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Psychedelics

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COMMENTARY

Psilocybin-assisted psychotherapy: Advancements, challenges, and future directions for treating resistant depression

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Depression is a global public health challenge that represents the world's largest cause of disability, especially in the context of traditional treatments. One potential solution being explored is psilocybin assisted psychotherapy (PAP) which shows promise for treating depression. A recent study by Rosenblat et al. explores the use of psilocybin in clinical mental care with promising results (1).

The increase in major depressive disorder (MDD) cases particularly since 2005 and worsened by COVID-19 is alarming (2). While monoaminergic antidepressants have been used as a treatment since the 1980's, they often take two to four weeks to show effects and may not work for up to one-third of patients (2). Additionally, side effects lead up to 50% of patients to stop treatment (2, 3). Therefore, there is a growing focus on finding better ways to address depression.

Responding to the need for antidepressant options, psychedelic compounds have garnered attention in recent times. Despite past disapproval due to recreational drug use, there is now renewed interest in exploring psychedelics like psilocybin for their therapeutic potential (2, 4).

Psilocybin, a naturally occurring psychedelic compound found in certain mushroom species, has been found to have a profound impact on consciousness by interacting with serotonin 5HT2A receptors (2, 3). Research on animals suggests that psilocybin is associated with an increase in brain derived factor (BDNF) which influences plasticity, neurogenesis and dendritic growth (5). Interestingly, lower levels of BDNF have been linked to depression in several studies (6). While the exact pathways through which psilocybin benefits conditions is still up for debate, there is promise in using it to help treat treatment-resistant depression (TRD) when combined with psychological support (3, 7).

The idea of PAP has been gaining traction as a supported method for addressing depression symptoms in individuals with bipolar II disorder as noted by Aaronson and colleagues (8). However, determining the combination of therapy sessions and dosage levels for effectiveness remains an area of concern.

One important area of concern is the critical issue of adverse reactions, which are particularly important in the light of reports of psychedelics-induced mania that could paradoxically indicate their effectiveness as antidepressants (9). A very germane point is that effectiveness and safety must be well ascertained in order to avoid investing in therapies that may not work. This is particularly relevant for long-term psychotherapy in combination with psychedelics (10). One of the frustrations experienced by clinicians is that most of the evidence supporting the use of psilocybin for depression comes from studies with very strict eligibility criteria, which makes it unclear if the findings from those rigorous trials are applicable in real-world settings, where conditions like personality disorders and suicidality (which tend to be clinical trial exclusion criteria) are highly prevalent (11).

In a March 2024 article titled "Psilocybin assisted psychotherapy for treatment depression: A randomized clinical trial (RCT) evaluating repeated doses of psilocybin," Rosenblat and colleagues shed light on these issues in the field of PAP research (1). This new RCT provides evidence supporting the use of psilocybin dosing in a population dealing with complex psychiatric issues such, as TRD bipolar II disorder (BPII) or other comorbid conditions.

In the study conducted by Rosenblat and colleagues, participants had an average Montgomery-Asberg Depression Rating Scale (MADRS) score of 30.5, experiencing depression for 18.3 years, and having gone through approximately 11.27 failed medication trials. Interestingly 40% of them had experience with electroconvulsive therapy or ketamine infusions. This trial involved 31 individuals with TRD; most were initially diagnosed with MDD (26 participants), while only four were diagnosed with BPII. Each participant also had at least another co-morbid psychiatric diagnosis. One participant withdrew before the study began. The trial aimed to evaluate the feasibility of using psilocybin in combination with therapy to address TRD. Participants were split into two groups: one receiving treatment ($n = 16$) and the other on a waitlist control ($n = 14$). Over six months all treated participants received one to three doses of psilocybin at 25 mg each along with preparatory and integration psychotherapy sessions over a six-month period.

Results showed significant reductions in depression severity in the full sample, with further MADRS score reductions from repeated doses. The results showed a reduction in depression severity across all participants after receiving repeated doses of psilocybin. The treatment was well tolerated without any reported events. The high retention rates and manageable side effects emphasized the effectiveness of this approach for individuals struggling with TRD.

The unique aspect of the research study conducted by Rosenblat and team was their method of dosing, which involved administering psilocybin based on relapse indicators. This sets it apart from studies that typically followed a fixed single dose protocol (4, 7, 9, 11, 12). As a comparison, in a study by Goodwin et al., a single dose approach was used to evaluate the effectiveness of psilocybin doses along with support for TRD (12). In this study, a 1 mg dose served as a reference point compared to doses. The findings revealed that the 25 mg dose improved participants symptoms after three weeks whereas the medium 10 mg dose did not show symptom reduction. Interestingly the control dose of 1 mg did not yield benefits. While this research emphasized the importance of dosing strategies it only observed patients for 12 weeks indicating the need for longer trials to fully understand the lasting effects of psilocybin treatment.

Following the examination of dosing frequency, the Rosenblat et al. study broke new ground by extending the follow-up period to six months and allowing for a schedule with doses given as needed (1). Evaluating outcomes two weeks post each dose, the study found that the primary depression measure, the MADRS, was significantly lower at the last post-dose follow-up compared with baseline. The authors conclude that their

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results indicate that when depression is recurrent, as it often is, treating it as one would treat the recurrence of other episodic disorders makes more sense than sticking with a more rigid fixed-dose schedule that may not be personalized to the needs of the patient.

I found that the approach taken in the Rosenblat et al. study to dosing was better than what other studies have shown. However, while the research by Rosenblat and colleagues shows promise, there are some limitations to consider. The fact that it was an open label study had a sample size. Using waitlist controls instead of a placebo group are significant issues that could make the antidepressant effects seem stronger than they actually are. Additionally, this study differed from ones by providing preparatory and integration psychotherapy, which might explain why the antidepressant effect was not as strong as seen in studies like Goodwin et al., where there was a greater reduction in MADRS scores (1, 12).

In studies involving psilocybin, including the one led by Rosenblat et al., participants receive support through three phases: preparation, dosing session and integration (1, 13). For patients with TRD, therapy is believed to enhance the effects of psilocybin and help individuals process their dosing experiences (5). This dynamic relationship makes it difficult to determine whether improvements in symptoms are due to psilocybin itself or the psychological support provided alongside it.

The effect of psychotherapies used in PAP trials on the effectiveness of treating depression has yet to be determined by researchers. Clinical trials vary in the number and type of preparation and integration sessions provided (14). As we noted previously, the range of background training for the therapists is equally diverse (13). These PAP trials have not tried to standardize either the psychotherapies or the therapists.

As we move forward, the integration of PAP into practice may present some real challenges. While there are those who believe that psilocybin therapy could well provide some lasting benefits when compared to ketamine, the potential cost of these therapies has some professionals concerned. If the cost of these therapies rises, it becomes an even bigger barrier to access. Right now, a couple of different efforts are exploring group therapy and virtual therapy as potential alternatives that could save people money, but the safety and efficacy of those therapies are not yet established. Another thing that is perhaps less frequently discussed is the huge importance of setting in enhancing the effects of these therapies. In short, places matter; and you need to have an accessible space if you are going to have a positive effect (15).

To sum up, an important step was taken by Rosenblat and associates when they recently illuminated the subject of psilocybin and its possible use as a treatment for depression. What they did was quite different from what has been done before in this area. They took a group of people who had serious mental health issues (in this instance, depression), in real-life settings that included multiple comorbidities. Future studies will be required to address constraints like an open label design sample sizes and controls.

One could make the case that future research must include larger, placebo-controlled trials over extended time so that we can clearly ascertain the long-term safety aspects of psilocybin and generate the evidence needed to optimize the combination of dosing with psychotherapy sessions. Addressing variations in psychotherapy techniques and therapist training will play a role in enhancing the effectiveness and consistency of PAP. Moreover, logistical and financial obstacles need to be addressed since PAP demands therapist engagement, specialized training and suitable clinical environments. Continuous research is vital to realize the potential of psilocybin as a treatment for depression offering renewed optimism for those struggling with TRD.

Rodolfo Myronn de Melo Rodrigues[1]
[1]*Internal Medicine Department, Texas Tech University Health Sciences Center, El Paso, Texas 79911, USA*
✉ *e-mail: rdemelor@ttuhsc.edu*

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