ORIGINAL ARTICLE

Trial of Psilocybin versus Escitalopram for Depression

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ABSTRACT

BACKGROUND

Psilocybin may have antidepressant properties, but direct comparisons between psilocybin and established treatments for depression are lacking.

METHODS

In a phase 2, double-blind, randomized, controlled trial involving patients with long-standing, moderate-to-severe major depressive disorder, we compared psilocybin with escitalopram, a selective serotonin-reuptake inhibitor, over a 6-week period. Patients were assigned in a 1:1 ratio to receive two separate doses of 25 mg of psilocybin 3 weeks apart plus 6 weeks of daily placebo (psilocybin group) or two separate doses of 1 mg of psilocybin 3 weeks apart plus 6 weeks of daily oral escitalopram (escitalopram group); all the patients received psychological support. The primary outcome was the change from baseline in the score on the 16-item Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR-16; scores range from 0 to 27, with higher scores indicating greater depression) at week 6. There were 16 secondary outcomes, including QIDS-SR-16 response (defined as a reduction in score of >50%) and QIDS-SR-16 remission (defined as a score of ≤5) at week 6.

RESULTS

A total of 59 patients were enrolled; 30 were assigned to the psilocybin group and 29 to the escitalopram group. The mean scores on the QIDS-SR-16 at baseline were 14.5 in the psilocybin group and 16.4 in the escitalopram group. The mean (±SE) changes in the scores from baseline to week 6 were −8.0±1.0 points in the psilocybin group and −6.0±1.0 in the escitalopram group, for a between-group difference of 2.0 points (95% confidence interval [CI], −5.0 to 0.9) (P=0.17). A QIDS-SR-16 response occurred in 70% of the patients in the psilocybin group and in 48% of those in the escitalopram group, for a between-group difference of 22 percentage points (95% CI, −3 to 48); QIDS-SR-16 remission occurred in 57% and 28%, respectively, for a between-group difference of 28 percentage points (95% CI, 2 to 54). Other secondary outcomes generally favored psilocybin over escitalopram, but the analyses were not corrected for multiple comparisons. The incidence of adverse events was similar in the trial groups.

CONCLUSIONS

On the basis of the change in depression scores on the QIDS-SR-16 at week 6, this trial did not show a significant difference in antidepressant effects between psilocybin and escitalopram in a selected group of patients. Secondary outcomes generally favored psilocybin over escitalopram, but the analyses of these outcomes lacked correction for multiple comparisons. Larger and longer trials are required to compare psilocybin with established antidepressants. (Funded by the Alexander Mosley Charitable Trust and Imperial College London's Centre for Psychedelic Research; ClinicalTrials.gov number, NCT03429075.)

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Major depressive disorder affects approximately 10% of the general population in the United Kingdom, impairs patients' lives, and is costly to society.[1] Selective serotonin-reuptake inhibitors are first-line treatments for major depressive disorder; however, these drugs take several weeks to work and, in some patients, do not induce a response.[2] Escitalopram, a selective serotonin-reuptake inhibitor, is representative of the currently used antidepressants in terms of safety and efficacy.[2,3]

The psychedelic compound psilocybin is the phosphorylated ester of its metabolite, psilocin (4-OH-N,N-dimethyltryptamine). Psilocybin and psilocin occur naturally in the psychoactive psilocybe genus of mushrooms. As with other traditional psychedelic substances,[4,5] the main effects of psilocin occur through serotonin 5-hydroxytryptamine type 2A (5-HT_{2A}) receptor agonism, which is part of a pathway implicated in depression.[4-6] Psilocybin showed promise as an adjunct to psychotherapy for mood disorders and addiction in the mid-20th century.[7,8]

One open-label trial[9] and four randomized, controlled clinical trials[10-13] of psilocybin for depression and anxiety have been conducted.[5,9-13] Reductions in depressive symptoms after the administration of one or two doses of psilocybin were observed in trials across several patient populations,[9-14] including a small open-label trial involving patients with treatment-resistant depression,[9,14] the results of which informed the current trial. We performed a phase 2, double-blind, randomized, controlled trial involving patients with long-standing, moderate-to-severe major depressive disorder to compare psilocybin with escitalopram over a 6-week period.

Methods

Trial Oversight

A Schedule 1 drug license from the U.K. Home Office was obtained by the investigators, and the trial was approved by the Brent Research Ethics Committee, the U.K. Medicines and Healthcare Products Regulatory Agency, the Health Research Authority, the Imperial College London Joint Research Compliance and General Data Protection Regulation Offices, and the risk assessment and trial management review board at the trial site (the National Institute for Health Research [NIHR] Imperial Clinical Research Facility [CRF]). Psilocybin was provided by COMPASS Pathways, and escitalopram and placebo were provided by the Pharmacy Manufacturing Unit at Guy's and St. Thomas's Hospital.

This was an investigator-initiated, university-sponsored trial. All medicinal products under investigation were stored and dispensed by Invicro. Trial visits occurred at the NIHR CRF from January 2019 through March 2020. The first author designed the trial and wrote the first draft of the manuscript with assistance from the second author. The second through seventh authors performed the trial and collected the data, and the eighth author analyzed the data. Clinical oversight of the trial was provided by the third, penultimate, and last authors, and the overall trial was overseen by the last author. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol (available with the full text of this article at NEJM.org). There was no industry involvement in the collection or analysis of the data, and no agreements were in place between the authors and any commercial entity.

Patients

Men and women between the ages of 18 and 80 years were recruited formally through trial networks, informally through social media, and through other sources, which directed patients to a recruitment website. The main exclusion criteria were an immediate family or personal history of psychosis, medically significant health conditions that make a person unsuitable to participate in the trial (as assessed by a physician), a history of serious suicide attempts, a positive pregnancy test, contraindications to taking selective serotonin-reuptake inhibitors or undergoing magnetic resonance imaging (MRI), previous use of escitalopram (although previous use of psilocybin was allowed), or suspected or known presence of a preexisting psychiatric condition (e.g., borderline personality disorder) that could jeopardize rapport between the patient and their two mental health caregivers within the trial. Additional details about the trial exclusion criteria are provided in the protocol.

Information about the trial, including inclusion and exclusion criteria, was made available online at the Centre for Psychedelic Research website (www.imperial.ac.uk/psychedelic-research-centre), the ClinicalTrials.gov website, the MQ mental health research recruitment platform (www.mqmentalhealth.org/home/), and the ISRCTN

Registry website. Volunteers initiated contact by emailing the recruitment coordinator after hearing about the trial. Most of the recruited patients referred themselves. Candidates were sent a patient information sheet and invited to a telephone screening. Assessments with the 17-item Hamilton Depression Scale (HAM-D-17) were performed by means of a video call; a score of at least 17 (indicating moderate-to-severe major depressive disorder) on a scale that ranges from 0 to 52, with higher scores indicating greater depression, was required for trial enrollment. Confirmation of a diagnosis of depression and medical history were obtained from the patient's general physician. Eligible patients then underwent face-to-face physical and mental health assessments with a trial psychiatrist, which was followed by their first psychological support session (see the protocol). The patients discontinued any use of a psychiatric medication before starting the trial, with full discontinuation occurring at least 2 weeks before starting a trial medication; any use of psychotherapy was stopped at least 3 weeks before starting a trial medication.

After the telephone screening, each patient was assigned to two supervising mental health professionals. The role of these mental health professionals was to build a therapeutic alliance with the patient before, during, and after each day of dosing. (Additional details are provided in Section S2.8 of the Supplementary Appendix, available at NEJM.org.) One of the pair was a clinical psychologist, psychotherapist, or psychiatrist, and the other could be an equivalent grade clinician or trainee. The mental health professionals were present for all trial visits. Baseline assessments were completed 7 to 10 days before trial visit 1.

TRIAL DESIGN

Randomization (performed with the use of a random-number generator) was implemented by staff members who were not part of the research team. (Details regarding the randomization process are provided in Section S2.6.) All the patients provided written informed consent and, after screening, were required to attend six visits over a 6-week trial period. Procedures for the ingestion of psychotherapeutic agents and size- and color-matched placebo capsules were consistent between the trial groups.

At visit 1 (baseline), all the patients underwent functional MRI, completed a battery of cognitive and affective processing tasks (data not yet analyzed), and attended a preparatory therapeutic session. At visit 2, which occurred 1 day after visit 1, the patients in the psilocybin group received 25 mg of psilocybin, and those in the escitalopram group received 1 mg of psilocybin, which was presumed to have negligible activity (dosing-day 1). To standardize expectations, all the patients were informed that they would receive psilocybin, but the dose was not disclosed to them. The medications and placebos were prepackaged with nondisclosing labels, and all the investigators and medication administering staff were unaware of the trial-group assignments. The dosing days for each patient were supervised by the two mental health professionals who had been assigned to the patient. Supervision consisted of caring for the physical and psychological well-being of the patient and responding to signs of patient discomfort during and immediately after the administration of a trial medication.[15] (Additional details regarding psychological support are provided in Section S2.8.) A trial psychiatrist assessed eligibility for discharge when the functional status of a patient had returned to the baseline level.

Before the patients left the CRF after visit 2, they received a screw-top bottle of capsules and were instructed to take one capsule each morning until their next scheduled day of psilocybin dosing. The capsules contained either microcrystalline cellulose (placebo), which were given to the patients who had received the 25-mg dose of psilocybin on dosing-day 1, or 10 mg of escitalopram, which were given to the patients who had received the 1-mg dose of psilocybin on dosing-day 1. Visit 3 occurred 1 day after dosing-day 1 and included a psychological debriefing. An additional debriefing by telephone or video call occurred 1 week later.

At visit 4, which occurred 3 weeks after dosing-day 1, the patients received their second dose of psilocybin or placebo (dosing-day 2), and at visit 5 (the next day), a psychological integration session involving open, attentive listening was held. After dosing-day 2, the patients were asked to take two capsules each morning (either placebo in the psilocybin group or an increased dose of 20 mg of escitalopram in the escitalopram group) for the next 3 weeks.

Three weeks after visit 5, the patients returned

for their final trial visit (visit 6) for the assessment of the primary outcome. The structure of this visit was similar to that of visit 1 and involved the performance of functional MRI (6 weeks after the first), cognitive and affective processing tasks, final clinician-rated assessments, and psychological debriefing. After these assessments, the patient and the trial staff were informed of the trial-group assignment, and a trial psychiatrist discussed future treatment options. In the escitalopram group, discontinuation of the trial drug was managed by the patients and their general physicians. After week 6, the patients were followed for 6 months by the investigators, but these data have not yet been fully collected. The initial trial design included a placebo group that was to receive 1 mg of psilocybin and placebo, but this group was not included in the final protocol because it was determined that a trial involving three groups would be too complex and expensive to conduct and power adequately, given the resources that were available at the time. The data obtained from an imaging group in the trial, in which functional MRI was used to predict responses to the trial drugs, have not been analyzed.

OUTCOMES

The primary clinical outcome was the change from baseline in the score on the 16-item Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR-16; scores range from 0 to 27, with higher scores indicating greater depression) at 6 weeks. Secondary outcomes included response at 6 weeks according to the QIDS-SR-16 (defined as a decrease in score of ≥50% from baseline); remission at 6 weeks according to the QIDS-SR-16 (defined as a score of 0 to 5); change in the score on the 14-item QIDS-SR (QIDS-SR-14) from the day before to the day after dosing-day 1; and the changes from baseline to week 6 in the scores on the Beck Depression Inventory 1A (BDI-1A), the 17-item Hamilton Depression Rating Scale (HAM-D-17), and the Montgomery and Asberg Depression Rating Scale (MADRS). Other secondary outcomes were the changes from baseline to 6 weeks in the scores on the Flourishing Scale (FS), the Spielberger's Trait Anxiety Inventory (STAI), the Brief Experiential Avoidance Questionnaire (BEAQ),[16] the Work and Social Adjustment Scale (WSAS), the Snaith Hamilton Anhedonia Pleasure Scale (SHAPS), the Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS), and the Suicidal Ideation Attributes Scale (SIDAS), as well as the scores at 6 weeks on the Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ), the Laukes Emotional Intensity Scale (LEIS),[17] and the Emotional Breakthrough Inventory,[18] which assessed acute subjective experiences after each dosing day (Fig. S4 and Table S5). An investigator-constructed patient-rated scale (the Post-Treatment Changes Scale [PTCS]) was used as a safety outcome measure for assessing post-treatment side effects and other phenomena that previous work has associated with psychedelic compounds or selective serotonin-reuptake inhibitors (Section S2.11 and Table S2). Additional details of these outcomes are provided in the protocol.

ADVERSE EVENTS

Adverse events were recorded at every visit and telephone call from dosing-day 1 through week 6. Adverse events were assessed by asking "how have you been since your last visit?" or on the basis of events that were observed at the trial site. Additional details of the criteria used for the reporting of adverse events are provided in the protocol. All adverse events that occurred or worsened between dosing-day 1 and week 6 were recorded and coded with the use of the *Medical Dictionary for Regulatory Activities*, version 23.0.

STATISTICAL ANALYSIS

The clinical component of the trial was powered on the basis of data from previous trials[10,14] and on an assumption of equal variance for both trial drugs with respect to the primary outcome and the ability to detect a difference between the groups at a two-sided level of $P<0.05$ with 80% power. This would require 20 patients per trial group, and we proposed recruiting a minimum of 30 patients per group (60 in total for the trial). Additional details are provided in Sections 4.2.1 and 10 of the protocol. All the patients who had undergone randomization were included in an intention-to-treat analysis.

The change from baseline in the score on the QIDS-SR-16 at week 6 (the primary outcome) was compared between the trial groups with the use of repeated-measures analysis of covariance (ANCOVA), with adjustment for baseline scores. Logistic regression, with adjustment for baseline scores, was used to analyze the secondary out-

comes of response and remission according to the QIDS-SR-16, as well as the additional outcomes of response and remission according to the BDI-1A, the HAM-D-17, and the MADRS. The changes from baseline to week 6 in the scores on the HAM-D-17, the QIDS-SR-14, the MADRS, the WEMWBS, the FS, the BEAQ, the WSAS, the SHAPS, the STAI, and the LEIS were analyzed with the use of ANCOVA or repeated-measures ANCOVA, with adjustment for baseline (if possible). The changes from baseline to week 6 in the scores on the BDI-1A and the SIDAS were analyzed with the use of the permutation test stratified according to baseline scores. The score at 6 weeks on the PRSexDQ was analyzed with the use of a Wilcoxon test. The score at 6 weeks on the PTCS was analyzed with the use of the Jonckheere–Terpstra trend test.

The results are presented as means, adjusted for baseline values. There was no imputation for missing data except for the WSAS, for which missing data were imputed with the overall mean calculated from nonmissing data. Because of the absence of a prespecified plan for adjustment of confidence intervals for multiple comparisons of secondary outcomes, P values are not reported and no clinical conclusions can be drawn from these data.

RESULTS

PATIENTS

Approximately 1000 patients underwent screening by telephone (103 of whom also attended a formal screening visit). A total of 891 patients did not meet inclusion criteria (19 of whom had a coexisting psychiatric condition), and 50 declined to participate (Section S2.7). Thus, 59 patients were enrolled and underwent randomization; 30 were assigned to the psilocybin group and 29 to the escitalopram group. Of the 59 patients enrolled, 23 (39%) had completely discontinued a psychiatric medication before entering the trial, and 4 (7%) had discontinued psychotherapy. In the escitalopram group, 5 of 29 patients did not complete the protocol requirements: 4 stopped taking their escitalopram capsules because of adverse events, and 1 missed dosing-day 2 and subsequent visits owing to restrictions related to coronavirus disease 2019 (Covid-19). One patient in the escitalopram group guessed that the capsules contained escitalopram and reduced the dose by half (from 20 mg to 10 mg) because of perceived adverse events; a reduction in the escitalopram dose to 10 mg was permitted in the protocol because it reflects clinical practice. In the psilocybin group, 3 of 30 patients did not complete all dosing procedures: 2 missed dosing-day 2 and subsequent visits because of Covid-19–related restrictions, and 1 stopped taking daily placebo capsules after guessing their content.

The mean age of the patients enrolled in the trial was 41 years; 20 (34%) were women and most were White. Depression had been present for a mean of 22 years among the patients in the psilocybin group and for a mean of 15 years among those in the escitalopram group; QIDS-SR-16 scores at baseline were 14.5 and 16.4, respectively. There was more alcohol use among the patients in the escitalopram group than in the psilocybin group; other characteristics were similar in the groups (Table 1).

EFFICACY OUTCOMES

The mean (±SE) change from baseline in the score on the QIDS-SR-16 at week 6 (the primary outcome) was −8.0±1.0 in the psilocybin group and −6.0±1.0 in the escitalopram group (difference, −2.0; 95% confidence interval [CI], −5.0 to 0.9; P=0.17), indicating no significant difference between the trial groups (Fig. 1 and Table 2). A per-protocol analysis produced similar results (Table S1).

The results of the secondary-outcome analyses are provided in Figure 1, Table 2, and Figures S3 and S4. A QIDS-SR-16 response at 6 weeks occurred in 21 patients (70%) in the psilocybin group and in 14 patients (48%) in the escitalopram group (difference, 22 percentage points; 95% CI, −3 to 48, indicating no significant difference) (Table 2). QIDS-SR-16 remission at week 6 occurred in 17 patients (57%) in the psilocybin group and in 8 patients (28%) in the escitalopram group (difference, 28.1 percentage points; 95% CI, 2.3 to 53.8) (Table 2). Other secondary measures of depression (changes from baseline to week 6 in the scores on the BDI-1A, HAM-D-17, and MADRS) and the between-group differences in the scores on other scales mostly favored psilocybin over escitalopram, although the confidence intervals for the between-group differences were

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Psilocybin (N=30)	Escitalopram (N=29)
Demographic		
Age (range) — yr	43.3±11.7 (21–64)	39.1±9.7 (22–60)
Female sex — no. (%)	11 (37)	9 (31)
White race — no. (%)†	28 (93)	24 (83)
Employment status — no. (%)		
Employed	21 (70)	21 (72)
Student	2 (7)	3 (10)
Unemployed	7 (23)	5 (17)
University level education — no. (%)	22 (73)	23 (79)
No previous psilocybin use — no. (%)	22 (73)	21 (72)
Weekly alcohol use (range) — g‡	36.8±43.1 (0–160)	67.7±66.6 (0–240)
Discontinued psychiatric medication for trial — no. (%)	11 (37)	12 (41)
Clinical		
Duration of illness (range) — yr	22.1±10.7 (3–44)	15.1±11.0 (2–46)
No. of psychiatric medications previously used (range)	2.2±1.6 (0–6)	1.8±1.5 (0–5)
Previous use of psychotherapy — no. (%)	28 (93)	26 (90)
QIDS-SR-16 score at pretreatment baseline (range)§	14.5±3.9 (7–23)	16.4±4.1 (6–22)
HAM-D-17 score at pretreatment baseline (range)¶	19.2±2.3 (16–23)	18.4±3.4 (11–26)
BDI-1A score at pretreatment baseline (range)‖	29.1±6.8 (16–41)	28.7±7.0 (10–44)

* Plus–minus values are means ±SD. Pretreatment baseline was 7 to 10 days before dosing-day 1.
† Race was reported by the patients.
‡ To convert grams to U.K. units, divide by 8.
§ The scores on the 16-item Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR-16) range from 0 to 27, with higher scores indicating greater depression.
¶ The scores on the 17-item Hamilton Depression Rating Scale (HAM-D-17) range from 0 to 50, with higher scores indicating greater depression. At screening, which was typically a few weeks before pretreatment baseline, all the patients had a score of at least 17 on the HAM-D-17. The depression scores reported in this table are from pretreatment baseline and not screening.
‖ The scores on the Beck Depression Inventory 1A (BDI-1A) range from 0 to 63, with higher scores indicating greater depression.

not adjusted for multiple comparisons (Table 2). Ratings on the Emotional Breakthrough Inventory are provided in Figure S7. With respect to the primary and secondary outcomes, the absolute values that were not adjusted for baseline values (Table S12) were in the same general direction as those in the adjusted analyses. Multiple imputation was performed for two patients with missing baseline values on the WSAS, and the results were similar to those in the main (baseline-adjusted) analysis (Section S13). A post hoc analysis for the imbalanced use of alcohol between the trial groups showed results in the same direction as those in the main analysis (Section S12).

SAFETY

No serious adverse events were observed in either trial group. The percentage of patients reporting adverse events was similar in the two groups: 26 (87%) in the psilocybin group and 24 (83%) in the escitalopram group (Table 3, and Fig. S6). The percentage of patients who had increased anxiety and dry mouth was higher in the escitalopram group than in the psilocybin group. Adverse events in the psilocybin group typically occurred within 24 hours after the dosing day; the most common adverse event was headache. A complete list of the adverse events that occurred in the trial groups is provided in Table S5.

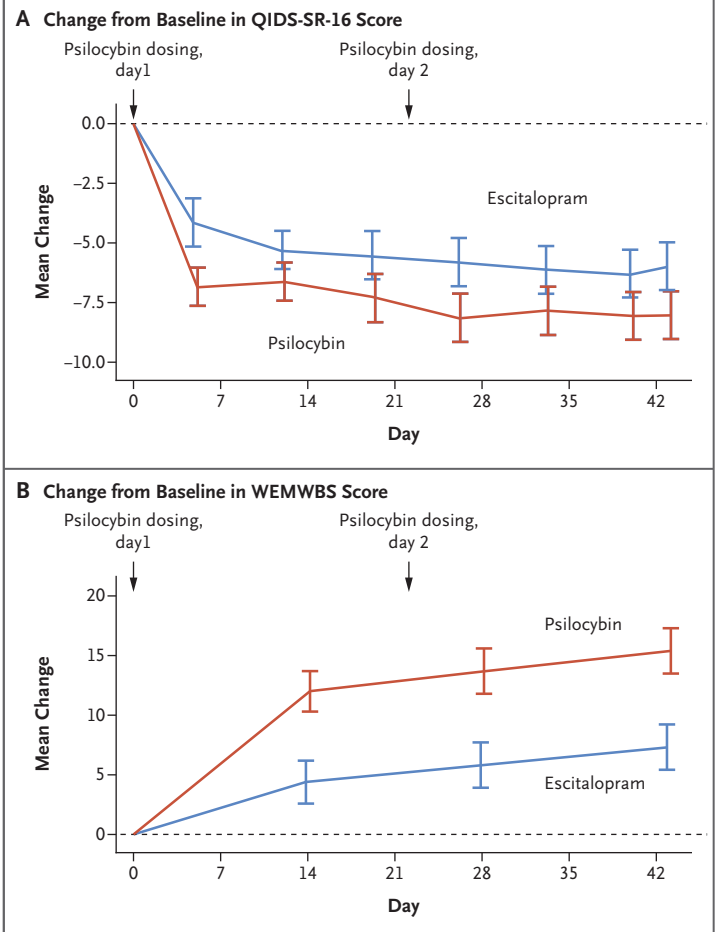

Figure 1. Change in Depression Severity and in Well-Being over 6 Weeks.

Panel A shows the mean change from baseline in the score on the 16-item Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR-16; on which scores range from 0 to 27, with higher scores indicating greater depression). Panel B shows the mean change in the score on the Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS; on which scores range from 14 to 70, with higher scores indicating greater mental well-being). These were the only outcomes for which there were data every week (QIDS-SR-16) or every 2 weeks (WEMWBS) and for which there were prespecified hypotheses (Section S2.1 in the Supplementary Appendix). P values are not shown because there was no correction for multiple comparisons in the analyses of the WEMWBS (a secondary outcome) or of the outcomes at any intermediate time points. I bars indicate standard errors.

When cued to report on specific emotional and side-effect–related phenomena through the PTCS (a description of this scale is provided in Section S2.11), patients in the psilocybin group reported greater perceived improvements in the ability to cry and feel compassion, intense emotion, and pleasure and reported feeling less drowsy than those in the escitalopram group (Table S2). No cases of visual perceptual changes, psychotic symptoms, or dependency-related behaviors were observed or reported in either trial group at 6 weeks.

DISCUSSION

In this 6-week randomized trial comparing psilocybin with escitalopram in patients with longstanding, mild-to-severe depression, the change in depression scores on the QIDS-SR-16 at week 6 (the primary outcome) did not differ significantly between the trial groups. Secondary outcomes generally favored psilocybin over escitalopram; however, the confidence intervals for the between-group differences were not adjusted for multiple comparisons, and no conclusions can be drawn from these data. In both trial groups, the scores on the depression scales at week 6 were numerically lower than the baseline scores, but the absence of a placebo group in the trial limits conclusions about the effect of either agent alone. The incidence of adverse events was similar in the trial groups, and no serious adverse events occurred. The percentages of patients who had anxiety, dry mouth, sexual dysfunction, or reduced emotional responsiveness were higher in the escitalopram group than in the psilocybin group.[19] Four patients in the escitalopram group stopped taking their daily capsules entirely, and 1 patient halved the dose because of perceived adverse events. No patient in the psilocybin group requested to cancel the second psilocybin dose. Three patients were unable to attend sessions to receive the second psilocybin dose owing to the Covid-19 lockdown (2 patients in the psilocybin group and 1 in the escitalopram group). The most common adverse event in the psilocybin group was transient headache reported within 24 hours after the day of psilocybin dosing. The incidence of headache was similar to those reported in previous studies of psilocybin.[9,10,13,20]

Acute subjective effects of psilocybin relating to the psychedelic experience were not included as adverse events in our trial, because previous studies have suggested that they may have a mediating influence on positive outcomes.[21] The altered quality of conscious experience typically induced by a 25-mg dose of psilocybin adds complexity to this treatment model, because it requires that psychological support be provided to patients during and after treatment sessions.[15] This requirement informed this trial's screening

Table 2. Primary and Secondary Outcomes.*

Outcome	Psilocybin (N=30)	Escitalopram (N=29)	Difference (95% CI)†
Primary			
Change in QIDS-SR-16 score at 6 wk — points	−8.0±1.0	−6.0±1.0	−2.0 (−5.0 to 0.9)‡
Secondary			
Depression-related outcomes			
Change in QIDS-SR-14 score from the day before to the day after dosing-day 1 — points	−5.7±0.9	−2.8±0.9	−3.0 (−5.5 to −0.4)
QIDS-SR-16 response at 6 wk — no. (%)§	21 (70)	14 (48)	22 (−3 to 48)
QIDS-SR-16 remission at 6 wk — no. (%)¶	17 (57)	8 (28)	28 (2 to 54)
Change in HAM-D-17 score at 6 wk — points	−10.5±1.0	−5.1±1.0	−5.3 (−8.2 to −2.4)
Change in MADRS score at 6 wk — points	−14.4±1.7	−7.2±1.7	−7.2 (−12.1 to −2.4)
Change in BDI-1A score at 6 wk — points	−18.4 (−22.6 to −13.8)	−10.8 (−14.3 to −7.3)	−7.6 (−13.3 to −1.8)
Change in WEMWBS score at 6 wk — points	15.4±1.9	7.3±1.9	8.1 (2.6 to 13.5)
Change in FS score at 6 wk — points	14.4±1.7	9.0±1.7	5.4 (0.5 to 10.3)
Change in STAI score at 6 wk — points	−17.6±2.2	−8.5±2.2	−9.0 (−15.2 to −2.8)
Change in BEAQ score at 6 wk — points	−10.5±2.2	−1.0±2.3	−9.5 (−15.9 to −3.1)
Change in WSAS score at 6 wk — points	−9.7±1.7	−3.8±1.7	−5.8 (−10.7 to −1.0)
Change in SHAPS score at 6 wk — points	−4.7±0.6	−2.5±0.6	−2.2 (−3.8 to −0.6)
Change in SIDAS score at 6 wk — points	−2.0 (−4.3 to 0.0)	−0.8 (−3.4 to 2.0)	−1.3 (−6.5 to −0.3)
PRSexDQ score at 6 wk	0 (0 to 0)	3 (0 to 7)	−2 (−4 to 0)
LEIS score at 6 wk	4.1±0.9	−2.2±1.0	6.3 (3.6 to 9.0)

* Changes in scores represent the mean change from baseline and are reported as mean ±SE, except for the changes in the BDI-1A and Suicidal Ideation Attributes Scale (SIDAS) scores, which are reported as mean (95% confidence interval). The PRSexDQ score at 6 weeks is reported as mean ±SE, and the LEIS score at 6 weeks is reported as mean (95% confidence interval). Scores range from 0 to 60 on the Montgomery and Asberg Depression Rating Scale (MADRS), from 20 to 80 on the Spielberger's Trait Anxiety Inventory (STAI), from 15 to 90 on the Brief Experiential Avoidance Questionnaire (BEAQ), from 0 to 40 on the Work and Social Adjustment Scale (WSAS), from 0 to 14 on the Snaith Hamilton Anhedonia Pleasure Scale (SHAPS), and from 0 to 50 on the SIDAS; greater reductions from baseline on all of these scales indicate greater reductions in symptom severity or impairment. Scores on the Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ) range from 0 to 15, with higher scores indicating greater dysfunction. Scores ranges from 14 to 70 on the Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS) and from 8 to 56 on the Flourishing Scale (FS) range; greater increases from baseline on these scales indicate greater improvements. Scores on the Laukes Emotional Intensity Scale (LEIS) range from −34 to +34, with positive scores indicating an increased intensity of emotional responsiveness and negative scores a reduced intensity of emotional responsiveness. The analysis of each efficacy outcome was generated from statistical models, as described in the statistical analysis plan, available in the protocol. All values shown were adjusted for the baseline value. Unadjusted values are provided in Table S12 in the Supplementary Appendix.

† The confidence intervals for the secondary outcomes have not been corrected for multiple comparisons, and no clinical conclusions can be drawn from these data.

‡ P=0.17.

§ A QIDS-SR-16 response was defined as a reduction in score of more than 50% from baseline. The difference between the groups is expressed as percentage points.

¶ QIDS-SR-16 remission was defined as a score of 5 or lower at week 6. The difference between the groups is expressed as percentage points.

criteria that excluded patients with preexisting psychiatric conditions believed to be incompatible with the limited psychological support that could be made available within the trial. This exclusion criterion may have biased the trial sample toward patients who could receive psilocybin without unacceptable side effects. However, psychological support was provided for both groups in this trial, and it is possible that the adjunctive psychological support improved outcomes among those in the escitalopram group.

A limitation of the trial is the brief duration of escitalopram treatment, because this drug has a delayed therapeutic action on depression.[22] Had the course of escitalopram been extended, it is possible that better efficacy would have been observed among the patients in the escitalopram group. Patients who received the 25-mg dose of

Table 3. Adverse Events Reported during the 6-Week Trial Period and on Dosing-Day 1.*

Event	6-Wk Trial Period		Dosing-Day 1	
	Psilocybin (N=30)	Escitalopram (N=29)	Psilocybin (N=30)	Escitalopram (N=29)
	number of patients (percent)			
Any adverse event	26 (87)	24 (83)	15 (50)	8 (28)
Serious adverse event	0	0	0	0
Related adverse event†	22 (73)	23 (79)	15 (50)	6 (21)
Adverse event reported in ≥3 patients during the full trial period				
Headache	20 (67)	15 (52)	13 (43)	5 (17)
Nausea	8 (27)	9 (31)	4 (13)	0
Fatigue	2 (7)	7 (24)	0	0
Anxiety	0	4 (14)	0	0
Dry mouth	0	4 (14)	0	0
Migraine	3 (10)	1 (3)	0	0
Palpitations	1 (3)	3 (10)	0	0
Sleep disorder	1 (3)	3 (10)	0	0
Diarrhea	1 (3)	2 (7)	0	0
Feeling abnormal	0	3 (10)	0	0
Feeling jittery	2 (7)	1 (3)	0	0
Vomiting	2 (7)	1 (3)	0	0

* These were the most prevalent adverse events that were reported during the trial.
† Whether an adverse event was related to the therapeutic intervention was determined by the study clinician through dialogue with each patient. Events deemed "probably" or "definitely" related were counted.

psilocybin rated the intensity of acute subjective effects higher than patients who received the 1-mg dose (Fig. S7). We did not assess the effectiveness of blinding within each treatment group. It was assumed that the active comparator design would mitigate expectancy bias, but we cannot be confident that guessing of the trial-group assignment or biased expectations in favor of psilocybin did not influence the results. Although efforts were made to recruit patients by external referrals, most of the recruited volunteers referred themselves, and many expressed a preference for psilocybin over escitalopram. This created a selected trial population and limits generalization of the results.

The patients in the trial were not from diverse ethnic or socioeconomic backgrounds. Strategies to improve recruitment of more diverse study populations are needed in studies of psilocybin for depression. Also, average symptom severity scores at baseline were in the range for moderate depression, thus limiting extrapolations to patients with severe depressive symptoms or treatment-resistant depression.

Psychedelic agents have been shown to enhance suggestibility,[23] and their psychological effects are assumed to be context-dependent.[24,25] In other words, the content and subjective quality of the psychedelic experience is influenced by a person's memories, perceptions, and degree to which the environment is supportive at the time of administration of the agent. In a study in which various psychedelic compounds were administered to rats, the compounds were shown to increase dendritic arbor complexity, promote dendritic spine growth, and stimulate synapse formation in the rat cortex, mediated by serotonin 5-HT_{2A} receptor agonism,[26] all of which are forms of neuronal plasticity that may be related to the principle that responses to psychedelics are especially dependent on contextual conditions.[24,25]

This trial comparing psilocybin with escitalopram in a selected group of patients showed that

the change in scores for depression at 6 weeks did not differ significantly between the trial groups. Secondary outcomes mostly favored psilocybin over escitalopram, but the confidence intervals for the between-group differences were not adjusted for multiple comparisons. Larger and longer trials are needed to compare psilocybin with established treatments for depression.

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