The Promise of Psilocybin
Psilocybin as a Treatment Modality for Depression

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1. Introduction

1.1 Psilocybin

Throughout history, humankind has sought to make sense of life in a variety of creative ways. It should come as no surprise then that psychedelics, with their capability to induce hallucinations, ecstasy, and other mind-expanding states of consciousness, are on this list. (Vollenweider and Kometer, 2010). Used in a variety of rituals, psychedelics have piqued human curiosity and become embedded in the cultural lifestyles of people across the globe, even today.

Specifically, naturally occurring indoleamines have a long history of use in the Americas. Psychoactive mushrooms, containing psilocybin and its dephosphorylated metabolite psilocin, were used by the Aztecs in the 15th century and have since been an important part of certain Mexican healing ceremonies. By the 1960s this knowledge arrived in the United States and research on psilocybin as a therapeutic had begun and indicated promising effects as an aid in shortening psychotherapy (Vollenweider and Kometer et al., 2010; Busch and Johnson, 1950). However, they were banned soon after, declared as drugs with no therapeutic use and a high potential for abuse.

Only recently, with the establishment of conditions for safe administration, has there been a willingness in the scientific community to study these drugs, leading to a well-documented rise in research in the last 10-15 years (Muttoni et al., 2019; Tullis, 2021). Today, psilocybin-assisted psychotherapy shows great promise as a novel therapeutic for depression and other mental health disorders (Tullis, 2021).

1.2 Depression

Mental health disorders are the leading cause of disability affecting approximately 350 million people worldwide (Murray, 2013; de Gregorio et al., 2021). More specifically, almost 40% of the Mental Health global disability burden is accounted for by depressive disorders alone (Whiteford, et al., 2013). Globally, the lifetime prevalence of depression is conservatively estimated to be around 10.8% (Lim et al., 2018). Impacted by the COVID-19 pandemic, this number is estimated to have increased to around 25% (Bueno-notivol et al., 2021).

Depression is not only prevalent but is a serious and unremitting disease with grave consequences, especially if left untreated. In its most severe form, depression can lead to suicidal ideation which disproportionately affects young adults and is now the second leading cause of death for adults aged 18-35 in the United States (CDC, 2020). Depressive episodes also lead to an increased risk of future episodes; approximately 80% of patients requiring psychiatric attention for a depressive episode will experience another one within the year (Kumagai et al., 2019; Kessler et al., 2003). Moreover, around 40% of patients who discontinue treatment relapse into a state of depression within the year (Kato et el., 2020).

Even though many treatments exist for depression today, the efficacy of these therapeutics remains relatively low. Selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), and atypical antidepressants, medicines collectively known as second-generation antidepressants (SGAs), are included in the first line of depression therapy (APA, 2019). Yet only 54% of adults show improvement after taking antidepressant medication (Levkovitz et al., 2011). Comparatively, 35-40% of adults showed improvement with just placebo treatment (Furukawa et al., 2016). Thus, compared to placebo, the efficacy of these medicines is still quite low. Moreover, we remain unable to predict which interventions will be most effective for individual patients (Holmes et al., 2018; Cuijpers et al., 2020). As a result, utilizing different treatments is necessary in order

to find one that is effective for each patient. Unfortunately, patients who do not respond to multiple treatments have a poor prognosis (Cleare et al., 2015). Currently, interventions to treat patients with treatment-resistant depression are not very effective, have a great deal of stigma around them, and have significant side effects (Rucker et al., 2016).

The potential seen in psychedelics, historically and in modern research, and the need for continued exploration of novel therapeutics for depression indicate that psilocybin may hold the \key to improving depression and other abnormal psychologies resulting from repetitive, entrenched, and often negative patterns of thought (Byock, 2018; Rucker et al., 2016; LaBua, 2021). In this article, I review current treatments used for depression, the need for new therapeutic modalities, and focus on the promise of psilocybin as a new therapeutic.

2. Treatments for Depression

2.2 Current

The APA recommends either psychotherapy, pharmacotherapy (using an SGA), or a combination of the two as first-line treatment for adult depression (APA, 2019).

2.2.1 Psychotherapies

Psychotherapies are interventions that approach depression from a psychological perspective and aim to reduce or eliminate depressive symptoms. They are often delivered by a trained professional or taught to be self-administered (Weisz et al., 2006). Psychotherapies differ in length, goals, and structure. It is possible that psychotherapies, being the multidimensional interventions they are, might have complicated mechanisms of action that cannot be captured in simple causal relationships (Lemmens et al., 2016). Different therapies used today include behavioral, cognitive, cognitive-behavioral, mindfulness-based cognitive, psychodynamic, supportive, and interpersonal therapy.

Although there have been mixed results in the literature, recent reviews indicate that there are no significant differences in the efficacy of various psychotherapies (Cuijpers et al., 2008). Thus, the APA recommends a combination of one of these psychotherapies and SGAs as the initial treatment for adults suffering from depression (APA, 2019).

Finally, even though psychotherapies are the gold standard of care for patients with depression, they have significant drawbacks. For example, reviews show that evidence-based psychotherapies will be beneficial for 75% of patients (APA, 2020). Although this is a large number, its impact is reduced by the fact that patients only need to show some benefit, an outcome that is difficult to standardize and measure, to qualify in this category. Psychotherapies also take a great deal of time to be effective with only 50% of patients showing reliable improvement after 8-10 weeks of therapy (Lambert and Vermeersch, 2002).

2.2.2 Pharmacotherapies

Meta-analyses also show that SGAs and CBT are both similarly effective in treating the symptoms of patients with mild to severe depression (Gartlehner et al., 2015; Khan et al., 2012). Furthermore, all SGAs are efficacious compared to placebo (Cipriani et al., 2018). Yet only around 60% of patients treated with an antidepressant will show a positive response (Arroll et al., 2005). Studies also suggest that a combination of psycho and pharmacotherapy may be more effective than anyone alone (Khan et al., 2012).

Finally, even though they are effective drugs, SGAs have important drawbacks. SGAs can take weeks to be effective and only around 50% of patients respond to the first antidepressant they try (Frodl, 2017). Furthermore, fear of adverse side effects keeps 20% of patients from even filling their prescriptions for antidepressants (Amick et al., 2015).

2.3 The Need for a New Treatment Modality

Psycho and pharmacotherapies have significant drawbacks that need to be considered and improved. For both psychotherapy and pharmacotherapy, delay of effectiveness is one of the largest disadvantages. The delay between initial treatment and maximum reduction of depressive symptoms can take 8-12 weeks for SGAs and 15-20 sessions for psychotherapies (Cipriani et al., 2018). Especially for antidepressants, this lag in effectiveness is associated with an increased risk of suicidal behavior (Jick et al., 2004), psychosocial losses

from continuing depressive symptoms, ineffective treatment, and consequent poor adherence to medication (Machado-Vieira et al., 2010). The risk of adverse effects in pharmacotherapies for depression is also significant with 60% of patients experiencing at least one adverse event during treatment with an SGA (Amick et al., 2015). These adverse side effects frequently lead to the discontinuation of treatment by patients as well (Amick et al., 2015). Research also shows that long-term dosage of SGAs may be ineffective and harmful to patients (Hengartner, 2020).

For about 70% of patients, their initial treatment will not work (whether medicine or therapy alone or together) necessitating second-step treatments (Gartlehner et al., 2015). The delay of efficacy, risk of adverse side effects, and lack of long-term effectiveness in current therapeutics emphasize the need for a novel depression treatment.

3. Psilocybin and Psychotherapy

Results from animal research with psilocybin contradict data from human studies. Most importantly, functional activity in certain resting state networks increases after psilocybin administration in humans. In mice, however, these effects were minor and may be due to the species specific different pharmacological mechanism of psilocybin or differing drug administration protocols (Grandjean et al., 2021). As a result, this review will focus on psilocybin's effects on humans.

The default mode network (DMN), a brain network important in high order cognitive functions and active in humans during periods of wakeful rest, is unsuccessfully downregulated in patients with depression (Sheline et al., 2009). Psilocybin treatment shows an initial decrease in functional connectivity between parts of the DMN followed by an increase in DMN connectivity long term, all while correlating with improved depressive symptoms. This indicates that psilocybin may work by 'resetting' the DMN, where its initial disintegration enables later re-integration (Carhart-Harris et al., 2017).

Furthermore, Psilocybin's effects are not limited to the DMN. Whole-brain analyses show increases in right-amygdalar activity, consequently increased responses to happy and fearful faces, and correlated with improvements in depressive symptoms (Roseman et al., 2018). Increased amygdalar activity irrespective of emotional valence suggests that psilocybin encourages patients to work through emotions rather than avoid them. Increased Openness and Extraversion scores on personality assessments (specifically the Revised NEO Personality Inventory, NEO-PI-R) post-psilocybin treatment support this (Erritzoe et al., 2018). These findings suggest that psilocybin may indeed work by modulating top-down emotional control.

Patients treated with psilocybin also showed immediate and lasting improvements in depressive symptoms (Roseman et al., 2018; Carhart-Harris et al., 2016; Griffiths et al., 2016; Ross et al., 2016). In two double-blind studies adopting a crossover model, patients exhibited significant anxiolytic and antidepressant effects that lasted for up to six months resulting from just one full dose of psilocybin (Griffiths et al., 2016; Ross et al., 2016). It is important to note that one study used a low dose of psilocybin (1 mg/70 kg) as a placebo and the other used niacin. Using low dose psilocybin as a placebo mitigates expectancy effects as patients expect to receive psilocybin in each session. This comes at the cost of being unable to ensure that patients will not have a psychoactive experience and create an effective control group. Meanwhile, niacin ensures that no psychoactive effects are experienced but participants can identify it as the placebo. These studies were also done in patients suffering from life-threatening cancer, a population that does not reflect the makeup of patients suffering from treatment-resistant depression. Even with these limitations, these initial studies indicate that psilocybin's rapid and long-lasting effects are worth further research (McCorvey et al., 2016).

Finally, few adverse events were reported with psilocybin treatment. Only 12% of study participants described a negative change in psychosocial or mental function compared to 60% of patients experiencing at least one adverse event while taking SGAs (Studerus et al. 2011). This effect may be confounded by the fact that many study participants were experienced with psychedelics; however, with the development of rigorous guidelines for human psychedelic research, significant adverse events are rare (Barrett et al., 2020; Johnson et al., 2008).

4. Future Directions

Even with this evidence, we are far from declaring psilocybin a panacea. Questions remain regarding how exactly it works, how it compares directly with modern antidepressants, and even what effects its continuous use might have on humans, to name a few. These are all important areas for future research.

The solution to our current mental health crisis then, may not be the immediate adoption and extensive use of psilocybin, but an openness to studying it further. Although psilocybin has been seen as an illicit substance by the modern world thus far, we must set this stigma aside so that we can learn more about this promising drug. Furthermore, the onus is on us, as members of the public, to help shift the global perspective on psilocybin. Whether it be advocating for changes in drug scheduling and helping speed up research on psilocybin or staying well informed about studies done with psychedelics and rectifying the modern stigma surrounding their use, we hold the power to help research that will improve the mental health of millions happen.

The gravity of the situation is such that we cannot afford to leave any stone unturned. In our ever-competitive and increasingly complex world, mental health issues are not going away. They are simply doing more harm to people earlier on in their lives. But, by remaining unbiased and letting the science move forward, we may be able to change that. Our openness today will improve mental healthcare tomorrow so we can mold strong people and forge a stronger future.

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