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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).