Editorial Review: Trial of Psilocybin versus Escitalopram for Depression

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Psilocybin for the treatment of depression has been under recent evaluation with several ongoing studies. A recent study comparing the efficacy of psilocybin versus escitalopram found no statistically significant difference in treating depression [1]. No other study has evaluated psilocybin in a head-to-head comparison of standard of care treatment. With a total of 59 enrolled patients, 30 assigned to psilocybin and 29 to escitalopram. Patients were both male and female. Exclusion criteria included previous use of citalopram; however previous use of psilocybin was not exclusionary. The trial was a double-blinded, randomized controlled phase 2 trial. The HAM-D 17 scale, a validated scale to screen for depression, was performed via video call. All patients met a score of at least 17, indicating moderate to severe depression. Patients discontinued any antidepressant treatment three weeks prior to the trial. The study modeled itself similar to the STAR*D trials, with modifications to allow for the unique properties of psilocybin [2].

Similar to the STAR*D trials, assessments were based on using HAM-D and Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR). However, where STAR*D utilized QIDS-SR as a secondary outcome measure for response and remission, this study utilized it as the primary assessment tool. HAM-D was only used in the psilocybin versus escitalopram study as an initial screening tool and not an ongoing assessment. Secondary outcomes were favored for psilocybin. However, the confidence intervals for between-group differences were not adjusted for multiple comparisons, so no information can be interpreted that would be statistically significant from the data. There was still a statistically significant difference in depression scores in both groups, with no significant difference between the groups. Due to psilocybin's subjective effects, it may have contributed to bias among the participants that received 25mg psilocybin. It has been established that 25mg of psilocybin does not result in a significant difference in subjective effects compared to weight-based dosing alternatives across a range of populations [3].

Another factor was the sample population of recruiting volunteers, who expressed a preference for escitalopram or psilocybin and some who had tried psilocybin previously but not escitalopram. Selection bias can invariably occur in any study, and this study lacked ethnic and socioeconomic diversity. Additionally, the study could have benefited from a longer course, as in STAR*D, with a 12 week course [2]. Escitalopram may not be at maximal efficacy in a six-week period and may have demonstrated more accurate results had the trial been over a more extended time. Additionally, there are currently no studies to determine the effectiveness and regimen of psilocybin dosing to produce a significant antidepressant effect. Studies with psilocybin require supportive psychotherapy, at minimum, due to the subjective psychedelic effects. It is difficult in any trial to separate the effect of psychotherapy, as any treatment with a psychedelic will invariably incorporate therapy. What has been lacking in studies has been the specific intervention combined with psychotherapy compared to standard of care. Because psilocybin cannot be separated from therapy, it should not be

treated as a single treatment modality compared with the standard of care. A study published by John Hopkins in 2020 demonstrated effectiveness with two psilocybin sessions (session 1: 20 mg/70 kg; session 2: 30 mg/70 kg) in the context of supportive psychotherapy (approximately 11 hours). Participants were randomized to begin treatment immediately or after an 8-week delay [4]. There has also been some potential with microdosing psilocybin. Most studies conducted are self-reports and not conducted as a part of a clinical trial [5]. Due to the unique nature of psilocybin, microdosing may be effective for depression. However, duration, dose, frequency, and efficacy for depression treatment have not been established or studied. A 1 mg dose, as utilized in this study, may not be effective in treating depression, but with so much unknown about the exact small dose, it is a potential confounding contribution. This study does well to demonstrate an effective model for future studies to expand on but does not take into account the potential range of treatments that may be beneficial. Once established studies have been done to determine efficacy, if any, of either microdosing or following a two-dose regimen or higher milligrams, then a head-to-head with the standard of treatment may demonstrate more accurate results [7]. It may be possible that psilocybin is a more effective and appropriate regimen for treatment-resistant depression [4].

Interestingly, there was more alcohol use reported in the escitalopram group than in the psilocybin group. While this was not clinically or statistically relevant, it does demonstrate an intriguing correlation for further study. A proof of concept study demonstrated some efficacy for psilocybin for alcohol dependence [6]. However, the proof of concept was the self-reported intensity of psilocybin effects with a significant association for efficacy in the treatment of alcohol dependence. Psilocybin effectiveness for alcohol dependence requires further study before any significant conclusions can be drawn.

This study did excel in being an exemplary example of the kind of studies needed for psychedelics and the challenges in studying psychedelics. Because a standard regimen of care has not yet been established or proven to be effective, it is difficult to interpret these results against an antidepressant standard of care that has been well established and studied [2]. This study is the first study to compare psilocybin with an antidepressant directly. Whether psilocybin can be demonstrated in future studies to be more effective or as effective as standard of care, this study succeeds in marking a clear path to follow in the study of psychedelics.

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