

REVIEW ARTICLE

Psilocybin occasioned mystical-type experiences

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Abstract

Objective: Research into psychedelic therapy models has shown promise for the treatment of specific psychiatric conditions. Mystical-type experiences occasioned by psilocybin have been correlated with therapeutic benefits and long-term improvements in positive mental outlook and attitudes. This article aims to provide an overview of the topic, highlight strengths and weaknesses in current research, generate novel perspectives and discussion, and consider future avenues for research.

Design: This narrative review was designed to summarise and assess the state of research on psilocybin occasioned mystical-type experiences and applications for the treatment of specific psychiatric conditions.

Results: Contemporary methods on the quantification of mystical-type experiences and their acute subjective effects are discussed. Recent studies provide some understanding of the pharmacological actions of psychedelics although the neurological similarities and differences between spontaneous and psychedelic mystical-type experiences are not well described. Applicability to modern clinical settings is assessed. Potential novel therapeutic applications include use in positive psychology interventions in healthy individuals.

Conclusions: Since 2006 significant advancements in understanding the therapeutic potential of psilocybin-assisted psychotherapy have been made; however, more work is required to understand the neuromechanistic processes and applicability in modern clinical settings. Despite promising results in recent studies, funding issues for clinical trials, legal concerns and socio-cultural resistance provide a counterpoint to experimental evidence.

KEYWORDS

Psilocybin, mystical-type experiences, psychotherapy, clinical applications, quantum change, current research

1 | INTRODUCTION

After 100 years of modern psychiatry, there remains a lack of consistency in the provision of effective services for people with mental health disorders. While the popular media often present a negative, stigmatising picture of mental disorders and a lack of effectiveness of treatments (Stuart, 2006), large meta-analyses have demonstrated that in reality psychiatric treatments—when delivered appropriately

by well-resourced services—are comparable in efficacy to general medical interventions (Seemüller, Möller, Dittmann, & Musil, 2012). The negative perception persists, nevertheless, with particular emphasis placed on the potential adverse impact of the pharmaceutical industry, which has prompted significant criticism (Greenberg, 2010).

Polypharmacy (the use of two or more medications to treat the same illness) is often observed and is frequently associated with a lack of efficacy and increased harms from combining multiple drug

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treatments (Kukreja, Kalra, Shah, & Shrivastava, 2013). Polypharmacy is especially the case when lack of attention is paid to the provision of non-drug, psychosocial interventions—especially outpatient psychotherapy (Mojtabai & Olfson, 2008). In this context, what has emerged in the last 50 years of biological psychiatry is an urgent need to rationalise pharmacological treatments and bolster the efficacy and efficiency of psychotherapies. It is into this environment that psychedelic-assisted psychotherapies are becoming increasingly explored as viable innovative approaches for the future of psychiatry (Sessa, 2012).

2 | PSILOCYBIN-ASSISTED PSYCHOTHERAPY

The prodrug psilocybin, from *Psilocybe* mushrooms (Figure 1), is demonstrating therapeutic potential for the treatment of psychiatric conditions including alcohol use disorder (Bogenschutz et al., 2015), tobacco addiction (Garcia-Romeu, Griffiths, & Johnson, 2014), depression (Carhart-Harris et al., 2016) and existential anxiety in palliative care (Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016). In many of these clinical studies, subjects' mystical-type experiences have been correlated with therapeutic outcomes and improvements in various aspects of mental well-being such as reductions in anxiety and an increase in the personality domain of openness (Griffiths



FIGURE 1 Wild *Psilocybe semilanceata*

et al., 2016; Johnson, Garcia-Romeu, & Griffiths, 2017; MacLean, Johnson, & Griffiths, 2011).

In 2006 a Roland Griffiths publication reported that “psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance” (Griffiths, Richards, McCann, & Jesse, 2006). Since then, a number of psilocybin-assisted psychotherapy studies have been conducted which employ experimental features such as randomisation and double-blind crossover designs to mitigate the effects of expectation in both participants and clinicians (Griffiths et al., 2016; Ross et al., 2016). While double-blinding in a clinical trial for psychedelic therapy presents inherent challenges the long-term enduring effects have been recorded to discern the applicability of psychedelic experiences as a form of psychiatric therapy (Barnby & Mehta, 2018). Contemporary research indicates that if medical health care professionals could reliably induce psychedelic experiences of an insightful and mystical-type nature eliciting sudden, dramatic and enduring transformations that affect personal emotion, cognition and behaviour (a phenomenon referred to as quantum change) then there could be improvements in public health and well-being (Griffiths et al., 2018; Griffiths, Richards, Johnson, McCann, & Jesse, 2008; Johnson, Hendricks, Barrett, & Griffiths, 2019; Miller, 2004).

Effects of psilocybin on cognitive processes and mental functioning of a participant during a psilocybin trial are typically measured by inviting the participant to complete validated questionnaires such as: 5-Dimension Altered States of Consciousness; the States of Consciousness Questionnaire (SOCQ); and the Mystical Experience Questionnaire (Barrett, Johnson, & Griffiths, 2015; Griffiths et al., 2016; MacLean, Leoutsakos, Johnson, & Griffiths, 2012; Majić, Schmidt, & Gallinat, 2015). In order to determine whether a participant has had a “complete mystical-type experience” the results of questionnaires are totalled rendering a score—such as 60% on each subscale of the SOCQ (MacLean et al., 2011). The core phenomenology of mystical experiences, as described by previous work, include feelings of unity and interconnectedness with all people and things, a sense of sacredness, feelings of joy, peace and awe, a sense of transcending normal time and space, ineffability and an intuitive belief that the experience is a source of objective truth about the nature of reality (Griffiths et al., 2006, 2018; James, 1902; Kundi, 2013; MacLean et al., 2011; Roseman, Nutt, & Carhart-Harris, 2018; Stace, 1960).

3 | PSYCHEDELIC AND NON-PSYCHEDELIC MYSTICAL EXPERIENCES

The results of recent studies into both psychedelic-induced and non-psychedelic-induced mystical experiences suggest that mystical experiences are “biologically normal” (Griffiths et al., 2011) and can occur in both religious and non-religious individuals (Yaden et al., 2017). Studies suggest that mystical experiences and quantum change can occur in non-drug conditions with reports of spontaneous occurrences in times of crisis or stagnation (Miller, 2004). While subjective effects of psychedelic and non-psychedelic-induced mystical

experiences differ, there are certain similarities such as the sense of transcendence of time and space which imply there are continuities between the psychological states (Yaden et al., 2017). In the case of mystical experiences induced through disciplined contemplative practices an individual is typically required to spend months or years training their mind in order to reliably occasion meaningful mystical experiences (Kundi, 2013). While in the case of psychedelic-induced mystical-type experiences, research suggests that the quality of the experience is improved while the probability of occurrence is also increased enabling this generally rare state to become more readily accessible (Winkelman, 2017; Yaden et al., 2017).

3.1 | Cultural debate about the validity of psychedelic-induced mystical-type experiences

The subject of psychedelics' place in the study of comparative religions has been well explored by the likes of Alan Watts (Watts, 1968) and Aldous Huxley (Huxley, 1954). But from the beginning of discourse on the subject there were opposing viewpoints. Following Huxley's widely read description of his mescaline experience in 1953 there came a rebuttal from other academics, notably Professor Robert Zaehner, who warned of the dangers of conflating the transient, drug-induced psychedelic state with attainment of mystical states through non-drug religious experiences (Zaehner, 1957). The debate increased as the 1960s progressed and whilst Zaehner later agreed that drug-induced states could provide some useful guidance towards leading a spiritual life he also highlighted examples of the misuse of psychedelic spirituality and its capacity to do harm (Zaehner, 1974).

This article focuses on the capacity of psilocybin to induce acute mystical-type and insight experiences which can mediate persisting changes in perspective and psychological well-being. While mystical experiences can occur spontaneously in non-drug conditions and the reported subjective effects and long-term alterations of the two types are comparable, the two experiences are not the same due to differing neuropharmacological states.

4 | MECHANISTIC UNDERSTANDING

Psilocin, the pharmacologically active dephosphorylated metabolite of psilocybin, is highly structurally related to serotonin with a dimethyl tertiary amine as opposed to a primary amine on the two carbon aliphatic chain and a hydroxyl group at the 4' carbon as opposed to the 5' carbon on the indole phenyl ring being the sole differences in the chemical structures of psilocin and serotonin (Figure 2). Psilocin is a functional agonist of the G protein-coupled 5-HT_{2A} serotonin receptors and modulation of these receptors has been implicated in neuroplasticity, environmental sensitivity, learning and psychological adaptability (Carhart-Harris et al., 2018b; Carhart-Harris & Nutt, 2017; Erritzoe et al., 2019).

Research suggests that psychedelics mediate their subjective effects partly by decreased connectivity within the default mode

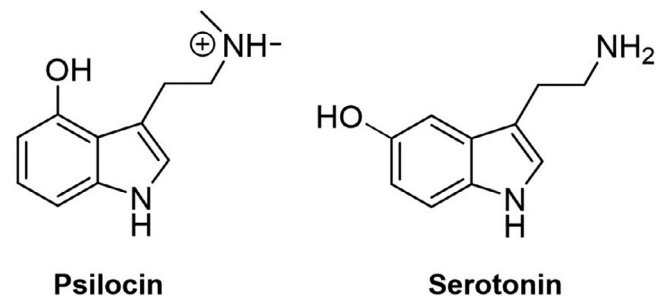


FIGURE 2 The chemical structures of psilocin and serotonin

network (DMN) (Johnson et al., 2019; Speth et al., 2016; Winkelman, 2017), modulation of the anterior and posterior cingulate cortex (Carhart-Harris, Leech, Williams, et al., 2012) and whole brain integration (Hendricks, 2018). The subjective mystical-type effects of psilocybin including ego dissolution have been at least partially attributed to disruption of the DMN (Griffiths et al., 2006). Psychedelics down-regulate expression of 5-HT_{2A} receptors in the prefrontal cortex (Hendricks, 2018); and subjective effects of psychedelics may result from 5-HT_{2A} receptor-mediated excitation of deep pyramidal cells leading to a desynchronization of oscillatory rhythms in the cortex (Muthukumaraswamy et al., 2013). Disruption of the prefrontal cortex allows ancient brain systems such as the mirror neuron system (Winkelman, 2017), which is located in numerous cortical regions, to occupy a more central role in subjective awareness (Rizzolatti & Sinigaglia, 2016). Current research into the effects of psilocybin on brain function suggests an increase in communication between brain networks accompanied by a decrease in communication within those networks (Hendricks, 2018).

The function of brain serotonin is reportedly “an enigma” (Carhart-Harris & Nutt, 2017) and the exact role of 5-HT_{2A} serotonin receptor signalling and how it relates to both psilocybin occasioned mystical-type experiences and naturally occurring spontaneous mystical experiences is poorly understood (Barnby & Mehta, 2018; Carhart-Harris & Nutt, 2017). Conducting controlled experiments to elucidate the neuromechanistic similarities and differences between the two types of experience presents significant challenges due to the difficulty of eliciting spontaneous mystical experiences in experimental settings.

4.1 | Sensitivity to meaning response

Psychotherapeutic benefits of psilocybin are not reportedly as dependent on dose or intensity of drug effect as they are dependent on the quality of the experience (Carhart-Harris, Roseman, et al., 2018; Griffiths et al., 2006; Roseman et al., 2018). While expectation and mood play a role in the therapeutic effects of all therapies, through the innate placebo and nocebo effects universal to all forms of medical treatment, psychedelics render the participant especially sensitive to the effects of set (the psychological mind-set in the build up to the experience including expectations and intentions) and setting (the

physical, social and political environment in which the experience takes place) (Hartogsohn, 2016, 2017; Metzner, Litwin, & Weil, 1965).

It has been proposed that the effects of set and setting and the placebo effect are not two differing extra-pharmacological components which contribute to mediating effects of treatment but are both expressions of meaning response. Meaning response is a broader concept which includes the many ways in which extra-pharmacological elements, including ritualistic and medical symbology, exert positive and negative effects on health in a variety of contexts. Psychedelics such as psilocybin are putative meaning response enhancers suggesting that one of their modes of action is to directly enhance the placebo effect itself. As potential magnifiers of the placebo response patients' expectations of the outcome of treatment may be more fundamental to successful therapeutic outcomes than in other forms of medical intervention (Hartogsohn, 2016). Furthermore, use of psilocybin to induce psychological transformations may result in modification of the epigenome *via* the enhanced placebo response (intent-oriented gene expression modulation) (Carey, 2012; Martin & Nichols, 2017).

The psychological construct "awe" has been proposed to be a key feature of spontaneous and psychedelic occasioned mystical-type experiences. The experience of awe can lead to the sensation of the "small self"—the feeling that one is small in comparison with the cosmos—and this has been proposed as being a psychological mediator of mystical experience (Piff, Dietze, Feinberg, Stancato, & Keltner, 2015). Individuals with high personality trait openness reportedly demonstrate a greater capacity to experience awe as participants who are able to fully absorb themselves in an external stimulus such as music are more likely to experience "chills"—an indication of subjectively experienced awe (Hendricks, 2018). Commonly reported elicitors of awe include the natural environment, art, music and religious/spiritualistic imagery. Greater emotional sensitivity to the environment may facilitate enhanced feelings of connectedness (Carhart-Harris et al., 2018a) and subjective effects of awe resulting in a psychological mind-set more receptive to mystical-type experience.

4.2 | Improved psychological flexibility mediates therapeutic outcomes

Recent studies have elucidated certain functional characteristics of a model of psychedelic-induced quantum change. Mystical-type and insight experiences as measured using validated questionnaires were found to be highly correlated with one another while only indirectly correlated with improved psychological well-being. Regression analyses showed mystical-type and insight experiences to be highly correlated with improved psychological flexibility and feelings of personal meaningfulness which in turn were highly correlated with improved psychological outlook (Davis, Barrett, & Griffiths, 2020; Garcia-Romeu et al., 2019; Garcia-Romeu et al., 2020). Therefore, these studies suggest that it is the improved psychological flexibility and personal meaningfulness associated with mystical-type and insight experiences which enables depressed and anxious individuals and people with substance use disorders to reframe how they view their medical

conditions, themselves, their lives and relationships with others (Belser et al., 2017; Davis et al., 2020; Garcia-Romeu et al., 2019, 2020; Spiegel, 2016; Watts, Day, Krzanowski, Nutt, & Carhart-Harris, 2017).

5 | PATIENT APPLICABILITY OF MYSTICAL-TYPE EXPERIENCES IN PSYCHOTHERAPY

"Siempre se tomaron para que los enfermos sanaran (They were always taken to cure the sick)" - Maria Sabina (Estrada, 1977)

As psilocybin is a putative meaning response enhancer, it is important that the medical health care profession inspires confidence that the treatment will be effective otherwise critical attitudes towards psilocybin use and mystical-type experiences among the general population may impair therapeutic efficacy (James et al., 2019). Preconceptions in any treatment will impact its efficacy as demonstrated by the fact that the placebo effect is different across cultures and personality types (Hartogsohn, 2016). The attitudes of participants in psilocybin trials are key to successful therapeutic outcomes as participants should reportedly have a desire to improve their condition, demonstrate a "clear intention and an open, enquiring attitude" and be willing to "surrender" to the experience (Carhart-Harris et al., 2018b; Russ, Carhart-Harris, Maruyama, & Elliot, 2019). In addition, trait absorption which is correlated with openness to experience has been indicated as being the second strongest predictor of mystical-type experience after drug dose (Hendricks, 2018; Studerus, Gamma, Kometer, & Vollenweider, 2012).

Consequently, inducing mystical-type experiences as a form of treatment is primarily likely to apply to specific groups of patients such as the types of patients who are currently included in psilocybin studies. These patients seek psilocybin treatment because they think it will help them and often on the basis of past experience. Additionally, many of the participants in psilocybin trials who reportedly meet the criteria for a complete mystical-type experience regularly engage in some form of spiritual practice (MacLean et al., 2011). Patients high in personality trait neuroticism may be less likely to benefit from psilocybin (Studerus et al., 2012). Patients currently taking medications prescribed to treat a range of psychiatric conditions such as tricyclic antidepressants, lithium, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors and the antipsychotic medication haloperidol are typically excluded from psilocybin trials due to impaired psychopharmacological effects of psilocybin (Johnson, Richards, & Griffiths, 2008). These patients would likely need to go through a period of abstinence from their medications prior to psilocybin-assisted psychotherapy and such a requirement demands individual assessment to determine if the potential risk to reward is acceptable.

Due to clinical literature and case reports of psychedelics (typically LSD) inducing prolonged psychoses, patients with psychotic disorders and people with a family history of psychotic disorders or bipolar disorder are currently excluded from psilocybin trials (Johnson

et al., 2008; Ross et al., 2016). Psilocybin can induce periods of anxiety, fear, panic, paranoia, sadness, depressed mood, anger, loss of sanity, delusions, dysphoria, perceptual effects and physiological symptoms (e.g., nausea and increased heart rate). Patients with disorders on the psychotic spectrum may be at increased risk of suffering paranoia whilst experiencing the effects of psilocybin (Johnson et al., 2008). Overwhelmingly difficult challenging experiences while under the influence of psychedelics can lead to dangerous behaviour such as leaving the study site and patients attempting to cause physical harm to themselves or others—with rare reports of attempted suicides. Challenging experiences have also been associated with apparent onset of psychotic symptoms although prolonged psychoses are rare and typically dissipate within 48 hr (Carbonaro et al., 2016; Johnson et al., 2008).

Groups of patients with psychotic illnesses such as schizophrenia, schizoaffective disorder, bipolar affective disorder, delusional disorder and severe depression with psychosis present significant complications to an already complex treatment model. Great care should be taken when considering psychedelic treatment for individuals in these groups to minimise the potential psychedelics have for exacerbating psychotic symptoms (Barrett, Bradstreet, Leoutsakos, Johnson, & Griffiths, 2016; Carbonaro et al., 2016). This risk may also translate to populations who are at high risk for developing psychosis. While the established wisdom is that psychedelics are contraindicated for individuals with a family history of psychosis; studies have suggested that psychedelics are not demonstrated to cause lasting anxiety, depression or psychosis and are associated with reduced negative mental health outcomes (Johnson et al., 2008; Krebs & Johansen, 2013). It could be that some patients currently excluded from psilocybin trials are not at significant risk from psilocybin use although there is no consensus on the issue of psychedelic use and psychosis and further research is warranted (Nesvag, Bramness, & Ystrom, 2015).

Investigations of challenging psychedelic experiences have shown a majority of individuals attribute increased life satisfaction to the event, and while the duration of the challenging experience has been negatively correlated with enduring increased well-being, increased life satisfaction is reportedly positively and significantly related to the difficulty of a psychedelic experience. As such it has been suggested that therapeutic interventions should focus on reducing the duration of a challenging experience rather than reducing its peak difficulty (Barrett et al., 2016; Carbonaro et al., 2016).

6 | INDUCING MYSTICAL-TYPE EXPERIENCES AS A MEDICAL TREATMENT

A considerable amount of time is spent on the preparation and monitoring of the participants for psilocybin-assisted psychotherapy in order to ensure an acceptable level of safety and efficacy of treatment:

Patients meet with monitors (also referred to as guides) on several occasions and visit the site where the experience will take place so that they are comfortable in that environment. Monitors are

typically a female–male dyadic pair although male–male and female–female dyads have also been utilised (Eisner & Cohen, 1958; Johnson et al., 2008). Participants are required to establish rapport with the monitors and the monitors should demonstrate supportive clinical sensitivity such as empathy and respect (Johnson et al., 2008). In recent studies participants are encouraged to wear a mask over their eyes, relax, listen to music and focus their attention inward while being monitored throughout the usual 7- to 8-hr session (Belsler et al., 2017; Johnson et al., 2008; Kaelen et al., 2018). Due to the afterglow effect and the potential long-term therapeutic window of psilocybin it may be possible to enhance the benefits of mystical-type experiences by preliminary and follow up activities. Meditation, mindfulness or other spiritual practices combined with exposure to stimuli that maintain awe such as nature, art and music are potential approaches to maintaining and enhancing the long-term benefits of mystical-type experiences (Brewer et al., 2011; Griffiths et al., 2018; Hendricks, 2018).

Some patients such as meditation and hallucinogen-naïve individuals are likely to require more extensive preparation than others (Studerus et al., 2012). It will be challenging to adapt psychedelic therapy to already overstretched public health care services and psychedelic therapy may initially be adopted as a form of private health care. However, the psychedelic treatment model, while costlier in terms of delivery in comparison with conventional therapies for mental illness, may ultimately be cost-saving in certain situations where individuals with severe and treatment-resistant anxiety, depression and trauma-related conditions could be saved years of conventional treatment by a course of controlled and supported psychedelic therapy sessions (Carhart-Harris et al., 2018b).

7 | FUTURE DIRECTIONS FOR PSILOCYBIN-ASSISTED PSYCHOTHERAPY

7.1 | Alternative applications of mystical-type experiences

Research has suggested that psilocybin use can lead to positive changes in personality and increased altruism such as enhanced nature-relatedness (Lyons & Carhart-Harris, 2018), pro-environmental behaviour (Forstmann & Sagioglou, 2017), decreased violent and criminal behaviour (Hendricks et al., 2018; Walsh et al., 2016), reduced suicidal ideation (Hendricks, Thorne, Clark, Coombs, & Johnson, 2015), tempered politically authoritarian views (Lyons & Carhart-Harris, 2018) and an increase in the personality domain of openness (MacLean et al., 2011; Nour, Evans, & Carhart-Harris, 2017). In light of the previously highlighted research, it could be argued that use of psilocybin in positive psychology interventions to induce changes in domains of personality could have benefits to society and the global environment (Else, 2017; James, Robertshaw, & Westwell, 2019; Shelton & Hendricks, 2016; Watts et al., 2017).

Psychedelics have been used to attempt to treat narcissistic personality disorder due to their effects on the ego (Majić et al., 2015).

Spontaneously occurring quantum change experiences have been associated with reduced egotistical attitudes and greater prosocial disposition (Miller, 2004). Using psilocybin to induce mystical-type experiences may be beneficial for individuals who excessively ruminate on the self. With the continually rising prevalence of social media and the reported crisis of meaning within society (Roberts, 2007), psilocybin's effects on the ego and connectedness could be of use to the mental healthcare profession (Carhart-Harris, 2018a).

7.2 | Clinical settings

The emergence of evidence-based psychedelic-assisted therapies will present new opportunities and challenges for existing health care systems; many aspects of psychedelic-assisted therapies will look familiar to doctors, nurses and therapists, with drug-free preparation sessions and integration sessions requiring little change from the logistics of usual practice. However, drug-assisted sessions are novel and will require specially dressed and comfortable rooms, the use of music, supportive and reassuring interaction, the presence of two therapists, overnight stays with night sitters in most cases and intensive clinical contact in between sessions. In some circumstances purpose-built facilities may be more suitable than using existing infrastructure.

8 | CONCLUDING COMMENTS

In the long-term, in order for psilocybin treatment to become established practice, rescheduling from Schedule I needs to be achieved and specific training for psychedelic therapy must be developed, standardised and licensed to maintain patient safety and efficacy of treatment (Carhart-Harris et al., 2018b; Rucker, Iliff, & Nutt, 2018). Despite the growing awareness of their potential therapeutic capabilities many regulatory authorities continue to consider these compounds to be controversial (Nutt, 2014). Such opinions threaten to hold back clinical research and deny patients the therapeutic potential of psychedelics. In addition, as psilocybin is a natural product the issues surrounding intellectual property mean that the investment route for progression through clinical trials and eventual approval by the FDA and EMA is challenging. Therefore, the funding for clinical trials will likely have to come via charitable or non-profit organisations.

Whilst this article has focused on mystical-type experiences and applicability for the treatment of specific conditions, it is worth noting that alternative treatment modalities such as microdosing may have therapeutic value and the treatment of obsessive compulsive disorder and cluster headaches are reported to be a result of pharmacological, rather than psycho-spiritual, mechanisms (Cameron, Benson, DeFelice, Fiehn, & Olson, 2019; Majić et al., 2015). Psilocybin occasioned mystical-type experiences represent an intriguing novel form of treatment; however, the cognitive and neural mechanistic processes are not well understood (Barnby & Mehta, 2018; Lieberman & Shalev, 2016). Correlation does famously not equal causality and

although current evidence suggests that inducing experiences of a highly "mystical" nature could lead to novel forms of psychiatric treatment, more work is needed to inform the psychiatry profession on how to reliably induce such experiences in clinical settings.

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CONFLICT OF INTEREST

Dr Hoskins has received MDMA-assisted therapy training and travel expenses from the Multidisciplinary Association for Psychedelic Studies (MAPS), and is a principal investigator on a MAPS sponsored phase II clinical trial of MDMA.

Dr Sessa is Managing Director of Mandala Therapy Ltd and has authored and co-authored several books on psychedelics for which he receives royalties.

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