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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.

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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.

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