We welcome the renewed interest in the therapeutic potential of psychedelic compounds. In their recent editorial, Sessa & Johnson1 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.5 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.7

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.8

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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.  
Correspondence

they take the drug. All the research studies Dr Johnson and I
mention in our review have appropriately paid attention to
the concepts of set and setting. 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.

Dr Sessa & 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. 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. 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 large sample of psychedelic users, illustrates the
relative safety and benefit of psychedelic drug use in
contemporary times.

Are conclusions overstated for placebo response?
The implications of Leuchter et al’s research not only have
to 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 irrefutably flawed. Interestingly, many scale
items were not found to sufficiently contribute to the measure of
depression severity. 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.

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.
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. 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.

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
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.

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.

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5 Oram M. Efficacy and enlightenment: LSD psychotherapy and the drug