

# The Utility of Psilocybin in Managing Anxiety and Depression in Cancer Patients



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Cancer patients experience a higher rate of depression and anxiety which can result in negative healthcare outcomes. With the limited treatment options available, there has been an interest in using psychedelics such as psilocybin to manage such complications. Recently, two studies demonstrated the potential of psilocybin in not only reducing distress, but also increasing positive emotions in cancer patients. It is thus interesting to further examine this issue. This review paper will first provide a brief introduction to psilocybin and proceed to summarize key findings from these two studies. The rest of the paper will be devoted to critically evaluating the findings and discussing potential future directions for the applications of psilocybin in treating anxiety and depression in cancer patients.

## INTRODUCTION

Depression and anxiety have been found to occur commonly in cancer patients, with 30 to 40% of cancer patients estimated to be suffering from such psychiatric illness in hospital settings (Mitchell et al., 2011). However, the exact prevalence of anxiety and depression in cancer patients are fundamentally imprecise, ranging from 15 to 50% due to diagnostic difficulty and complexity (Rosenstein, 2011). First, it is extremely challenging to distinguish somatic symptoms that masquerade as anxiety and depression due to the inevitable transience of sadness and the fear of death which accompany the knowledge of a cancer diagnosis (Dauchy et al., 2013). Secondly, misdiagnosis may also be precipitated by physiological and pharmacological mimics of anxiety and depression associated with long term medications (Rosenstein, 2011). For example, dopamine-blocking antiemetics like metoclopramide and prochlorperazine can result in akathisia, which may present superimposed syndromes related to anxiety or agitated depression (Rosenstein, 2011).

Despite the statistical uncertainty, the myriad of poor outcomes associated with depression and anxiety in cancer patients, such as increased medication non-adherence, increased desire for hastened death, increased suicide rates, decreased social function

and decreased rates of survival (Jaiswal et al., 2014) highlight the crucial need for more effective palliative care and treatment options. This need is also emphasized by the limitations of current interventions used to treat anxiety and depression in cancer patients, such as antidepressants and benzodiazepine. These treatments have mixed efficacy and are generally recommended for short-term use due to their side effects and withdrawal symptoms (Ostuzzi et al., 2015). Coupled with increasing evidence highlighting the importance of mental and spiritual well-being in mitigating distress and improving quality of life, psilocybin has recently emerged as an attractive therapeutic candidate. Research on psilocybin will not only fuel more investigations into the therapeutic potential of other psychedelics, they will also spearhead more comprehensive treatment pathways for cancer patients.

## WHAT IS PSILOCYBIN?

First isolated from *Psilocybe mexicana* by the Swiss chemist Albert Hofmann in 1958, psilocybin (O-phosphoryl-4-hydroxy-N,N-dimethyltryptamine) and its active dephosphorylated metabolite psilocin (4-hydroxy-N,N-DMT) are primary psychoactive compounds in several species of hallucinogenic mushrooms found in different parts of the globe (Dos et al., 2016). Similar to other hallucinogens, psilocybin is as an agent that changes one's cognition and emotion without resulting in addiction, delirium, or memory deterioration (Halberstadt, 2015). However, as this definition includes the effects of other drugs such as cannabinoids and N-methyl-D-aspartate (NMDA) antagonist in addition to the above-mentioned classification, a hallucinogen (including psilocybin) must also structurally bind to the 5HT<sub>2A</sub> receptor and produce full substitution in animals trained to discriminate the prototypical hallucinogen 2,5-dimethoxy-4-methylamphetamine (Glennon, 1999). More specifically, under the umbrella classification of hallucinogen, psilocybin, with other compounds such as like lysergic acid diethylamide (LSD), structurally belong to the group of indolamine hallucinogens.

Regarding its pharmacokinetics, psilocybin has been shown to

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persist in blood plasma for as long as 20 to 40 minutes after oral administration (Passie et al., 2002). While the half-life of psilocybin in blood plasma is 120 minutes after orally ingesting psilocybin, its half-life after intravenous administration is approximately 74 minutes (Tylš et al., 2014). In terms of its receptor mechanism, psilocybin predominantly produces agonist activity on serotonin 5HT<sub>2A/C</sub> and 5HT<sub>1A</sub> receptors, with varying affinities for different sub-receptors (Table 1). The activity of psilocybin has also been demonstrated with selective agonists and antagonists 5HT<sub>2A/C</sub> and 5HT<sub>1A</sub> discrimination studies on rodents, (Winter et al., 2007), studies on head twitch behavior, and wet dog shakes (typical symptoms resulting from the stimulation of 5HT<sub>2A/C</sub> receptor) (Fantegrossi et al., 2008; Halberstadt et al., 2011) The restoration effects on locomotor inhibition via antagonists 5-HT<sub>1A</sub> and 5-HT<sub>2B/C</sub> receptors also elucidate the mediation of psilocybin on this specific serotonergic mechanism.(Halberstadt et al., 2011).

In humans, psilocybin marginally stimulates sympathetic processes, such as mild increase in blood pressure and increased heart rate, at doses higher than 3 to 5mg p.o. and the full effect at 8 to 25mg p.o. – an effect similarly seen in animals (Griffiths et al., 2006). Psilocybin’s psychotropic and neuropsychological consequences also follow the conventional dose-response functions of most drugs. Psilocybin causes drowsiness and emphasizes the pre-existing mood at low doses (Hasler et al., 2004), a manageable altered consciousness state at medium doses (Passie et al., 2002), and a strong psychedelic experience at higher doses. Studies in humans have demonstrated that most of the hallucinogenic effects of psilocybin are primarily mediated by the 5HT<sub>2A</sub> receptor (Halberstadt & Geyer, 2011). For example, by showing that effects of psilocybin are blocked by the 5-HT<sub>2</sub> antagonist ketanserin (Carter et al., 2005), psilocybin is demonstrated to predominantly act via the 5HT<sub>2A</sub> receptor. A recent PET study with the 5HT<sub>2A</sub> ligand [<sup>18</sup>F]altanserin also showed that the intensity of psilocybin-induced subjective effects is directly correlated with 5HT<sub>2A</sub> occupation in the anterior cingulate and medial prefrontal cortices (Quednow et al., 2010). Despite all its effects, it is interesting to note that psilocybin has a low abuse potential. As chronic hallucinogenic exposure has been demonstrated to decrease the amount of 5HT<sub>2A</sub> receptors, there is a rapid onset of short-lasting tolerance, leading to a low risk of addiction (Roth et al., 1998). Behavioral studies in non-human primates have also shown that psilocybin does not produce reward-seeking behavior (Fantegrossi et al., 2004a). In humans, psilocybin is shown to have no direct effects on the mesolimbic dopaminergic pathway (Nichols, 2004), which is often known as the reward system. This is supported by findings indicating that humans do not experience craving or withdrawal symptoms upon taking psilocybin (Johnson et al., 2008).

**SUMMARY OF RECENT FINDINGS**

Ross et al. (2016) and Griffiths et al. (2016) recently demonstrated the effects of psilocybin on treating depression and anxiety among patients suffering from advanced-stage cancer. Types of cancer ranged from breast, gastrointestinal, genitourinary, upper aerodi-

Binding Site	K <sub>i</sub> (nM) <sup>a</sup>
SERT	3801
5-HT <sub>1A</sub>	567.4
5-HT <sub>1B</sub>	219.6
5-HT <sub>1D</sub>	36.4
5-HT <sub>2A</sub>	107.2
5-HT <sub>2B</sub>	4.6
5-HT <sub>2C</sub>	97.3
5-HT <sub>3</sub>	>10,000
5-HT <sub>5</sub>	83.7
5-HT <sub>6</sub>	57.0
5-HT <sub>7</sub>	3.5
α <sub>1A</sub>	>10,000
α <sub>1B</sub>	>10,000
α <sub>2A</sub>	1,379
α <sub>2B</sub>	1,894
α <sub>2C</sub>	>10,000
β <sub>1</sub>	>10,000
D <sub>1</sub>	>10,000
D <sub>2</sub>	>10,000
D <sub>3</sub>	2,645
D <sub>4</sub>	>10,000
D <sub>5</sub>	>10,000
H <sub>1</sub>	304.6

**Table 1. Binding of psilocin to 5-HT and other monoamine receptors (Halberstadt and Geyer, 2011).**

gestive, hematologic malignancies and others. Findings from both studies are promising since they suggest the possibility of using a drug with low abuse potential as a treatment for mitigating the distress of terminally ill patients.

For the study conducted by Ross et al. (2016), 29 cancer patients were sampled with a two-session, double-blind crossover (seven weeks after dose 1) methodology with either psilocybin administered first and niacin second, or niacin first and psilocybin second. Results showed that 83% in the psilocybin-first group (vs. 14% in the niacin-first group) met the criteria for antidepressant response seven weeks after dose 1, suggesting that psilocybin had an immediate and ongoing anxiolytic and antidepressant effect. The antidepressant or anxiolytic response rates were still as high as 60 to 80% at six and a half months. On

the other hand, Griffiths et al. (2016) conducted a study with 51 cancer patients with a similar two-session, double-blind crossover (five weeks after dose 1) methodology. However, instead of a non-psilocybin versus psilocybin design, the study employed a high-dose psilocybin versus a very low-dose (placebo-like) psilocybin approach. Specifically, two random groups were given either high-dose psilocybin first then very low-dose psilocybin second, or very low-dose psilocybin first and high-dose psilocybin second. The high-dose psilocybin was shown to produce a significantly large decrease in clinician and self-rated measures of depressed mood and anxiety. Five weeks post session one, 92% of patients in the high-dose psilocybin-first group (vs. 32% in the low-dose-first group) were found to show a significant positive response and 60% of patients in the high-dose psilocybin-first group (vs. 16% in the low-dose-first group) experienced symptom remission. Similar to Ross et al. (2016), the effects of psilocybin were long-lasting. After six months of receiving high-dose psilocybin, 80% of participants continued to demonstrate clinically significant decreases in anxiety and depression. Both studies also found that taking psilocybin was highly correlated with subjects’ mystical and spiritual experiences, which were respectively assessed using self-reported outcomes such as positive mood; transcendence of time and space; and sense of inner peace, purpose, and faith-derived strength (Griffiths et al., 2016; Ross et al., 2016).

## CRITICAL EVALUATIONS

To comprehensively understand the implications of such findings, this paper will now highlight several challenges and limitations inherent in the design methodologies of the aforementioned studies. Fundamentally, it is critical to consider participant profiles for both studies. Most subjects have had histories of taking one form of hallucinogen or another. Due to their baby boomer demographic, most of the participants would have had access to psilocybin as it was a popular recreational drug during the 1960s before the banning of hallucinogens as a Class A substance. (Nichols, 2004). In addition, most subjects also had previously taken anti-depressants and anxiolytic medications. Given psilocybin's long-lasting effects and the importance of drug-taking history as a confounding factor in influencing the effects of any drug, it is likely that the subjects' psilocybin-induced experiences are not entirely novel (Bryant et al., 2015).

Besides prior experience of drug exposure, the subjects, being willing participants of the studies biased the sample population. Specifically, their willingness to participate may be associated with higher expectations and increased open-mindedness – attributes that are inherently profound in influencing the bias for positive effects of psilocybin. Indeed, the subjective effects of taking any hallucinogen are known to be highly dependent on one's expectations, thereby accounting for the great variability of effects across individuals (Nichols, 2004). Additionally, many participants were from a more affluent socio-economic background compared to that of the general population. With these factors taken together, it is clear that the sample population for these studies have limited generalizability. To adequately demonstrate the therapeutic effects of psilocybin, a better sampling methodology is imperative. For example, research participants should be screened for no prior psilocybin exposure and be sampled from a normally distributed socio-economic background.

In addition to the subjects' profile, the effectiveness of blinding both subjects and research personnel is also critical, especially given the intense effects of psilocybin. By employing a low-dose psilocybin instead of another drug type (niacin) as the control drug, the study conducted by Griffiths et al. (2016) strategically increased the extent of blinding in its methodology. Nevertheless, to obtain a direct read-out regarding the integrity of the blinding procedure, both studies could have added a component asking the subjects to guess their respective treatment assignments. This can ensure more objective findings.

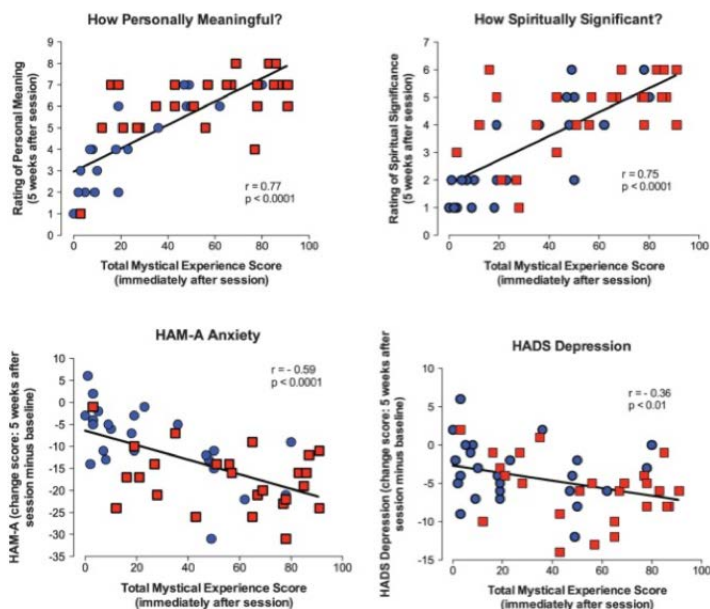
Although there is little doubt that that the explicit patient experience after taking psilocybin is the mediating mechanism, besides psilocybin exposure, participants in both studies were given psychotherapy with highly supportive and existential elements. For example, not only were participants placed in settings designed for inducing tranquility, they were encouraged to remember and reconstruct their daily narratives, essentially engaging in a meaning-making process. Given that both studies found participants to experience a long-term change in their outlook of life in relation to their terminal illness, understanding the role of psychotherapy

and its interaction with psilocybin are of paramount importance. Indeed, the mystical-type transcendence experience that many rated among their most personally meaningful experiences often happens in cases where high-dose psychedelics were administered in a supportive setting (Griffiths et al., 2008). Here, the aim of highlighting this underlying psychological scaffold behind the intervention is not discounting the effects of psilocybin or presenting a false dichotomy between the drug and psychotherapy, but rather providing a consideration of how one interacts with the other.

Using the neuroplasticity hypothesis, this approach can be interpreted as a form of pharmacology-assisted psychotherapy, in which psilocybin induces psychological experiences that facilitate the psychotherapeutic process to produce neuroplasticity and behavioural changes (Goodwin, 2016). Indeed, some scientists have postulated that through enhancement of  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor functions, psilocybin changes glutamatergic neurotransmission in prefrontal- limbic circuitries which results in neuroplasticity (Vollenweider & Kometer, 2010). In this regard, it is interesting to draw insights from studies done on temporal delays and short-term memory training in the field of neuroeconomics. Specifically, given the participants' prior exposure to hallucinogens, taking psilocybin can be thought of as a temporal manipulation of memory in which the participants have a past-oriented bias for re-experiencing positive moments associated with the hallucinogenic experiences of their younger selves (Stein et al., 2016). Relatedly, psilocybin exposure can also open a window of time delay where the effects of psychotherapy-mediated learning are significantly enhanced (Goodwin, 2016). The short and long-lasting attenuation of anxiety and depression in cancer patients can thus be attributed to an intense learning session built upon psilocybin-induced experiences and these experiences' derivative integration into the psychotherapist processes.

Fundamentally, many outcomes for both studies are subjective since they are based on self-reported measures following psilocybin exposure (Figure 1). For instance, the Mystical Experience Questionnaire (MEQ30) employed for the study is based on self-reported outcomes like one's sense of unity, being "outside of time" and ecstasy (Barrett et al., 2015). While this limitation is shared among studies examining introspective effects of drugs, there has been increasing efforts to formulate such experiences in terms of more objective biomarkers. For example, findings from neuroimaging studies of psilocybin have illuminated possible anti-depressant mechanism of action at the level of brain structure activity and network circuitry. Specifically, functional magnetic resonance imaging (fMRI) studies in healthy participants upon psilocybin intake has shown decreased activity in the medial prefrontal cortex (PFC). This is a significant finding as 1) depressive symptoms have been correlated with increased activity in the medial PFC (Farb et al., 2011) and 2) normalization of such an activity has been associated with anti-depressant treatment (Holtzheimer and Mayberg, 2011). Similarly, while depression has been linked to increased connectivity within the default mode network (DMN)





**Figure 1.** Graphs illustrating the relationship between the Mystical Experience Questionnaire (MEQ30) total score assessed at the end of the first session and four outcome measures assessed 5 weeks after the first session. The four outcomes (clockwise from top left) are self-reported measures of the person’s sense of meaning, spiritual significance, clinician-rated measures of anxiety HAM-A and self-rated measures of depression HADS. Data points represent individual subjects; blue circles and red squares represent the respective group that received the low dose and high dose on the first session (Griffiths et al., 2016).

(Berman et al., 2011) – a brain system that is most active when individuals are left to think to themselves in an undisturbed manner (Buckner et al., 2008), psilocybin has shown decreased DMN connectivity (Carhart-Harris et al., 2012, 2014). Although these self-reported findings suggest potential neuro-indicators of psilocybin effects, they are at best correlational.

Insights from studies investigating receptor-mediated mechanisms of psilocybin may be useful in providing a more comprehensive picture. As 5HT<sub>2A</sub> receptors are established to be part of a larger and more complicated family of proteins, agonists of 5HT<sub>2A</sub> receptors may alter the receptor’s conformation and directly mediate antidepressant and anxiolytic actions (McCorry and Roth, 2015). As psilocybin is one example of a 5HT<sub>2A</sub> agonist, the effects of its intake may be taken as an automatic indicator of agonist actions (Goodwin, 2016). Admittedly, more mechanistic studies are needed to prove this postulation. Specifically, not only do we have to demonstrate the attenuation of hallucinatory effects using a 5HT<sub>2A</sub> selective antagonist, we must also test if more selective 5HT<sub>2A</sub> agonists produce similar emergent effects. More targeted neuroimaging and behavioral studies investigating the effects of other 5HT<sub>2A</sub> agonists and antagonists are likewise necessary to increase understanding of psilocybin’s receptor-mediated mechanisms.

**CONCLUSION**

Although the findings from both studies are promisingly demonstrate both acute and enduring (six-and-a-half months) antidepressant and anxiolytic effects of psilocybin in cancer patients, there remain several key challenges in the sampling procedure, quantification of subjective effects and effects of psychotherapy that must be addressed to find more conclusive evidence. Yet, with the above information, one important question still lingers: even if psilocybin were proven to work, should we accept it? Although this paper did not explicitly discuss the ethical considerations associated with using hallucinogens to induce neuroplasticity at the end of life, albeit reducing depression and anxiety, such bioethical dimensions warrant further contemplation. Not only are the essence of personhood and self-perception of meaning important clinical mediators, they are ultimately intangible but critical crucibles that cannot be divorced from the goal of inventing better end-of-life therapeutic interventions.

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