

# Will psilocybin lose its magic in the clinical setting?

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**Abstract:** Psilocybin as a novel treatment for depression is garnering a lot of attention from both the mainstream media and the academic community. Although phase 3 trials are only just beginning, we feel that it is important for clinicians to consider what psilocybin-assisted psychotherapy might look like in the clinical setting. In this narrative review article we have considered the difficulties that may arise as psilocybin emerges from the research setting, which may hamper its progress towards becoming a licenced medication. Psilocybin has its own unique challenges: the expectation patients come to dosing with having read overwhelmingly positive media; patient suggestibility under the influence of psilocybin and requirement for specialised therapists to name a few. We have also made some recommendations for measures that should be taken in both the phase 3 trials and with clinicians to try and minimise some of the issues raised. In doing so our hope is that psilocybin will continue towards becoming a licenced medication that suitable patients are able to access with relative ease. Practicing psychiatrists need to have an awareness of the potential pitfalls of psilocybin as they will be responsible for prescribing it in the future.

**Keywords:** psychedelics, psilocybin, affective disorders, review, novel psychoactive drugs

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## Introduction

Psychedelics,<sup>1,2</sup> particularly psilocybin,<sup>3</sup> are increasingly being evaluated in clinical trials. This article examines the practical considerations required for them to progress from substances mainly used for ceremonial, recreational, and other non-clinical purposes, to routine clinical practice.

## History

Psilocybin containing mushrooms were used ceremonially in 16<sup>th</sup> century Mexico prior to Spanish prohibition. There are some indications that use extended far earlier than this; stone sculptures of mushrooms capped with faces of Gods or animal-like demons were found in El Salvador, Guatemala, and Mexico, the oldest of which dates back to before 500 B.C.<sup>4,5</sup> Despite this long history of use, psilocybin mushrooms were only popularised in Western culture in the 1950s through the article ‘Seeking the magic mushroom’, written by mycologist Gordon Wasson and published in *Life* magazine.<sup>6</sup> He was inspired

to write the article after being introduced to the ritualistic use in Mexico, where he ingested psychoactive mushrooms in a group session and emerged ‘awestruck’ from the experience.<sup>6</sup>

## Mechanism of action

### Serotonergic effects

Psilocybin belongs to the tryptamine/indolamine class of psychedelics.<sup>7</sup> Its metabolite psilocin is the main psychoactive compound found in psychedelic mushrooms of the psilocybe genus. Once consumed orally psilocybin is quickly dephosphorylated into psilocin which has been shown to bind to 5-HT<sub>1A</sub>, 5-HT<sub>1B</sub>, 5-HT<sub>1D</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>2B</sub>, 5-HT<sub>2C</sub>, 5-HT<sub>5</sub>, 5-HT<sub>6</sub>, and 5-HT<sub>7</sub> receptors.<sup>8</sup> However, it appears that the psychedelic effects of psilocin are largely mediated by just one 5-HT receptor: 5HT<sub>2A</sub>.<sup>9</sup> Blocking the 5-HT<sub>2A</sub> receptor with the antagonist ketanserin attenuates the psychedelic effects significantly.<sup>10</sup> In addition, psilocybin’s effects in humans have

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been shown to correlate with 5HT<sub>2A</sub> receptor occupancy measured by positron emission tomography in the prefrontal cortex and other regions.<sup>11</sup>

### *Connectivity*

Functional MRI of resting state connectivity shows that psilocybin induces changes in global brain connectivity, namely a synchronisation (hyperconnectivity) of sensory networks and a disintegration (hypoconnectivity) in subcortical and bilateral cortical areas comprising associative networks (e.g. the medial and lateral prefrontal cortex, the cingulum, insula, and temporoparietal junction),<sup>8</sup> adding to the evidence that psilocybin disrupts the normal associative mechanisms of the brain's connector hubs.<sup>12</sup> Evidence has also shown that there are changes to network-level functioning i.e. increased cortical entropy (where entropy is defined as a quantity that measures uncertainty, with increasing entropy being synonymous with an increase in disorder within a system), disintegration of networks, and improved communication between brain regions that are normally segregated.<sup>13</sup> These connectivity changes may underlie the demonstration that ingestion of psilocybin or psilocybin containing mushrooms triggers a profound change in consciousness, leading to changes in cognition, emotion, perception, and sense of self that can lead onto a flurry of effects including visual illusions, distorted perception of time, depersonalisation and mystical-type experiences.<sup>14</sup>

### *The Bayesian model*

One hypothesised mechanism of action of psilocybin and other classical psychedelics could be described using a predictive processing model. Broadly, this model ascribes predictive properties to the brain, where it is not viewed as a passive organ in receipt of information, but an active generative organ which encodes prior beliefs about sensory input and their causes, and generates predictions accordingly. Sensory information which conflicts with these predictions must therefore cause the brain to revise its model of the world, or to attenuate the salience given to the input signal in order to preserve its model of the world.<sup>15</sup> The direction of flow of information—whether the model is updated with bottom up sensory information, or the sensory information is attenuated via top down control—is believed to be dependent on the weighting given to the signals.<sup>16</sup> Using this model, psychopathology may be caused by an overly rigid predictive model, where more weighting is

given to top down predictions than bottom up information flow, thereby attenuating all information contradicting this model. For example, it has been argued that people with MDD frequently anticipate negative events, where negative predictions continue to shape perspective<sup>17</sup> regardless of the sensory information received. In their comprehensive paper 'REBUS and the Anarchic Brain: Towards a Unified Model of the Brain Action of Psychedelics', -where rebus is an acronym for relaxed beliefs under psychedelics- the authors argue that psychedelics may help reduce the impact of prior beliefs on immediate perception by relaxing the weighting of pathologically over-weighted priors (or schema) underpinning various expressions of mental illness, thereby increasing sensitisation to bottom up information, and reducing top down control.<sup>16</sup> Consequently, this may create a window where these beliefs can be challenged and re-examined.

### *Psychological flexibility*

Psychological flexibility is defined as the ability to stay in contact with the present moment regardless of unpleasant thoughts, feelings, and bodily sensations, while choosing one's behaviours based on the situation and personal values.<sup>18</sup> The 'Accept, Connect, Embody' model (a psilocybin therapy model based on Acceptance and Commitment Therapy) capitalises on this concept, working on the premise that psilocybin can enhance psychological flexibility and can catalyse acceptance and connection.<sup>19</sup> Acceptance is defined here as cognitive de-fusion (being able to 'see through' thoughts- observing them rather than fusing with them), present moment awareness (mindful connection to sensory experience, where patients are invited to 'embody' their experience, directing attention to it with intent rather than engage in practices to avoid it), and willingness (the will to change). Connection is defined as 'self-as-context' (where the self is described as a space within which thoughts, emotions, physical sensations, and other phenomena arise, and emphasis is placed on an observer self that can notice these phenomena while building distance from it, rather than identify with them), values (one's idea of what is important in life), and committed action (steps needed to live by values).

### *Neuroplasticity*

Psilocybin appears to offer longevity of symptom resolution after short term treatment,<sup>13,20</sup> rendering

it favourable to those who would rather avoid medications requiring daily dosing. This may be mediated by increased neuroplastic changes in the brain. Pre-clinical trials have shown that psychedelics such as lysergic acid diethylamide (LSD) and N, N-dimethyltryptamine (DMT) robustly increase neuritogenesis (the sprouting of neurites e.g. an axon or dendrite from a cell, before differentiation) and synaptogenesis in vivo and in vitro.<sup>21</sup> Moreover, a recent rodent trial investigating psilocybin showed that a single dose resulted in a 10% increase in spine size and density which occurred within 24 hours and persisted up to a month later.<sup>22</sup>

## Efficacy

### *Therapeutic effects*

Over the past few years, psilocybin therapy has shown promise in preliminary studies investigating its safety and efficacy in substance misuse, Obsessive Compulsive Disorder, Major Depressive Disorder<sup>23,24</sup> and Treatment-Resistant Depression,<sup>25</sup> and end of life anxiety associated with cancer<sup>26</sup> and AIDS.<sup>27</sup> This suggests that psilocybin may be a versatile tool that can be used to alleviate transdiagnostic psychological distress.

### *Expectancy*

A significant number of those who volunteer to take part in trials have previous experience with psychedelics, and they often come with a high expectation of a positive experience.<sup>28</sup> With extensive positive coverage in the mainstream media this bias is likely to become more evident in those who have never tried psilocybin before, perhaps falsely inflating the positive results generated by research. A recent study looking at microdosing of psychedelics showed that, overall, there was little objective therapeutic benefit. However, those who had positive expectancy scores at baseline reported improvement in psychological wellbeing and improvement in depressive symptoms. This suggests a significant placebo response,<sup>29</sup> and highlights the role of this expectancy bias in psychedelic research. At the other end of the spectrum there are those who have been sold the idea of an experience that is a life-changing miracle cure, only to be dissatisfied by the reality. One patient described being ‘underwhelmed’ and ‘disappointed’ with the short-term effects of psilocybin and its impact on his life.<sup>30</sup> As positive media coverage of research continues to be present in the mainstream media this experience is likely to be replicated many times over.

### *Diversity*

In the vast majority (70.6%) of psilocybin studies, 75% of all participants were white.<sup>31</sup> This is important because, as Michaels *et al.*<sup>32</sup> point out, we are currently testing a highly specific therapy under narrow conditions on an exclusive group. This is reiterated by Sellers *et al.*<sup>28</sup> who describe the study population as ‘Often mainly Caucasian, highly educated living in major urban centers with access to tertiary medical care.’ Consequently, clinicians should be mindful that the reality of clinical psilocybin on a broader population may not match the promising picture painted by the research. This is a particular concern when psilocybin is being researched as a treatment for depression as its prevalence is greater in those of a lower socioeconomic status.<sup>33</sup> It is essential that any future phase three trials aim to recruit a more diverse range of subjects to ensure that this imbalance is addressed.

In addition, we should consider whether this narrow pool of study participants could reflect a relatively low interest in medical psilocybin in the general population.<sup>28</sup> The Global Drug Survey (2019) found that only 18% of those who have not tried psychedelics would accept them as a therapy for depression or PTSD.<sup>34</sup>

### **Therapist input**

In clinical trials,<sup>20,23,27</sup> psilocybin is used as an adjunct to psychotherapy; the experience comprises only a part of a larger treatment programme with emphasis on preparation and integration to make the most out of the experience and maximise therapeutic outcome. In this model, therapist input is an essential ingredient. While the therapeutic model itself may change from ACT<sup>35</sup> (Acceptance and Commitment Therapy) to ACE (a model based on ACT, described above in *Psychological Flexibility*), to bespoke models devised specifically for psilocybin, their overall structure remains the same. The Therapist provides support in the process of preparation, dosing and of integrating newly-generated insights into the participants’ lives to help lead to changes in cognition and behaviour.<sup>36,37</sup> Furthermore, in this model, a skilled therapist is expected to act as a container for the participant and to support them through challenging experiences that may arise during the session, figuratively (and at times literally) holding their hand as they navigate the more difficult parts of the experience. It has been found that an extended period of overwhelming

emotional arousal may be detrimental to treatment outcomes,<sup>38</sup> as well as being very distressing for the patient. The consistency of the delivery of therapist support is fundamental to both efficacy and patient safety,<sup>37</sup> and so it is important that the high standard of training of therapists working in clinical trials is maintained if and when psilocybin eventually makes it into the clinical setting. However, there are some potential barriers to this that should be anticipated and addressed.

#### *Availability of therapist training*

Psychedelic therapists who practice in the research setting tend to have undergone training that includes a minimum amount of clinical experience with subjects under the influence of psilocybin.<sup>37</sup> If psilocybin is licenced for clinical use in the next few years it is likely that demand for trained therapists will outstrip supply due to the relatively small number of patients being dosed as part of clinical trials. Steps should be taken to ensure that only those with sufficient training should undertake psychedelic therapy alongside psilocybin. This may mean that patients who would benefit from psilocybin might be denied treatment or end up on long waiting lists. There is some evidence to suggest that a delay in treatment may lead to poorer therapeutic outcomes.<sup>39</sup> How such training of therapists will be encouraged, supported and managed is an as yet unanswered question.

Tai *et al.*<sup>37</sup> have described the development and implementation of a therapist training programme for the phase IIb trial sponsored by Compass Pathways. In order to be eligible to train, participants had to be mental health practitioners with a professional licence in good standing. The trainers were described as ‘experts by experience’, who had delivered therapy during previous clinical trials. The training programme consisted of 20 hours of online learning followed by 5 days of in-person training. Trainees must then sit in on four psilocybin sessions before they can lead one themselves. Once therapists are competent to lead, they have on-going mentoring and attend webinars so they remain up to date and can share experience. All therapists who took part had committed to a code of ethics to help ensure patient safety.

#### *Therapists’ personal experience of psychedelics*

Questions have also been raised about how a therapists’ own firsthand experience of psychedelics

may affect patient outcomes, and as yet there is no research into this.<sup>40</sup> Some are of the opinion that psychedelic therapists who have themselves had a psychedelic experience are better able to be empathetic and effective than those therapists who are psychedelic-naïve, therefore leading to improved therapeutic outcomes.<sup>36</sup> In a climate in which psychedelic drugs are illegal, personal use by professionals is a highly sensitive topic. Those who have used psychedelics may not be willing to disclose this due to fear of stigma or having their work discredited.<sup>36</sup> Both factors may put off professionals training as psychedelic therapists. Going forward it is important to establish the benefit or otherwise of therapist’s own psychedelic experience and that barriers other than training are addressed when recruiting professionals into this role.

#### *Cost of therapy*

A full course of psilocybin therapy requires a lot of therapist input which is expensive.<sup>41</sup> Sellers *et al.*<sup>28</sup> describe the follow up after the psychedelic experience as ‘critical’ as the impact on the patient can be very profound. In a publicly funded health-care system there may be a temptation to economise and cut the time spent with a therapist to the bare minimum. Alternatively, psilocybin therapy may be very difficult to access if it is heavily rationed. Carhart-Harris and Goodwin<sup>41</sup> suggest that a minimum standard be set for therapy and that this should be ‘manualised’ to ensure the standard is maintained. It is essential that therapist time is not cut to the extent that it affects patient safety.<sup>42</sup>

#### **Potential adverse effects**

Within research studies, screening, supervision and setting are carefully controlled and, on the whole, psilocybin is well tolerated by patients. The most commonly reported immediate adverse events are nausea, vomiting, transient anxiety and mild increases in heart rate and blood pressure, with headache being the most commonly reported delayed adverse event.<sup>43</sup> These may be easily managed in the clinical setting.

When used recreationally, there have been reports of acute psychological distress, dangerous behaviour and enduring psychological problems. In a survey study looking at challenging experiences as a result of recreational psilocybin use, 39% of 1993 respondents rated their ‘bad trip’ as one of

the top five most challenging experiences of their lifetime.<sup>44</sup>

Thirty percent of sufferers of treatment-resistant depression will attempt suicide at least once.<sup>45</sup> In the recently released results of the Phase IIb trial sponsored by Compass Pathways, we can see that 5.2% of patients who received Psilocybin reported a serious adverse event, including suicidal ideation and suicidal behaviour.<sup>46</sup> With regards to set and setting, it may be that those experiencing low mood may be in a mind-set that might predispose them to a more challenging experience, and therefore potentially significant distress. More so if it doesn't come to a resolution as it sometimes does with psychedelic therapy. Alternatively, suicidality can be a result of a 'disappointment reaction', where participants with high hopes of a potential treatment falling through, or not achieving desirable results, leads to disappointment and suicidal behaviour. Preliminary results from the Compass phase 2b trial suggest that all patients with suicidal behaviour had a history of suicidal thoughts, and the behaviour took place 1 month after psilocybin administration. In addition, all patients reporting these events were non responders at their last assessment prior to the event or at the time of the event.

That being said, Phase III trials must continue to carefully monitor suicidality following administration of Psilocybin to see how significant a risk this may pose, particularly in patients with pre-existing suicidal ideation. At the present time there simply is not enough data around patient safety in this area.

#### *Patient vulnerability*

Carhart-Harris and Goodwin<sup>41</sup> talk about the 'special vulnerability' of those under the influence of psilocybin. Sjöberg and Hollister<sup>47</sup> found that those having a psychedelic experience might be more suggestible, meaning that they are more vulnerable than in other types of therapy. Many psychiatric patients have a history of trauma, and so lone working by therapists during dosing sessions should be avoided, to protect both patients and therapists. Sellers *et al.*<sup>28</sup> have also suggested that ideally the two professionals accompanying the patient should never both be of a different gender to the patient. Chaperones are currently used in the research setting. However, in a busy clinical setting that may be short-staffed, there may be a temptation to go without. In order to

protect both patients and therapists, chaperones should be considered mandatory.

#### *Patients with psychiatric co-morbidities*

Existing psilocybin studies have been highly selective and excluded patients with psychiatric co-morbidities, and so the risks associated with psilocybin in this group of patients has not been very well explored. This means that results may not be generalizable and there may be significant risk associated with using psilocybin in naturalistic clinical practice where comorbidity is the norm rather than the exception.<sup>28</sup>

#### *Potential for abuse*

With psilocybin being known first and foremost as a drug of abuse, would use of psilocybin in the clinical setting lead patients to seeking it in the community? Furthermore, if psilocybin became a licenced medication would it encourage people to seek it themselves to self-medicate outside of controlled clinical settings and without the guidance of therapists, where they are more likely to experience adverse effects? We know that users quickly become tolerant following repeated doses of psilocybin. However, physical dependence does not develop.<sup>10</sup> Psilocybin has much less potential for abuse than other psychoactive drugs,<sup>43</sup> but diversion and abuse of prescription medication is a recognised problem and there would likely be concern around greater access to psilocybin by the public.<sup>28</sup> There are documented incidences of those given psilocybin as part of a trial successfully obtaining it afterwards in the community: In a trial carried out by Carhart-Harris *et al.*<sup>13</sup> 5 of the 20 patients dosed did so. This may be because of patients seeking help for their symptoms after the positive effects of dosing had worn off, as has been seen in patients followed up longer term.<sup>13</sup> It is important to differentiate between an individual taking psilocybin to regain therapeutic benefit from drug dependency. It is also important to highlight the risks of taking psilocybin outside a controlled setting and provide harm reduction information where appropriate.

#### **Ethical considerations in psychedelic therapy**

Langlitz *et al.*<sup>48</sup> beautifully highlight a somewhat idiosyncratic challenge to psychedelic therapy that may not be as prominent in other psychopharmacological interventions; namely the subject of moral psychopharmacology.

Potential Pitfall	Proposed solution
Current studies have had non-diverse subject populations, not reflective of patients who may benefit from Psilocybin in the clinical setting.	Phase III trials to recruit a more diverse and representative group of subjects.
Stigma; psilocybin may be considered a drug of abuse amongst both patients and professionals.	Inclusion of psychedelics, including proposed mechanisms of action, potential clinical uses, and balanced information around addiction potential into training curricula for mental health professionals.
Risk to patients due to vulnerability under the influence of Psilocybin.	Ensure chaperone provision by making it mandatory.
Patients self-medicating in the community with illicit Psilocybin, or psilocybin-containing mushrooms.	Where appropriate, provide harm reduction advice, highlight risks of outside of a controlled setting.
Shortage of trained therapists, leading to greater difficulty accessing Psilocybin therapy, or those with insufficient training delivering therapy.	Minimum training standards to be set, and training to be manualised. Mental health trusts to support Psilocybin therapist training where able.

**Figure 1.** Table summarising proposed solutions to issues that might arise if Psilocybin becomes a licenced medication.

Psilocybin, among other psychedelics, has been associated with changes in character and social cognition.<sup>49</sup> For example, three months after psilocybin treatment, patients showed an increase in extraversion and openness scores,<sup>50</sup> with some patients reporting an ability to re-connect with close relationships, including people who had wronged them.<sup>51</sup> There was also a significant increase in nature relatedness (subjective connection to nature), sustained up to a year after administration.<sup>52</sup> Participants taking part in a smoking cessation trial described engaging in prosocial and altruistic behaviours after their psilocybin sessions,<sup>53</sup> and psilocybin was shown to reduce altruistic punishment as rejections were reduced in the ultimatum game<sup>54</sup> and ‘social pain signals’ in the Cyberball game, suggesting that it attenuates responses to negative stimuli correlating to changes in self-processing rather than a lack of awareness of their exclusion.<sup>55</sup>

Although other substances can also alter social cognition and behaviour,<sup>56–58</sup> the importance of context and the ‘noetic quality’ ascribed to psychedelic experiences renders their users particularly vulnerable to these changes, with these characteristics acting as a ‘double edged sword’<sup>59</sup> in terms of benefits and harms. Psychedelics ingested in different settings have been utilised to induce different, and sometimes opposing changes, from liberation from society to aides of initiation and integration into society, and from inducers of unity and connection to tools used in

rituals to prepare for conflict.<sup>48</sup> Context and culture have a profound influence on the malleable state of mind that occurs with psilocybin, which is only intensified by the sense of revelation and intrinsic ‘knowing’ reported by users, reducing the need for external validation of these revelations. Timmermann *et al.*<sup>59</sup> highlights the influence of these factors as seen in the rising of false memories in clinical settings, the influence of spiritual beliefs at retreat centres on their attendees, and meta-physical explanations given to experiences while under the influence of DMT. The potential for iatrogenic harm that could arise as a result of this is clear, especially as psychedelic use becomes more mainstream and extra-pharmacological factors become more diverse.

It is therefore important that special care should be given to the consent process and to psychoeducation around the use of psychedelic substances. It will certainly be a challenge to standardise this and fine tune the process to maximise benefits and reduce harms as psilocybin moves into the clinical setting.

### Conclusion

It may indeed be the case that psilocybin facilitates the relaxation of long-held beliefs, which under a therapeutic framework can lead to revision of such beliefs and translate to enduring therapeutic benefit, outlasting its acute effects.<sup>60</sup> This would make it a valuable and versatile tool

in the treatment of several mental disorders when utilised with the appropriate therapeutic support.

However, there are several measures that need to be taken to ensure future patient safety, summarised in Figure 1. Ideally future phase 3 trials should recruit study populations that better represent the full population for whom this treatment is intended. This will make the results more generalizable and will minimise the risk to those patients who fall outside the very narrow existing study population. There is also the need for more information about long-term effects before psilocybin can be used in psychiatric practice.<sup>61</sup> Moreover, it is important to be aware of both the expectancy bias that seem to accompany psychedelics among proponents of their use, and the negative connotations they have among those who are not so inclined. There is a need for a balanced portrayal of both positive effects and potential pitfalls, where psilocybin and other psychedelic substances can be viewed through a critical, evidence-based lens without the weight of negative cultural stigmas or unrealistic expectations. One aspect that may support this is the incorporation of modules on psychedelic substances and their effects within training curricula for mental health professionals. Finally, it is paramount that strict standards around therapist training, chaperone provision, and course of therapy are maintained in clinical settings to maximise benefits and minimise risks. This list of considerations is by no means exhaustive and is sure to grow as more research is conducted. A stance of openness, curiosity, and willingness to change is essential as we slowly understand how to work with this powerful substance.

#### Author contributions

**Caroline Hayes:** Writing – original draft; Writing – review & editing.

**Mourad Wahba:** Writing – original draft; Writing – review & editing.

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