Original Research

Psilocybin Treatment Plan for Major Depressive Disorder: Microdosing vs. Macrodosing

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Abstract

Introduction: Psilocybin will soon be an option for treating unipolar depression. Prior to prescribing psilocybin, psychiatrists will need to develop their own treatment plans. This article serves as a guide for those devising their own treatment plan and provides helpful information for psychiatrists to do so, as well as a suggested treatment plan. Currently, no study clearly shows psilocybin outperforming antidepressant medications, but the results are comparable. Evidence supports macrodosing and microdosing, but no studies have compared the efficacy of the two. Microdosing is a popular trend in the populace, prompting some research on the topic. In theory, microdosing would require less time and personnel if it was equally effective as macrodosing. **Methods**: The literature was searched using keywords in the following databases: PubMed, Google Scholar, and connected papers. **Results**: Contrary to the initial hypothesis, there is enough theoretical evidence to advise against microdosing for a long period of time based on permanent changes to brain physiology in rats and 5-HT2B mediated cardiovascular risk. Although many patients microdose for depression, this article advises microdosing only for the purpose of neuropathic pain relief, migraines, and cluster headaches. **Conclusion**: An outline of a potential treatment plan using psilocybin macrodoses involves the following steps: Determine the patient is a candidate, devise a psychotherapy plan, devise a tapering schedule, determine an adequate dose, assess if a second dose is necessary, and maintain patient follow up.

INTRODUCTION

With the recent rescheduling of psilocybin and MDMA (methylenedioxy-methamphetamine) in Australia for the treatment of Unipolar Depression and PTSD (post-traumatic stress disorder), respectively, clinicians planning to prescribe these medications will need to develop their own treatment algorithms prior to obtaining certification. There are currently no widely established guidelines for these therapies. It is imperative that we begin composing standardized treatment plans for the safe use of these substances. This article will focus on compiling information that will be helpful for psychiatrists composing their own treatment plans using psilocybin to treat depression.

In a study comparing psilocybin to escitalopram, a selective serotonin reuptake inhibitor (SSRI), the primary outcomes did not differ significantly, but the results were comparable [1]. Psilocybin has also proven to be an effective treatment for anxiety in end-stage cancer patients [2]. There is enough evidence in research, historical use, and anecdotally to warrant further research [3]. This article will only examine the effectiveness of psilocybin as a therapy in the context of comparing macrodosing and microdosing. More large-scale studies comparing psilocybin to SSRIs are needed before recommendations can be made about which is more effective; current evidence suggests that psilocybin has proven to be competitive.

Templates for treatment algorithms are available in research studies that have used macrodoses but none examine microdosing. One study that surveyed 8703 individuals via a mobile app found that among individuals

reporting mental health concerns, microdosers exhibited lower levels of depression, anxiety, and stress across gender [4]. More research needs to be done comparing both treatment options as macrodosing is time and personnel intensive and requires more infrastructure than microdosing. In addition, some patients may be averse to macrodose therapies due to fear of the experience or difficulties with access. Thus, if a microdosing regimen can achieve similar results to a macrodose, more patients can be treated with fewer resources. Given that there are no articles that expand on psilocybin's use in the clinical literature, this article will attempt to do so by providing helpful information to develop a treatment plan for depression using psilocybin.

METHODS

Using resources within UMass Chan Medical School's Lamar Soutter Library, search strings were developed consisting of keywords and the boolean command "AND" to search titles and/or abstracts using PubMed, Google Scholar, and Connected Papers databases. Keywords included depressive disorder, microdosing, psilocybin, dosing, tapering, SSRI (selective serotonin reuptake inhibitor), SNRI (selective serotonin and norepinephrine reuptake inhibitor), MAOI (monoamine oxidase inhibitor), TCAs (tricyclic antidepressant), lithium, bupropion, serotonin syndrome, mania, psychosis, set and setting, personality, and hallucinogenic persisting perception disorder. Studies included involved administration of psilocybin to human participants, randomized controlled trials, population-based epidemiologic studies, self-reported surveys, case studies, and literature reviews. One animal study was cited in the section "Chronicity of Microdosing" because there were no human studies involving chronic (daily use or every other day use for several months) microdose administration.

CONSIDERATIONS WHEN DOSING

This section will expand on several items to consider when deciding what dose to treat a patient with. These items include the actual dose, how often to dose (chronicity), the absorptive personality type, other antidepressant medications, and potential safety concerns.

Chronicity of Microdosing

Due to the fact that there are no published studies examining chronic microdosing of psilocybin, there is no widely accepted definition of how to microdose. The closest approximation was a survey (primarily from Reddit) of a population of 909 individuals reported using psilocybin (n=235, Mdose= 0.3 g of dried psilocybin mushrooms) on a one-day-on, two-days-off schedule [8]. Unfortunately, this study did not answer the question of how long one should maintain this schedule of one-day-on, two-days-off. Respondents were not a differentiated population and were not necessarily diagnosed with depression. The optimal schedule for a microdoser trying to enhance their performance at work may be different from a patient trying to alleviate depressive symptoms. Regardless, a question that remains to be answered in the form of a clinical trial is how long or how often one needs to microdose to alleviate depressive symptoms and whether or not this is a safe practice.

Regarding its safety for chronic use, psilocybin binds to the 5-HT2B receptor, which is located in endovascular cells and cardiac myocytes. Its activation promotes thickening and hardening of these cells and heart valves. Chronic use of serotonergic agents, in theory, has the potential to increase cardiovascular disease risk [9-12]. This is also supported by acute increases in blood pressure while using classical psychedelics [12]. Given this data, a

schedule that is too long could have negative cardiovascular effects; however, the literature on psychedelics and cardiovascular disease is conflicting.

What is a Macrodose? What is a Microdose? Dosing Recommendations

Route of Administration	Recreational Dose	Intoxication Threshold	Subthreshold
Psilocybe cubensis dried mushroom: PO	3–5g	0.5–1.5g	0.1–0.5g
Psilocybin synthetic: PO	17–30 mg	3–8mg	0.8–5mg
Psilocybin synthetic: IV	2mg/70kg	1mg	0.5mg

Figure 1. Dosing of Psilocybin [5]

Some studies evaluating lifetime users show decreased rates of obesity and hypertension [13, 14]. This effect has been attributed to secondary improvements in mental health disorders. There is also data suggesting anti-inflammatory and immunomodulatory effects of classical psychedelics (Lysergic Acid Diethylamide(LSD), Psilocybin, Mescaline, and N,N-Dimethyltryptamine (DMT)) [12]. To understand the effect of chronic microdosing, a controlled study would need to be done evaluating valvular disease and other negative cardiovascular outcomes.

The closest approximation of chronic psilocybin administration is a study in which rats were given LSD at .16mcg/kg/day every other day for 3-months. Permanent changes in neurochemistry and behavior were observed 24hrs, 2 weeks, and 4 weeks after the 3-month period. Subjects had increased locomotor activity (alleviated with Haldol and Olanzapine). At 1-month, rats had altered social behavior, with reduced sniffing, grooming, and following. They also showed markedly enhanced aggressive behavior (boxing, kicking, wrestling) and exploratory behaviors (sniffing, rearing, hole poking). They found more RNA for dopamine D1 and D2 receptors, brain-derived neurotrophic factor (BDNF), receptor tyrosine-protein kinase erbB-4 (ERBB4), and various NMDA and GABA receptor subunits [15]. This suggests that chronic microdosing is not a safe practice as it increases the risk for schizophrenic changes in this animal model.

Given the increase in dopamine receptors, neurobehavioral changes after 3-months of LSD administration in rats, and 5-HT2b mediated cardiovascular risk, minimizing the length of a microdosing schedule would be wise. This is especially true in those with a family history of schizophrenia. Unfortunately, not many studies evaluate the safety and efficacy of various microdosing regimens.

Although microdosing may not have a role in treating depression, it may be useful in treating chronic neuropathic pain. In a case study examining three individuals with chronic nerve pain, all found relief by microdosing psilocybin. One patient with quadriplegia achieved 90-95% pain relief for 6-8 hours via daily 250mg of ground mushrooms daily and has been doing so for 6-months. A second patient with complex regional pain syndrome achieved 80% pain relief for 3-4 hours via 500mg of ground mushroom. A third patient with degenerative disk disease and lumbar radiculopathy achieved nearly complete pain relief for 2-4 weeks via 1000mg mushroom chocolate bar in combination with physical therapy [16]. Of note, these patients were self-selected, their reports could not be validated as they were outside of

the research facility's health network, and the effect of a placebo could not be determined.

CHRONICITY OF MACRODOSING

Most studies have used 1-2 large doses, supplemented with psychotherapy before and after sessions. The timing of macrodoses is less debated than microdosing. One study of 59 subjects evaluated psilocybin in comparison to escitalopram. They used two separate doses of 25 mg of psilocybin 3 weeks apart[7]. Patients received psychological support prior to and between sessions. There appeared to be a dose-dependent effect of psilocybin dose and reduction in depression scores. There was also evidence for the effectiveness of a single dose of psilocybin in combination with psychotherapy [17]. One study claimed that two doses of psilocybin was superior, although a benefit was still seen with a single dose [18]. There was a dose-dependent reduction in symptoms, with the greatest reduction at .8mg/kg, with most studies having a treatment interval of 1 week. In summary, two doses may not be necessary if the quality of the first session is satisfactory and the probability of a successful session increases with the dose, adequate and informed preparation, and a quality setting.

Absorptive Personality

Psychedelic substances are unique because personality type plays a role in the individual's response to the substance. Of note is the personality trait of absorption, defined as the predisposition to get deeply immersed in sensory (e.g., smells, sounds, images, memories) or mystical experiences. People with this personality trait are prone to experiencing overall consciousness alteration, dissociation, mystical-type experiences, and visual effects induced by psilocybin [6]. This personality trait is important to assess prior to the administration of large doses as the subjective experience is of greater magnitude. The Tellegen Absorption Scale (TAS) may be helpful when assessing this personality trait [7]. This trait can briefly be assessed by assessing a patient on a 5-point scale (1-never/2-rarely/3-sometimes/4-most of the time/5-all the time) using the following characteristics of an absorptive personality.

Absorptive Characteristic	Sample Screening Sentence
Responsiveness to Stimuli	I can be deeply moved by a sunset.
Synesthesia	Some music reminds me of pictures or changing colors.
Enhanced Cognition	I can often sense the presence of another person before I see or hear them.
Dissociative Involvement	While watching a film I may become so involved that I forget about my surroundings and experience the film as if I was in it.
Vivid Reminiscence	Sometimes I feel and experience things as I did when I was a child.
Enhanced Awareness	Things that seem meaningless to others often make sense to me.

Figure 2. Sample sentences to screen for an absorptive personality

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ANTIDEPRESSANT MEDICATIONS AND PSILOCYBIN

Most medications have unfavorable interactions with psilocybin. Bupropion (Wellbutrin) does not require discontinuation, but all other psychiatric medications will likely need to be tapered prior to psilocybin administration. Due to the fact that chronic use of SSRIs and SNRIs blunt the effects of classical psychedelics via downregulation of 5HT2AR (SSRIs/SNRIs) [19], patients currently taking an SSRI or SNRI will need to refrain from using such medications for at least five half-

lives before psilocybin sessions. MAO (monoamine oxidase) is the enzyme responsible for breaking down psilocin (active molecule). MAOIs should be discontinued to avoid excessive intoxication. Mirtazapine also blunts the effects of psilocybin due to 5HT2AR blockade and will also need to be discontinued. Chronic administration of tricyclic antidepressants, lithium, acute administration of serotonin reuptake inhibitors, and use of haloperidol has been shown to potentiate hallucinogen effects [20]. One study conducted an online survey and found that 47% of 62 cases in which lithium was combined with a psychedelic resulted in a seizure. None of the subjects using lamotrigine experienced seizures [21]. Patients taking the supplements 5-Hydroxytryptophan and St. John's Wart are at risk of serotonin intoxication and should discontinue use prior to psilocybin administration.

When tapering off antidepressants, it is important to be aware of withdrawal symptoms, which are a sign that the tapering schedule needs to be delayed. The acronym FINISH may be helpful: flu-like symptoms/ insomnia/ nausea/ imbalance/ sensory disturbances/ hyperarousal [22]. When tapering off antidepressants, it is important to maintain communication with patients and encourage psychotherapy, physical activity, a healthy diet, and consistent sleep schedules. Figure 2 showcases a time frame for the tapering process, but a 2-week schedule should be employed for the safest results. Fluoxetine will need a schedule on the order of two months as it has a long half-life. Lastly, it is important to note that drugs with shorter half-lives have a higher incidence and severity of withdrawal symptoms [23].

Drug	Half Life	99% out of body
Paroxetine (Paxil)	24 hours	4.4 days
Sertraline (Zoloft)	26 hours	5.4 days
Escitalopram (Lexapro)	27 -32 hours	6.1 days
Citalopram (Celexa)	36 hours	7.3 days
Fluoxetine (Prozac)	4-6 days	25 days
Venlafaxine (Effexor)	5 hours	1 day
Duloxetine (Cymbalta)	12 hours	2.5 days
Desvenlafaxine (Pristiq)	12 hours	2.5 days
Tranylcypromine	2 hours	14 hours
Phenelzine	12 hours	3.5 days
Isocarboxazid	36 hours	10.5 days
Amitriptyline	9 - 25 hours	7.3 days
Lofepramine	12 -24 hours	7 days
Clomipramine	12 -36 hours	10.5 days
Imipramine	9 hours	2.6 days
Trimipramine	23 hours	6.7 days
Doxepin	33 - 80 hours (1.5 - 3.3 days)	23 days
Nortriptyline	36 hours	10.5 days
Dosulepin	50 hours (just over 2 days)	14.6 days

Figure 3. Half-Life for common SSRIs, SNRIs, MAOIs, and TCAs.

SAFETY PROFILE OF PSILOCYBIN

As with any drug used in medicine, side effects, and safety concerns must be taken into consideration. With regard to psilocybin, serotonin syndrome, physiological and psychological effects, induced psychosis and mania, and hallucinogen persisting perception disorder will be discussed.

Serotonin Toxicity- Signs and symptoms warranting immediate medical attention include myoclonus, extreme and fluctuating vital signs, agitation or comatose mental state, muscle rigidity, pronounced hyperthermia (fever), and or seizure activity [24]. The risk of serotonin syndrome can be mitigated by tapering psychoactive medications prior to use and avoiding polysubstance use.

Physiological and Psychological Toxicity- Hallucinogens generally possess relatively low physiological toxicity and have not been shown to result in organ damage or neuropsychological deficits. Some physiological symptoms may occur during hallucinogen action, such as dizziness, weakness, tremors, nausea, drowsiness, paresthesia, blurred vision, dilated pupils, and increased tendon reflexes. In addition, hallucinogens can moderately increase pulse and systolic and diastolic blood pressure. However, these somatic effects vary and are relatively unimpressive even at doses yielding powerful psychological effects [20]. Regarding patients developing a dependence on psilocybin, hallucinogens have historically not been associated with withdrawal syndromes, and they are not reliably self-administered in animal studies. In general, patients should be in good physiological health established by routine medical history, physical exam, 12-lead ECG, blood chemistry profile, hematology, and urinalysis. For reference, while excluding patients with a systolic blood pressure above 140 and diastolic above 90 (mmHg) averaged over four measurements across 2 days, no increases in blood pressure resulting in the administration of an anti-hypertensive have occurred in one university's trials [20].

The largest risk with psilocybin administration is psychological distress, as hallucinogens are physiologically well tolerated. Emotions are experienced more strongly while under the influence. Disturbing experiences are colloquially described as a "bad trip". To handle this risk, psychedelic compounds should be administered in a safe environment that does not allow for self-harm. In addition, adequate preparation about handling negative emotions while under the influence can mitigate the risk of psychological distress. Patients need to approach negative emotions without resistance or fear and with an open mind. They can be counseled that negative emotions will arise in the same way that they do every day. Instead of trying to suppress negative thoughts, they should be accepted and examined with compassion, as this can be a powerful opportunity for self-exploration.

Psychosis- There is a risk of catalyzing a psychotic episode via the administration of psilocybin. Most cases have been in the setting of unsupervised administration, which increases the risk of polypharmacy and unsafe settings. Psychosis has been seen with LSD administration at a rate of .8/1000. This rate was obtained after a single incident out of 1200 LSD administrations in which the patient had an identical twin diagnosed with schizophrenia [25]. As such, patients with a history of schizophrenia or a first-degree relative with schizophrenia should avoid psilocybin in a non-clinical setting. Until more research involving psilocybin and the schizophrenic population is done, psilocybin should be reserved for schizophrenic patients with severe depressive symptoms (e.g., a score of 31 or higher on the Beck Depression Inventory).

Mania- Although there is little research involving psilocybin and the bipolar population, it would be wise to exercise caution

when using psilocybin in patients prone to mania. The rationale is that psilocybin is a potent serotonergic antidepressant which have been known to carry the risk of inducing mania. About 25%-33% of bipolar patients may be inherently susceptible to antidepressant-induced manias [34]. Bipolar patients with a strong genetic loading for bipolar illness whose initial illness begins in adolescence or young adulthood (typically Bipolar 1) and those with prior episodes of antidepressant-induced mania may be especially at risk [26]. Epidemiologic studies suggest that the risk of induced mania or psychosis is quite low. In a study of approximately 22,000 individuals, hallucinogen use did not predict subsequent mania, psychosis, or mental health treatment [27]. Of 130,000 doses of ayahuasca, four subsequent psychiatric diagnoses were labeled 'bipolar affective disorder; psychotic manic episode.' These researchers concluded that the number of psychosis and other cases from this sample is slightly less than expected in the base rate of the population [28].

Several case studies have been documented regarding the use of psychedelics and subsequent cases of mania or psychosis [29]. In summary, there were a total of 17 case studies in which a psychedelic compound could have contributed to the precipitation of a manic episode. Establishing a causal relationship is difficult due to polysubstance use, family histories positive for bipolar disorder, and those with a diagnosis of bipolar disorder may have been at risk for developing mania regardless of substance use. In 9 of the 17 cases, subjects used psychedelics multiple times in a short time-period. In 5 of the 17 cases, subjects used other substances. Of note, there were no studies in which an individual with bipolar disorder ingested a psychedelic and died due to an accident or suicide. When looking at the epidemiologic studies and case studies, there seems to be a risk of inducing mania, even if the risk is small. Despite this, the risk can be reduced even further by avoiding risk factors: polysubstance use, using psychedelics many times in a short time-period (i.e., recreational doses more than once in 72 hours), avoiding use in individuals displaying symptoms of mania or hypomania, and supervised use in a safe setting for individuals with a strong family history of bipolar disorder.

Hallucinogenic Persisting Perception Disorder(HPPD)- HPPD consists of perceptual disturbances (usually visual) while no longer under the influence of a psychedelic. To be considered a disorder, these disturbances must disrupt the individual's day-to-day life. HPPD has an incidence of about 4.2% of 2455 responders to a web-based questionnaire claimed to have visual disturbances prompting them to seek treatment [30]. There are case reports describing successful treatment with oral risperidone, neuroleptics, anticonvulsants (lamotrigine), benzodiazepines, and clonidine [12, 35, 36]. Given the evidence of multiple classes of medications alleviating HPPD symptoms it is difficult to establish a possible mechanism. The current hypothesis is that HPPD is due to chronic disinhibition of visual processors and subsequent dysfunction in the central nervous system [37]. It is important to note that HPPD is more common in recreational use and is rarely seen when psychedelics are used in a clinical setting [35].

SET AND SETTING

Set and setting (referring to the environment, music, and people involved with a psychedelic user's experience) have been posited to be crucial to the outcome of a psychedelic experience. Music is an important component of an individual's setting. A study at Johns Hopkins comparing Western Classical music to Overtone-Based Music did not show any significant differences between the groups when looking at biologically verified tobacco

cessation [31]. This finding in combination with the lack of research on music choice, suggests that it would be more optimal to have patients create their own playlists lasting 6-8 hours or select from a list of genres.

Concerning setting, it has been shown that the setting of an MRI or PET scanner has led to dissatisfactory experiences [6]. This suggests that the environment should be familiar and welcoming and not in a clinical setting. Successful studies have put subjects at ease via a living-room style room. It is important to include activities (e.g., paper, pens, paint, crayons, books, poetry, tv, movies, knitting supplies, fidget toys, simple video games, etc.) to allow personal expression and play therapy. It is also important to allow subjects to move about as they wish to limit feelings of claustrophobia and boredom.

DISCUSSION

The nature of microdosing requires chronic administration, which has not been adequately researched in humans. Some risks include potentially irreversible schizophrenic changes to brain physiology and 5-HT2B mediated negative cardiovascular effects. These risks are largely theoretical and need to be evaluated in a research setting. There is currently much more research available surrounding macrodoses, and thus is assumed to be safer. The initial hypothesis that microdosing may be a more accessible but equally effective treatment method was found to be inaccurate. In comparison to the standard acute administration of a macrodose of psilocybin in a safe clinical setting, microdosing has several theoretical risks that have not been disproven. =

Although microdosing may not currently have a role in treating depression, several case studies demonstrated efficacy for neuropathic pain. There is also evidence for the treatment of migraines [32] at .143mg/kg and cluster headaches [33]. The mechanism for this is not fully understood, but these studies warrant further research. This is especially important given the conflicting evidence that psychedelics indirectly improve cardiovascular health and reduce inflammation. If the cardiovascular risk is found to be minimal, microdosing will allow for more access to psychedelic treatment, as microdosing requires fewer resources and less observation for safety. As a result, macrodosing may be preferred by clinicians at this time as it is more likely to produce acute results, requires less follow-up visits for dose titration and symptom evaluation, and is less likely to have negative cardiovascular outcomes.

This article aims to make a clinical judgment based on the limited evidence available. Given the available research, if a patient is microdosing of their own accord, it is important to advise them. Based on the available research, it would be prudent to limit microdosing schedules to no more than twice a month in patients with an ASCVD (Atherosclerotic Cardiovascular Disease) risk <5% if the goal is to alleviate depressive symptoms. If ASCVD risk is >5% but < 10%, once a month is more reasonable. Patients should be evaluated to assess the need for future doses every 3-6 months, but patients should also be encouraged to titrate their microdose in consultation with their psychiatrist. Treatment should be stopped or reduced in frequency as symptoms decrease. This schedule would minimize cardiovascular risk while also catering to the chronic nature of unipolar depression.

If the goal is to manage chronic pain, the lowest dose that alleviates 80-90% of pain should be used and at the lowest frequency. If patients have chronic neuropathic pain as well as an ASCVD risk over 5%, each decision should be on a case-by-case basis considering the cardiovascular history and pain intensity.

CONCLUSIONS

The suggestions summarized below are based on the findings in this literature review for a treatment plan involving a macrodose.

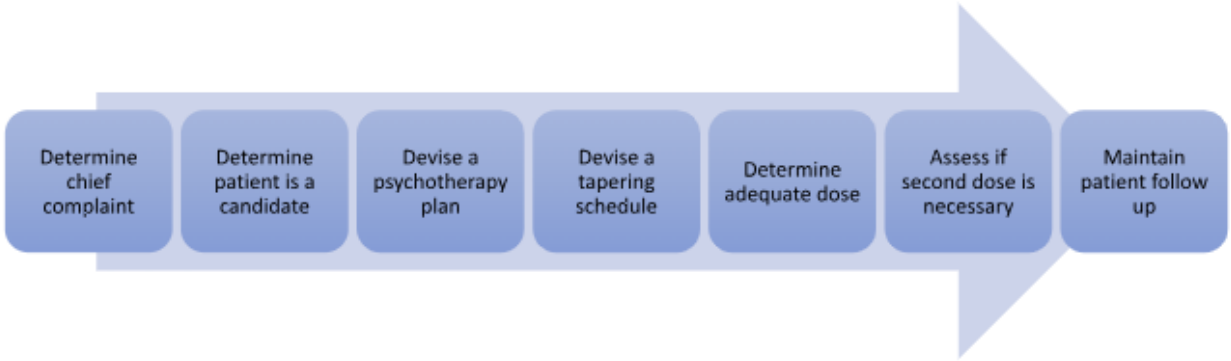

Figure 4. Flow diagram of sample psilocybin treatment plan for depression.

1. Determine the chief complaint, which will likely be a depressive episode that has not resolved with conventional therapies;
2. Determine whether the patient is a candidate (diagnosis of depression, physiologically fit for a psilocybin session, not showing signs of mania/hypomania, no history of antidepressant-induced mania, displaying signs of severe depression if diagnosed with schizophrenia or a first-degree relative with schizophrenia);
3. Devise a psychotherapeutic treatment plan for before and after psilocybin sessions (sessions leading up to psilocybin session should include education and managing expectations about psilocybin experience);
4. Review medications and devise a tapering schedule (monitor for Antidepressant Withdrawal Syndrome and adjust schedule);
5. Decide on a dose after assessment of personality type, experience with psychedelics, and patient comfort level;
6. Assess if a second dose is necessary and conduct an analysis of why the first session did not produce results. Some reasons for an unsatisfactory experience could be incorrect dose, poor relationship with the chaperones, inadequate attention to set and setting, incorrect expectations surrounding the experience, or inadequate psychotherapy prior to the session; and
7. Maintain patient follow-up

This article is limited by the lack of research on psychedelic substances (particularly microdosing) due to federal policies and widespread misconceptions. It is difficult to make recommendations on treating the bipolar population, the cardiovascular disease risk associated with psilocybin, and comparing microdosing to macrodosing. However, between medicalization and an increase in people turning to psychedelics to self-medicate as the standard treatment algorithms have failed them, the need for treatment algorithms to guide psychiatrists in the safe practice of psychedelic therapy is greater than ever, even if there is limited research to do so. More research is needed to evaluate the safety of microdosing, which will allow for safer recommendations regarding the practice. Despite this, as with any new therapies, the research

must be looked at through a clinical lens, and a treatment plan must be developed regardless of the amount of research available. This article serves as the first reference of information that will be helpful for clinicians who are tasked with developing their own treatment plans for treating depression via psilocybin.

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Enabulele, K (2023, June). Psilocybin treatment Plan for Major Depressive Disorder: Microdosing vs. Macrodosing. *The Journal of Psychedelic Psychiatry*, 5(2).

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