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Therapeutic Potential of Psychedelics in Treatment of Psychiatric Disorders, Part 2: Review of the Evidence

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Psychedelics have recently gained attention as compounds with therapeutic potential in the treatment of psychiatric disorders. The US Food and Drug Administration (FDA) has granted Breakthrough Therapy Designations for (±)-3,4-methylenedioxymethamphetamine (MDMA) as an adjunct to psychotherapy in severe posttraumatic stress disorder (PTSD) (in 2017) and for the adjunctive use of psilocybin with psychotherapy in both treatment-resistant depression (TRD) (in 2018) and major depressive disorder (MDD) (in 2019). Additionally, a number of clinical trials with psychedelics are ongoing for other indications such as eating disorders, cognitive impairment, and substance use disorders (SUD). This article is the second in a 2-part series[1] on the psychopharmacology and therapeutic effects of psychedelics, and it provides a review of the evidence for use of psychedelics, with a focus on psilocybin, lysergic acid diethylamide (LSD), MDMA, and ayahuasca.

Psilocybin

The efficacy of psilocybin has been examined in open-label studies of treatment-resistant obsessive-compulsive disorder, TRD, and SUD such as alcohol and tobacco use disorders with promising results.[2] Randomized controlled trials (RCTs) of psilocybin are limited to the treatment of depression and anxiety in advanced cancer. In a double-blind crossover design RCT, 12 patients with advanced cancer received a single dose of psilocybin (0.2 mg/kg) and niacin (placebo) in 2 experimental sessions. Psilocybin resulted in a nonsignificant trend toward improvements in mood from the first session to 6-month follow-up.[3] A larger crossover design RCT that included patients with advanced cancer (n = 51), randomized to receive high-dose psilocybin (22 mg or 30 mg/70 kg) and low-dose psilocybin (1 mg or 3 mg/70 kg) in 2 experimental sessions, found that high-dose psilocybin produced large decreases in clinician- and self-rated measures of depression and anxiety, increased quality of life, and decreased death-anxiety. This response was sustained at 6-month follow-up in about 80% of participants when the data were collapsed across both groups. Of note, 4 patients with disease progression had missing data at the 6-month time-point, making this a "completer" rather than an "intent-to-treat" analysis. Interestingly, therapeutic response was found to be mediated by mystical experience during the psilocybin session.[4] In another similarly designed RCT, 29 patients with advanced cancer received a single dose of 0.3 mg/kg psilocybin or 250 mg niacin (active placebo) with crossover at week 7.[5] Psilocybin was associated with sustained improvement in anxiety and depression, decreased cancer-related demoralization and hopelessness, improved spiritual well-being, and increased quality of life, which was sustained at 6.5 months and 4.5 years after dosing.[5,6] The results of larger ongoing studies by the UK-based company COMPASS Pathways and by the US company Usona are awaited.

LSD

Clinical efficacy studies of LSD have been carried out in anxiety and depression associated with life-threatening diseases and SUD. A pilot study in 12 patients with anxiety associated with life-threatening diseases who underwent 2 LSD-assisted psychotherapy sessions showed a significant reduction in state anxiety and a positive trend in reducing trait anxiety with the 200-µg dose of LSD compared to the 20-µg dose.[7] Interestingly, these improvements were found to be sustained at 1-year follow-up.[8] Participants consistently reported insightful, cathartic, and interpersonal experiences, accompanied by a reduction in anxiety and an increase in quality of life. While the study characterized the sample as comprising patients with life-threatening diseases, 3 out of 10 had a non-cancer diagnosis, including celiac disease, Parkinson's disease, and ankylosing spondylitis. A meta-analysis of 6 randomized trials of varying doses of LSD in alcohol use disorder in over 500 subjects found that a single dose of LSD had a significantly beneficial effect on alcohol use at the first reported follow-up assessment (ranging from 1–12 months) with sustained significant beneficial effects at 2–3 months and 6 months, but these effects were not statistically significant at 12 months posttreatment.[9] While results from recently concluded trials are awaited, several controlled studies in healthy and clinical populations are currently underway in Basel, Switzerland.

MDMA

Besides limited studies in SUD and social anxiety associated with autism, modern clinical MDMA studies have mainly focused on PTSD. In the largest published study of MDMA in PTSD (n = 26), Mithoefer et al[10] reported a significant reduction in the Clinician-Administered PTSD Scale score at doses of 75 and 125 mg at 1 month. A pooled analysis of 6 phase 2 trials (n = 105) also found a large treatment effect (Cohen $d = 0.8$) between active MDMA (75–125 mg) and placebo.[11] Long-term follow-up of these data at 12 months showed that PTSD symptom improvement continued

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for at least 12 months posttreatment.[12] However, the conclusions were limited by the lack of a long-term control group. Another meta-analysis found comparable effect sizes (Hedges *g*) between the pooled results of 2 MDMA trials ($g = 1.17$; 95% confidence interval [CI], 0.38–1.90) and the results of a separate meta-analysis of prolonged exposure therapy ($g = 1.08$; 95% CI, 0.69–1.46).[13] A phase 3 trial of n = 100 subjects, the results of which have yet to be published, concluded in August 2020 (NCT03537014).[14]

Ayahuasca

Efficacy studies of ayahuasca have predominantly been limited to open trials. In a small open-label study in patients with MDD, participants showed significant improvement in several MADRS items (expressed sadness, pessimistic thinking, suicidal ideation, and concentration difficulties) on days 1 and 21.[15] This study was subsequently replicated in a larger sample.[16] Clinical studies have been hampered by the lack of standardization of the concoction with variability in the composition of individual compounds. A recent RCT of 35 TRD patients found that depression severity changed significantly in both ayahuasca and placebo groups with greater improvement in the ayahuasca group, with increasing between-group effect sizes from day 1 to day 7. The between-groups remission rate showed a trend toward significance at day 7.[17]

Clinical Trial Design Considerations in Psychedelic Research

Unlike clinical trial design for most CNS drugs, the clinical trial methodology for psychedelics research has some unique features. One is the emphasis on supportive psychotherapy. The study design typically includes (*a*) preparatory/introductory psychotherapy sessions, followed by (*b*) experimental sessions, in which the psychedelic (or control) is administered, after which (*c*) participants undergo integrative sessions to "make meaning" of the psychedelic experience. Second, the dose of psychedelics is not based on receptor occupancy but rather on their ability to produce a psychedelic experience. Studies show that the "trip" or psychedelic experience has a neurobiological correlate[18] and may be associated with therapeutic effects.[4] Third, based on studies in the 1950s–1960s, psychedelic research has a strong emphasis on "set and setting"; that is, the environment in which the treatment is conducted commonly includes mystical themes, use of psychedelic imagery such as mandalas, and music. Whether the psychotherapy sessions, psychedelic "trip," and "set and setting" are integral to, and necessary for, the therapeutic effects or contribute to nonspecific expectancy effects is not known. While psychedelics have shown robust responses following a single session that last as long as 6 months, the question arises whether the diagnostic overlap between adjustment disorder and MDD explains some of these robust improvements. For example, in the psilocybin studies in advanced cancer patients, the majority of patients were diagnosed with adjustment disorder. The results in patients with a terminal diagnosis may also be confounded by the role of psychotherapy in alleviating adjustment disorder; for example, by "making meaning" of the psychedelic experience and providing a new cognitive schema to cope with the existential crisis or death-anxiety associated with a terminal condition. The severity of cancer, prognosis, and response to cancer treatment may therefore be potential confounders that need to be measured in future studies. Another challenge in psychedelic trials is the inability to ensure adequate blinding, given the profound psychedelic effects, and the inclusion of subjects with past experience with the compounds. Some studies have used niacin and psychedelics at very low doses as an active control to minimize placebo/expectancy effects.[3,4,7]

Clinical Considerations

While there is a lot of interest in using psychedelics for treatment-resistant patients, the small sample size in the few RCTs limits their generalizability at the present time. Other clinical considerations include abuse potential associated with use of psychedelics outside the setting of a clinical trial, drug-drug interactions including risk of serotonin syndrome with other serotonergic medications, adverse physiological effects (eg, hypertension, hyperthermia), and rare, persistent effects (eg, persistent psychosis, hallucinogen persisting perception disorder). Given the concerns for abuse and adverse outcomes, it would be prudent to await FDA approval and acquire more data in well-controlled research settings. Additional safeguards, such as monitoring for worsening of symptoms during washout from serotonergic agents prior to psychedelic treatment and exclusion of patients with a history of psychosis or a previous adverse reaction to psychedelics, may be required to further mitigate the risk of a negative outcome. While microdosing (eg, using one-tenth or one-twentieth the psychedelic "trip" dose with dosing every 1–3 days) is popular among laypersons to enhance general well-being, creativity, and mental health,[19] there is not strong evidence to support this practice. One study[8] using microdoses of LSD as a control group showed no improvement in depressive symptoms. Large epidemiologic studies show lifetime rates of psychedelics use up to 10%,[20] but significant associations between lifetime use and increased rates of psychiatric problems or suicidal behaviors have not been found.[21] Just the same, reports of drug abuse and rare but serious adverse outcomes, such as psychosis with unsupervised LSD and psilocybin use,[22] suggest the need to proceed cautiously.

Conclusions

Psychedelics hold promise as an alternate treatment option for a subset of patients with psychiatric disorders. Future studies need to be carried out in larger RCTs at different doses with careful consideration of blinding to better characterize the therapeutic effect and who would benefit from these unique compounds and at what doses. The roles of psychotherapy, "set and setting," and expectancy also remain to be delineated.

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