant, 24% loss to follow-up. Given that the report does not reference a power calculation, are the authors able to provide clarity regarding their choice of sample size?

The process of recruitment also requires clarification. Recruitment via advertisement can be prone to selection bias and can account for loss of external validity within studies.[4] We suggest that advertisement recruitment may have attracted participants particularly keen to seek active treatment, possibly in order to avoid healthcare expenditure. It is understood that random allocation of recruited participants took place. Further clarification regarding this process would be helpful.

It is also understood that research coordinators were blinded during supportive-care interactions. Double-blinding is clearly essential in a study that involves a subjective outcome measure. Given that the research coordinators were often trained nurses, we raise the concern that they may have recognised relevant side-effects and unintentionally deduced a participant's group assignment. With any loss of their impartiality, clinicians form expectations and these have the power to significantly influence outcomes.[5] As trained nurses, it is also likely that their interactions might have provided therapeutic input aside from that considered to be consistent with supportive care. Were certain professionals more likely to report improvements in the placebo group?

Of further interest, we cannot find evidence to rule out suicidal behaviour as another potential confounder in this study. Participants' response to antidepressant medication may have been influenced by differences in serotonergic functioning, which has been linked to having a history of suicidal acts.[6]

With the above concerns in mind, we suggest that further consideration of the risk of type II error may be of value. We would be interested in the extent to which the authors have explored the potential for type II error and welcome their response.

1 Leuchter AF, Hunter AM, Tartter M, Cook IA. Role of pill-taking, expectation and therapeutic alliance in the placebo response in clinical trials for major depression. *Br J Psychiatry* 2014; **205**: 443–9.

2 Bagby RM, Ryder AG, Schuller DR, Marshall MB. The Hamilton Depression Rating Scale: Has the gold standard become a lead weight? *Am J Psychiatry* 2014; **161**: 2163–77.