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Psychedelic-assisted psychotherapy for depression: How dire is the need? How could we do it?

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ABSTRACT

Despite the popular support for psychedelics as aids for depression, academics and the public frequently overestimate the efficacy of available medications and psychotherapies. Metaanalyses reveal that antidepressant medications alone help only one in four patients and rarely surpass credible placebos. Their effects, though statistically significant, might not impress depressed patients themselves. Psychotherapies create better outcomes than antidepressant drugs alone; combining the two provides measurable advantages. Nevertheless, the best combinations help only 65% of the clients who complete treatment. The drugs create side-effects and withdrawal surprisingly more severe than professional guidelines imply, too. Psychedelics appear to improve depression through some of the same mechanisms as psychotherapy, as well as some novel ones, suggesting that the combination could work very well. In addition, subjective experiences during the psychedelic sessions covary with improvement. Guiding clients to focus on these targeted thoughts and feelings could improve outcome. These data underscore the serious need for clinical trials of psychedelic-assisted, empirically supported treatment for depression with guided experiences during the psychedelic session. These trials would require important components to maximize their impact, including meaningful preparatory sessions designed to enhance motivation and explain empirically supported approaches, guided administration sessions that focus on oceanic boundlessness, integration sessions that support progress, and follow-up sessions consistent with established research. This combination involves markedly more than a simple pairing of medication and talk therapy, but proper application could have an unparalleled impact on public health.

KEYWORDS

psychedelic psychotherapy, depression, psilocybin, ketamine, benefits, LSD

The 300+ million people who suffer from Major Depressive Disorder generate an immeasurable personal sadness as well as alarming costs. Losses include poor quality of life for affected individuals and their families, increased mortality, and economic burden (WHO, 2017). Lifetime prevalence in the United States is approximately 20% (Hasin et al., 2018). Over 500 clinical trials and 70 meta-analyses of relevant medications and psychotherapies suggest moderate but imperfect rates of treatment successes (Cuijpers, 2017; Cuijpers et al., 2019). Impressions of efficacy can appear optimistically biased. Media depictions and academic publications suggest that the vast majority of patients recover, implying that the need for improvements is minor. For example, one academic journal's aside suggests that only 20% of patients would need novel approaches like psychedelics (Cowen, 2016). A CNN report suggests that non-psychedelic treatments do not work “for everybody,” as if almost all patients recovered from depression with the therapies commonly in use (Yeung, 2019). In addition, *Time Magazine's* coverage of ketamine's use as an antidepressant suggests that “30% of patients” do not respond to conventional treatments (Oaklander, 2017).

Meta-analytic reviews suggest that a 70% recovery rate is a fantasy. With 300 million people affected worldwide, an exaggeration of 1% incorrectly implies 3,000,000 people treated successfully. Neither medications, psychotherapy, nor the combination succeed with more

than 65% of patients. For example, pharmacotherapies, a common defense against depression, often help no more than one-third of patients. A comparison among seven antidepressants found that they helped from 1/9 to 1/6 of patients—hardly the winning percentages commonly described to depressed clients (Citrome, 2016). Given the methodological issues and publication bias common to this literature, critics justifiably assert that reviews overestimate efficacy. These confounds led one commentator to suggest that the glass is not half full, but, “full by one-ninth.” That is, nine people need to receive one of these drugs for a single person to recover (Hengartner, 2019).

Other concerns include the slow onset of antidepressant-induced improvement, large placebo responses, side effects, and withdrawal. Antidepressants require weeks to heighten mood (Ramaker & Dulawa, 2017). Placebos create 30–80% of the active drug's response, which gives prescribers and patients pause (e.g., Li, Nasir, Olten, & Bloch, 2019; Kirsch, 2019). Side effects range from dry mouth to sexual dysfunction (Read & Williams, 2018) to increased mortality (Konttinen, Kilpi, Moustgaard, & Martikainen, 2016). Withdrawal is also more severe, long-lasting, and prevalent than recommendations often suggest. Guidelines describe withdrawal as weeks of nuisances for a handful of clients, but nearly half (46%) rate these effects as “severe” discomfort lasting months (Davies & Read, 2019). Meaningful contributors to quality of life, including side effects and withdrawal, can often go unmeasured in studies of efficacy.

How much help do these medications provide? Critiques emphasize that statistically significant effects might not prove clinically meaningful. Statistical significance confounds effect size and sample size. A large effect in a small sample can reach the hallowed threshold of $P < 0.05$, but so can a small effect in a large sample. To combat this problem, the United Kingdom's National Institute for Health and Care Excellence (NICE) suggests that anything less than a seven-point difference on the Hamilton Depression Scale (HAM-D) (or a 0.875 standardized mean difference) does not qualify as clinical improvement (Kirsch, 2019). The average antidepressant beats placebo by less than two points (Jakobsen, Gluud, & Kirsch, 2019)—a far cry from clinically meaningful. A two-point change might mean a great deal on serious symptoms, but the items central to depression scales rarely matter most to patients. Clients prioritize returning to work and activities (Eiring et al., 2015), but common measures of depression rarely mention employment directly. Interpreting the meaningfulness of these changes can be complicated for any research on the topic.

Understandably, people often prefer psychotherapy (Hanson, Webb, Sheeran, & Turpin, 2016). Weekly sessions with a professional requires more effort than trips to the pharmacy, but psychotherapies create few side effects. Empirically supported treatments help 1/3 to 1/2 of patients regardless of focus (Cuijpers et al., 2013). For example, behavioral activation (BA), a treatment devoted to increasing activities consistent with the client's identified values, shows replicable support. Cognitive-behavioral treatments (CBT), which focus on altering the beliefs that

covary with the disorder, succeed at comparable rates (Stein, Carl, Cuijpers, Karyotaki, & Smits, 2020). Interpersonal psychotherapy (IPT), which focuses on new roles in relationships, alleviates symptoms equally well despite a different emphasis (Cuijpers et al., 2011). These therapies create statistically significant improvement, but no treatment surpasses the NICE recommendation of a standardized mean difference of 0.875, at least among experiments with large enough samples to provide reasonable estimates of the population effect (Jakobsen, Gluud, & Kirsch, 2019). Thus, psychotherapies rarely meet criterion for clinically meaningful improvement.

Adding psychotherapy to antidepressant medications creates better outcomes than medication alone (Karyotaki et al., 2016). In addition, adding medication to psychotherapy decreases relapse. No specific combination clearly dominates (Barth et al., 2016). In one of the most successful combinations, 62% of patients no longer qualified for depressive disorder by treatment's end (Cuijpers et al., 2014), meaning 1 in 1.6 recovered. Nevertheless, even with this combined treatment, half relapse within two years (Vittengl, Clark, Dunn, & Jarrett, 2007). Ideal treatments for depression benefit by approaching the disorder like a chronic, relapsing condition. Despite reputations to the contrary, an intervention that creates rapid, clinically meaningful, long-lasting relief remains elusive.

New approaches are essential. An ideal therapy would have rapid onset, no side effects or withdrawal, and impressive efficacy. A reasonable cost would also ensure broader application. (Inpatient visits average over \$6,000 each, and over 5% are readmitted within the next 30 days (Citrome et al., 2019)). In contrast to standard antidepressant medications, psychedelic sessions often create improvement quickly, but the shortcomings of the outcome measures are the same as those mentioned for standard antidepressant medications and psychotherapies. That is, the scales fit standard definitions of depression that might or might not matter to depressed clients themselves. In addition, progress can dissipate rapidly. At five-week follow-up, only 4 of 20 participants in a two-session psilocybin trial met criteria for remission (Carhart-Harris et al., 2018), a rate comparable to that of placebos (Kirsch, 2019). Ketamine infusions improve mood and other symptoms almost immediately, and benefits remain at day 7, but few studies have follow-ups past day 30 (Salloum et al., 2020).

Despite these shortcomings, psychedelic-induced changes, however brief, provide an opportunity. Clinicians could use these days of improved mood to lay the groundwork for a successful response to psychotherapy. Some of the same mechanisms underlying psychotherapy's success change in response to ayahuasca, psilocybin, and ketamine. For example, both enhanced behavioral activation and cognition mediate antidepressant effects of ayahuasca (Mian, Altman, & Earleywine, 2020). Cognitive changes broadly fit the notion of improved *cognitive flexibility*—avoiding rigid, rule-governed actions. Multiple studies show that psychedelics improve cognitive flexibility, including a prospective web survey (Close et al., In press), psilocybin administration

(Davis et al., 2020), and Ayahuasca ceremonies (Murphy-Beiner & Soar, 2020). If the psychedelic sessions can jumpstart these gains, the active components of psychotherapy can enhance the duration of the improvements, leading more patients to benefit longer. A simple *preparatory* session could orient clients for the psychedelic *exploration* by helping them understand the role of adaptive thoughts and valued action in their recovery. An *integration* session afterward could help clients ensure that their own thoughts and values remained consistent with recovery. In a sense, the structure of psychedelic sessions can serve as scaffolding that assists clients in the development of new thoughts and actions.

Identifying the best approach to building this scaffolding will require research. Initial sessions could present the rationale for empirically validated approaches like CBT, BA, and IPT, and then encourage clients to choose the treatment that they find most compelling. Clinicians could then outline the chosen approach and ask clients if they are willing to lay the groundwork for making relevant changes outside of session. Preparatory sessions might allow clinicians to enhance motivation more generally, which has improved progress in cognitive-behavioral interventions (Keeley et al., 2016). Note that this approach would underscore the import of effort outside of session, potentially challenging simpler desires for the psychedelic to magically make all symptoms diminish. (Previous work suggests that homework, presented deftly, can improve CBT for depression (Burns & Spangler, 2000)).

Recommendations related to the psychedelic session itself might also prove fruitful. Formal trials and underground practices explicitly encourage clients *not* to expect a novel, pleasant experience, if only to avoid feelings of pressure or disappointment. Nevertheless, some subjective experiences that appear during psilocybin administration lead to stronger antidepressant effects, particularly “oceanic boundlessness” – feelings of oneness, connection, and joy. Typical items appear on the Altered States of Consciousness Scale (Dittrich, 1998), and assess unifying time and space (e.g., “My sense of time and space was altered as if I was dreaming”), connecting to delights (e.g., “I experienced boundless joy”), and recognizing the brilliant and weighty (e.g., “I felt particularly profound”). In contrast, and in support of discriminant validity of oceanic boundlessness, ketamine-induced dissociation (an experience of disconnection) leads to worse outcomes for depression (Mathai et al., 2020). Perhaps enhancing motivation to attend to targeted subjective effects could improve mood more dramatically. Only randomized clinical trials can answer these questions, but gently encouraging clients to note these experiences (without demanding that the effects should arise) might help identify if the sensations are causal or epiphenomenal. Further, these experiences could buttress motivation to make cognitive and behavioral changes consistent with psychotherapy. The chance to alter thought and behavior during the period when psychedelics have enhanced mood, energy, and cognitive flexibility, could facilitate a return to the actions that clients value most,

improve their communication with loved ones, and enhance an optimistic view of themselves, the world, and their futures.

The tacit assumption that treatments require only a handful of psychedelic administrations might also prove worthy of challenge. As an alternative, those who note a return of symptoms might engage in booster sessions of psychotherapy, psychedelic administration, or both. Given the cost of inpatient stays, even a few such boosters could benefit public health in the long run despite the price. Religious rituals that use psychedelics often include regular administration, sometimes at monthly intervals. Perhaps the approach has some wisdom (Shannon, 2002). The psychedelic and psychotherapy sessions might function less like surgery and more like physical exercise. Framing them as a set of new, regular activities instead of a sweeping, time-limited experience, could help make clients and the public treat these actions like general self-care, potentially minimizing stigma and relapse. Comparable strategies using psychotherapy with THC (Liu & Burnham, 2019) or microdosed psychedelics (Cameron et al., 2020) might also show promise.

In conclusion, despite reputations to the contrary, even the best of the antidepressant medications and psychotherapies often leave at least 1/3 of clients without meaningful improvement. The administration of psychedelic medicines in a supportive context with reasonable expectations (“set and setting”) appears to have potential for the treatment of depression and could add meaningfully to empirically supported psychotherapy. Some subjective experiences during drug administration covary with improvement more than others, so enhancing these experiences might (or might not) also improve outcomes. A combination treatment would require nuanced presentation but could take advantage of the rapid onset of psychedelic-induced improvements to get clients to benefit from the natural reinforcers inherent in the new actions and perspectives inspired by psychotherapy. Given the chronic, relapsing nature of the disorder and the high price of inpatient stays, regular assessment with the potential to return for additional sessions could also prove a wise investment. Appropriately powered, randomized controlled trials with long-term follow-up and meaningful dependent measures could help shed light on the potential of this combination. The 300 million affected citizens of the world, as well as their family, friends, coworkers, and communities, would certainly appreciate meaningful improvements.

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