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Effect of psilocybin versus escitalopram on depression symptom severity in patients with moderate-to-severe major depressive disorder: observational 6-month follow-up of a phase 2, double-blind, randomised, controlled trial

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Summary

Background Psilocybin therapy (PT) produces rapid and persistent antidepressant effects in major depressive disorder (MDD). However, the long-term effects of PT have never been compared with gold-standard treatments for MDD such as pharmacotherapy or psychotherapy alone or in combination.

Methods This is a 6-month follow-up study of a phase 2, double-blind, randomised, controlled trial involving patients with moderate-to-severe MDD. Participants were recruited from a hospital in the UK. Male or female patients with major depressive disorder (DSM-IV), moderate to severe depression (HAM-D ≥17), no MRI or SSRI contraindications, confirmed diagnosis by a GP or mental healthcare professional, aged 18–80, and competent in English were eligible. Patients were randomly assigned (1:1) to receive either two 25 mg doses of the psychedelic drug psilocybin administered orally combined with psychological support ('psilocybin therapy' or PT) and book-ended by further support or a 6-week course of the selective serotonin reuptake inhibitor (SSRI) escitalopram (administered daily at 10 mg for three weeks and 20 mg for the subsequent three weeks) plus matched psychological support ('escitalopram treatment' or ET). The primary outcome measure was change from baseline in the score on the 16-item Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR-16) at week 6, which has been reported previously. Herein, we present results at the 6-month follow-up time point. Measures of social functioning, connectedness, and meaning in life constituted the study's secondary outcomes during follow-up. Safety in the follow-up period was not assessed. This trial is registered at ClinicalTrials.gov, NCT03429075.

Findings Between January 15th, 2019 and March 20th, 2020, 59 patients were enrolled and 30 (11 females [37%] and 19 males [63%]) were assigned to the psilocybin group and 29 (9 females [31%] and 20 males [69%]) to the escitalopram group. 25 participants in the PT group and 21 in the ET group completed the 6-month follow-up. At the 6-month follow-up, both PT and ET conditions yielded sustained improvements in depressive symptom severity. The mean between-condition difference in QIDS-SR-16 scores at 6-months was 1.51 (95% CI: −1.35, 4.38; p = 0.311). Secondary outcomes demonstrated that PT had greater mean between-condition differences in functioning (WSAS: −7.46; 95% CI: −12.4, −2.47; p < 0.001), psychological connectedness (WCS: 11.02; 95% CI: 1.25, 20.83; p = 0.033), and meaning in life (MLQ: 4.86; 95% CI: 0.67, 9.05; p = 0.021) compared to ET.

Interpretation Six-week intensive treatments with either psilocybin or escitalopram (with psychological support) for MDD were associated with long-term improvements in depressive symptom severity. The greater degree of improvement in the PT arm at follow-up on psychosocial functioning, meaning in life, and psychological connectedness suggests warrant future research. However, these results are descriptive and should be interpreted with caution. Key limitations of the study include its suboptimal power to detect small but meaningful differences between treatments, missing data, the potential use of additional interventions during the follow-up period, and

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reliance on self-reported treatment assessments. These factors may affect the interpretation of the study findings and should be considered when evaluating the results.

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Keywords: Psilocybin; SSRIs; Depression; Follow-up

Research in context

Evidence before this study

We searched PubMed for publications in English using the search terms "psilocybin," "depression," and "randomised controlled trial" and identified 9 studies published before June 11th, 2024. Of these, 2 studies focused on treatment-resistant depression, 3 on major depressive disorder, and 4 on depression and anxiety associated with end-of-life distress or cancer diagnoses. Prior research has shown the potential of psilocybin therapy for sustained antidepressant effects, but previous studies lacked robust comparison with gold-standard treatments and long-term follow-up. A prior study comparing two 25 mg doses of psilocybin separated by 3 weeks plus 6 weeks of daily placebo (psilocybin therapy; PT) and two separate doses of 1 mg of psilocybin 3 weeks apart plus 6 weeks of daily oral escitalopram (escitalopram treatment; ET), a widely used SSRI, with the same amount of psychological support found PT as effective as ET in reducing depressive symptoms but significantly better in well-being, anhedonia, emotional acceptance, suicidality, and work and social functioning. However, comprehensive comparative data on long-term outcomes remain limited.

Added value of this study

This study represents a preliminary attempt in understanding the long-term therapeutic profiles of PT and ET for depression, providing data from a six-month follow-up period. It is the first to compare the long-term antidepressant effects of these two treatments as well as global mental health measures such as work and social functioning, connectedness, and meaning in life. The findings suggest that while both PT and ET may have comparable long-term effects on depressive symptomatology, PT may be associated with greater improvements in overall mental health.

Implications of all the available evidence

There are several relevant implications from these findings. Clinically, they suggest that PT and ET could be effective over a six-month period for treating depression, with PT possibly providing additional benefits including enhanced functioning, connectedness, and meaning in life. These results could inform clinical guidelines to consider the broader aspects of mental health recovery, rather than focusing solely on symptom remission. However, important study limitations must be considered. The study was not optimally powered to detect small but meaningful differences between treatments, there was missing data, and the potential use of additional interventions during the follow-up period could have influenced the results. Additionally, the reliance on self-reported treatment assessments introduces subjectivity. A significant proportion of patients sought additional treatment post-trial, signalling a need for careful consideration of treatment strategies after the initial intervention. These limitations suggest that the results should be interpreted with caution. The findings highlight the need for future research to investigate the duration and factors affecting the longevity of PT's benefits, as well as the neuroplastic and learning mechanisms that may contribute to the sustained effects of both PT and ET. Finally, the study hopes to inspire a nuanced understanding of therapeutic efficacy by emphasizing the importance of functional recovery and quality of life improvements.

Introduction

This study investigated the sustained effects of Psilocybin Therapy (PT) versus Escitalopram Treatment (ET) in Major Depressive Disorder (MDD) over a six-month follow-up period. MDD, the first or second leading cause of disability globally,[1,2] is characterized by marked changes in mood, motivation, pleasure and cognition.[3] Even when an episode of MDD has been successfully treated, the risks of relapse or recurrence are high—roughly one in three patients achieving remission will relapse within one year.[4] A key consideration of any treatment of MDD, therefore, is its capacity to produce sustained antidepressant response or remission.

In the original 6-week trial,[5] 59 patients were randomised to one of two active treatment conditions: PT or ET. The PT condition consisted of two high-dose (25 mg) treatment sessions with the serotonergic psychedelic psilocybin, administered with support from two study therapists (at least one being a qualified mental health professional), in addition to preparatory and integrative psychotherapy and daily placebo capsules. The ET condition consisted of daily doses of the

selective serotonin reuptake inhibitor (SSRI) escitalopram—10 mg for three weeks followed by 20 mg for a further three weeks—as well as equivalent psychological support including dosing sessions with placebo-like doses of psilocybin (1 mg). This ET condition thus approximated a gold-standard treatment for depression of concomitant evidence-based pharmacotherapy plus psychotherapy, albeit at a somewhat briefer and more intensive treatment rhythm. That is, typical antidepressant drug effects are usually seen after 4–6 weeks of treatment, and most (non-private) psychotherapies for depression, such as cognitive behavioural therapy, are administered at a frequency of 1 h per week.[6]

Conventional antidepressants such as the SSRI used in this trial (i.e., escitalopram) and psychotherapy are generally considered effective treatments for depression, and their combination produces greater and more persistent benefits, as well as greater tolerability, than either intervention alone.[7,8] Nevertheless, even gold-standard treatments have limitations. SSRI pharmacotherapy typically involves long-term daily dosing even after positive responses to mitigate risks of depression relapse or recurrence.[9] This is a particularly important drawback given that SSRIs are associated with adverse side-effects like sexual dysfunction, weight gain, fatigue, and emotional blunting,[10,11] and non-adherence rates up to 50%.[12] Psychotherapy is associated with fewer side-effects and more persistent benefits,[13] but also relatively high treatment drop-rates of approximately 17.5% in depression.[14,15] Further, both SSRIs and psychotherapy are relatively slow-acting, often requiring weeks or months to achieve clinical response.[15,16] There is thus a clear need for new treatment options for depression.

PT is being increasingly investigated as a rapid-acting treatment for MDD and treatment-resistant depression (TRD). Phase 1,[17] Phase 2A[5,18] and Phase 2B[19,20] trials have demonstrated that one or two doses of psilocybin, administered with psychological support, can produce almost immediate reductions in depressive symptoms that may persist for months. These are primarily attributed to serotonin 2A receptor signaling in the brain[21,22] altering neural information processing that, in appropriate contexts, can lead to experiences like emotional catharsis,[23] ego dissolution,[24] cognitive reappraisal[25] and psychological insight.[26]

In our original study, PT and ET induced comparable reductions in depressive symptoms on the primary outcome of self-reported depression at 6-weeks.[5] However, the PT group exhibited signs of superior response on certain domains of depression, including mood and anhedonia,[27] as well as on all secondary outcomes, including measures of work and social functioning, well-being, rumination, and suppression of negative emotions.[5,28] PT also appeared positively affect several sexual functioning domains, while those on ET reported declines.[29]

The purpose of this study was to investigate the antidepressant response and evolution of all acquired secondary measures up to six months of naturalistic follow-up after the trial's primary endpoint at 6 weeks, including the differential response between PT and ET conditions. Such questions are of great relevance for evaluating the viability of psilocybin-assisted therapy as an emerging treatment of depression.

Methods

Study design and participants

This is a 6-month follow up study of a double-blind randomised control trial (RCT) comparing psilocybin (Compass Pathways' investigational, proprietary, synthetic, psilocybin formulation COMP360) to the SSRI escitalopram in 59 participants with MDD.[5] All the patients provided written informed consent and after discontinuing any pre-trial antidepressants, enrollees received two oral doses of psilocybin (1 mg or 25 mg) with accompaniment from two experienced therapists for ~6–8 h, separated by 3 weeks, as well as daily pills (escitalopram 10–20 mg or placebo capsules). Thirty patients were randomised to PT and 29 to ET. Participants were required to be 18–85 years, physically healthy, be diagnosed with unipolar MDD by a physician, and be willing to stop any antidepressants and/or psychological therapies before the trial's baseline timepoint. Detailed eligibility requirements can be found in Carhart-Harris et al.[5]

During the treatment period, each participant worked with study therapists and psychiatrists employing the ACE (Accept, Connect and Embody) model as a therapeutic framework. The model is based on six psychological flexibility processes (Experiential Acceptance, Present Moment Focus, Cognitive Defusion, Self as Context, Values, Committed Action) that are the core of Acceptance and Commitment Therapy.[30] On dosing days, the therapists accompanied them from the moment they ingested the drug until the day's end. Before and after dosing days, participants underwent psychological preparation and integration, respectively. Taking into account screening, preparation, dosing, and integration, participants in each condition received approximately 20 h of in-person therapeutic support during the trial, as well as up to six further integration calls over Skype or by telephone. There was no difference between conditions in the adoption of these optional calls.

Follow-up assessments took place via online questionnaires at monthly intervals for six months after the trial's end, during which time patients received no additional treatment from the study team and had no restrictions on their psychiatric care. Follow-up assessments were delivered to participants via email via the online survey platform Alchemer. Each questionnaire consisted of a series of validated scales arranged sequentially, designed to be self-explanatory and user-friendly. The participants were asked to complete the questionnaires within one week of receipt to maintain

consistency in response timing across the study cohort. The questionnaire interface was accessible on a variety of electronic devices, ensuring that participants could complete the forms at their convenience. Upon completion, participants submitted their responses directly through the online system. Of note, patients in the ET condition were neither required to stop nor to continue escitalopram. Please see[5] and[30] for further details of the original study and treatment.

All procedures involving human patients were approved by the Brent Research Ethics Committee, the U.K. MHRA, HRA and Imperial College London JRO and GDPR, as well as the risk assessment and trial management review board at the site (NIHR, Imperial CRF). ClinicalTrials.gov number, NCT03429075, Approval Number 17HH3790.

Procedures

Participants were randomly assigned in a 1:1 ratio to receive either PT) or ET. Patients in the PT group received two doses of 25 mg of psilocybin administered orally at visit 2 and visit 4, with psychological support on dosing days and subsequent integration sessions. The ET group received 1 mg of psilocybin at visit 2, followed by daily doses of 10 mg of escitalopram for the first three weeks, increased to 20 mg for the next three weeks. The second dose of 1 mg of psilocybin was given at visit 4, with placebo capsules on other days. Assessments included functional MRI, cognitive and affective processing tasks, and clinician-rated evaluations at baseline and week 6. Psychological support was provided at each visit. Follow-up continued for 6 months to monitor long-term outcomes. All outcome measures reported were pre-specified in the study protocol. Detailed information about protocol violations can be found in the original trial publication. Psilocybin was provided by COMPASS Pathways, and escitalopram and placebo by the Pharmacy Manufacturing Unit at Guy's and St. Thomas's Hospital.

Randomization and masking

In the original study, randomization was performed by Members of Imperial College London who were not part of the research team, using a random number generator. No stratification variables were included for randomisation, however there were no differences in baseline demographics between the two groups. Details on this can be found in.[5]

Outcomes

Depressive symptoms were assessed primarily with the 16-item Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR-16;[31]). The QIDS-SR-16 served as the primary trial outcome measure and the only depression severity measure employed for long-term follow up assessment. Work and social functioning was assessed with the Work and Social Adjustment Scale (WSAS;[32]). Psychological connectedness was assessed with the Watts' Connectedness Scale (WCS;[33]). Flourishing, a scale measuring wellbeing with a focus on competence and self-respect, was assessed with the Flourishing Scale (FS;[34]). Meaning in life was assessed with the Meaning in Life Questionnaire (MLQ;[35]). Depressive symptoms were assessed monthly using the QIDS-SR-16 alone, while the remaining measures were assessed every three months. All scales demonstrated internal consistency ranging from acceptable to very good[36] and were thus analyzed as unitary constructs. For detailed information on subjective measures see Supplementary Materials 1.

At the end of 6-month follow-up, patients were asked to retrospectively report any utilization of psychiatric medications, non-pharmacological treatments, and/or psychedelic drugs since the trial's completion. The questions used to code these three binary variables were as follows: *Do you recall if you had ANY formal mental health treatment between study end (6 weeks) and follow-up (month 6)? And if so, what was it? e.g., antidepressant drugs? Psychotherapy? Did you take psychedelics within this period?*

Statistical analyses

Primary analyses

To assess attrition bias, patients were classified according to the proportion of data completeness for the primary outcome: more than or equal to 85%, less than 85%, or no follow-up timepoints completed. An 85% cut-off point was selected based on evidence that average missing data rates greater than 20% pose significant threats to validity.[37] Of note, this approach reduced the sample size in each group, increasing the risks of Type 2 error and potentially obscuring group differences.

Next, chi-square tests were employed to explore the potential influences on follow-up rates of illness duration, gender, smoking status, education, employment status, QIDS-SR-16 response at 6 weeks, QIDS-SR-16 remission at 6 weeks, and pre-trial antidepressant discontinuation. T-tests were additionally employed to assess differences between completers and non-completers in age and QIDS-SR-16 scores at both baseline and the main trial endpoint. Chi-squared tests were also employed to explore the potential differences in the use of antidepressants, psychedelics and talking therapy between the two study groups in the follow-up period.

Four primary sets of analyses were conducted. Across analyses, the statistical significance threshold was set at $p < 0.05$. However, for the first and second sets of analyses, Benjamini and Hochberg's[38] False Discovery Rate (FDR) adjustment was applied to correct for multiple comparisons, using the Sgof R package.[39] FDR was applied to the first set of analyses (involving omnibus tests). Then, to adjust for family-wise error, a second FDR adjustment was applied to the first and second sets of analyses (containing both omnibus tests and pairwise comparisons).

In the first set of analyses, omnibus linear mixed effects models (equivalent to two-way repeated measures ANOVA) were conducted *without correction for missing data* to examine between-condition differences in QIDS-SR-16, WSAS, FS, WCS and MLQ, separately, between any two pairs of timepoints. The models took the form of:

$$Outcome \sim Timepoint * Condition + (1|Participant)$$

In the second set of analyses, for models showing significant main effects of time, pairwise comparisons were conducted without correction for missing data to examine between-condition differences between specific pairs of timepoints. We further performed single arm analyses for both PT and ET conditions to explore changes in outcomes from baseline within the two arms separately. For pairwise comparisons, effect sizes are presented using Cohen's *d* and normative benchmarks of small (0.2), medium (0.5) and large (0.8) effects.[40]

A third set of analyses employed a conservative single imputation for missing data to more stringently test for the potential superiority of PT in the face of potential attrition bias. Missing data at one or more follow-up timepoints was thus imputed using the *worst* follow-up score for participants in the PT condition and the *best* follow-up score for patients in the ET condition across timepoints. This additional set of analyses was motivated by concerns that the somewhat greater levels of missing data in the ET condition may reflect asymmetrical patient factors, like greater positive regard for PT[41] versus ET.

In the fourth set of analyses, we examined between-condition differences in therapeutic changes on each outcome while controlling for treatment seeking behaviour in the follow-up period. Specifically, 2e conducted linear mixed models (utilizing the same conservative imputation method as the third set of analyses) that included three covariates controlling for the impact of (1) psychiatric medications, (2) non-pharmacological therapy, and (3) psychedelic drug use during follow-up. The models took the form of:

$$Outcome \sim Timepoint*Condition + \text{Follow-up Psychedelics} + \text{Follow-up Therapy} + \text{Follow-up Medication} + (1|Participant)$$

Supplementary analyses

While the main focus of the present study was on the between-condition differences in outcomes over the 6-month follow-up period, we also present within-condition changes in outcomes in Supplementary Materials. We also included sensitivity analyses while excluding missing data at either 3- or 6-month FU and participants who used psilocybin in the follow-up period as well as analyses using both the conservative imputation method and additional controlling by including missingness as a covariate in the models. These analyses are considered supplementary and exploratory and therefore were not corrected for multiple comparisons.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to the data in the present study and had final responsibility for the decision to submit for publication.

Results

Demographics

Information on baseline demographics, presented in,[5] can be found in Table 1. The study included 19 males (63%) and 11 females (37%) in the PT condition, and 9 females (31%) and 20 males (69%) in the ET condition. Information about gender was not collected at baseline, just sex assigned at birth, which was collected during the screening process by one of the researchers. Additionally, Fig. 1 contains a detailed description of the amount of participants enrolled, allocated to each condition and that completed each follow-up timepoint.

Missing data

Across all follow-up timepoints, average missing data across patients for QIDS was 13% (range: 3–29%) for PT

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)
Male sex – no. (%)	19 (63)	20 (69)
White race — no. (%)[a]	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[b]	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)[c]	14.5 ± 3.9 (7–23)	16.4 ± 4.1 (6–22)
HAM-D-17 score at pretreatment baseline (range)[d]	19.2 ± 2.3 (16–23)	18.4 ± 3.4 (11–26)

Pretreatment baseline was 7–10 days before dosing-day 1. [a]Race was reported by the patients. [b]To convert grams to U.K. units, divide by 8. [c]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. [d]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 all the patients had a score of minimum 17 on the HAM-D-17. The depression scores reported in this table are from pretreatment baseline and not screening.

Table 1: **Demographic and clinical characteristics of the patients at baseline*Plus–minus values are means ± SD.**

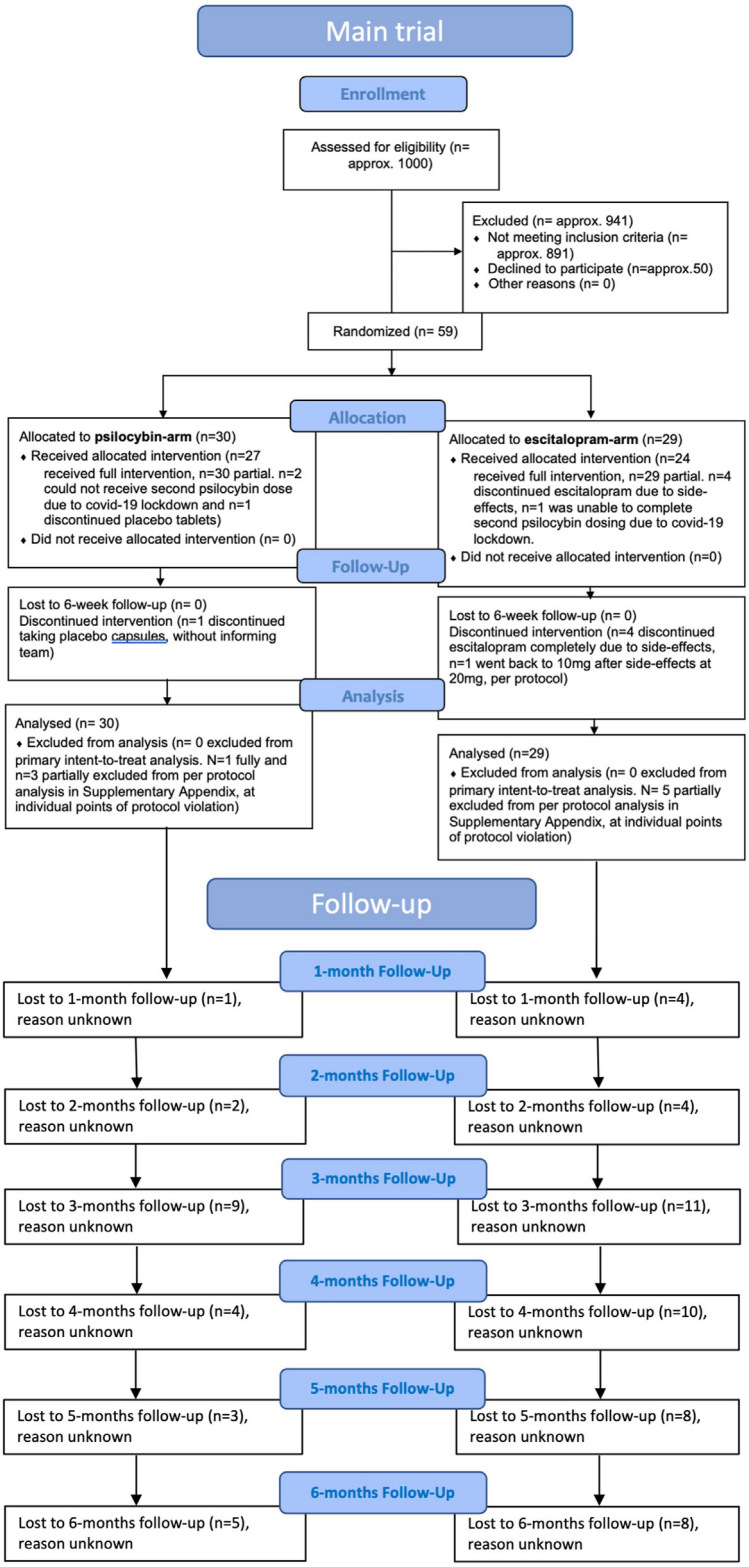

Fig. 1: **Trial profile and follow-up profile with missing data at each follow-up timepoint.**

and 26% (range: 14–38%) for ET. Missing data for WSAS, WCS, MLQ and FS exhibited a similar trend, with an average missing data of 19% (range: 13–23%) for PT and 31% (range 24–38%) for ET. No significant differences in demographics between ≥85% completers, <85% completers, and non-completers were found in either the PT or ET condition (Supplementary Table S2). More details on missing data can be found in Supplementary Materials 2.

Potential treatment confounds during follow-up

In total, 37 of 59 (62.7%) trial patients received some form of additional intervention in the follow-up period. Chi-squared tests showed no significant group differences in medication initiation, therapy initiation, or psychedelic use during follow-up. Full results can be found in Table 2.

Depressive symptomology

Without correction for missing data, a significant Time × Condition interaction ($F(7, 279) = 7.33$, $p = 0.006$, $pFDR = 0.02$) was observed, indicating the presence of a significant between-condition difference in QIDS-SR-16 scores for at least one timepoint. Subsequent post-hoc comparisons revealed a significant Time × Condition interaction at 1 month follow-up ($p = 0.011$, $pFDR = 0.021$), indicating greater reductions in depressive symptoms were found between baseline and one month following the trial endpoint for PT (mean difference: −7.63, $p < 0.001$, $d = 1.55$) versus ET (mean difference: −4.04, $p < 0.001$, $d = 0.74$). All other Time × Condition interactions were non-significant ($p > 0.05$).

Single-arm analyses found significant reductions in depressive symptoms with similarly large effect sizes for both conditions (ET mean difference at 3-month follow-up: −6.59, $p < 0.001$, $d = 1.33$, at 6-month follow-up: −6.83, $p < 0.001$, $d = 1.35$, PT mean difference at 3-month follow-up: −6.48, $p < 0.001$, $d = 1.24$, at 6-month follow-up: −5.27, $p < 0.001$, $d = 1.33$). Full results for between-condition and within-condition estimates of change can be found in Table 1, Fig. 2 and Supplementary Tables S5–S7. Specifically, Table 3 presents the degree to which PT and ET differed in estimates of change between baseline and subsequent timepoints, and the degree of change estimated for PT and ET, separately. The percentage of responders (≥50% QIDS-SR-16 reduction) and remitters (QIDS-SR-16 scores ≤5) as well as associated relevant statistics in PT and ET conditions during follow-up are shown in Supplementary Table S7. A descriptive representation is presented in Fig. 2. Notably, at 1-month FU remitters were significantly more in the PT condition.

Work and social functioning

Without adjustments for missing data, a significant Time × Condition interaction was found ($F(3143 = 6.05$, $p < 0.001$, $pFDR < 0.001$) for WSAS scores, indicating the presence of a significant between-condition difference for at least one timepoint. Subsequent post-hoc comparisons observed significant Time × Condition interactions at 6-week endpoint ($p < 0.001$, $pFDR = 0.004$), 3-month follow-up ($p < 0.001$, $pFDR = <0.001$) and 6-month follow-up ($p < 0.001$, $pFDR = 0.01$), indicating greater improvements in work and social functioning between baseline and all follow-up for PT versus ET (ET mean difference at 3-month follow-up: −1.00, $p = 0.31$, $d = 0.18$, at 6-month follow-up: −3.10, $p = 0.002$, $d = 0.66$, PT mean difference at 3-month follow-up: −12.09, $p < 0.001$, $d = 1.41$, at 6-month follow-up: −12.73, $p < 0.001$, $d = 1.69$). Full results of both between-condition differences and single arm analyses can be found in Table 3 (presenting the degree to which PT and ET differed in estimates of change between baseline and subsequent timepoints, and the degree of change estimated for PT and ET, separately), Fig. 3, and Supplementary Tables S3–S5. A supplementary item-level analysis of WSAS can be found in Supplementary Table S6.

Meaning in life

Without adjustments for missing data, a significant Time × Condition interaction was found ($F(3,143) = 5.31$, $p < 0.001$, $pFDR = 0.004$) for MLQ scores, indicating the presence of a significant between-condition difference for at least one timepoint. Subsequent post-hoc comparisons observed significant Time × Condition interactions at 6-week endpoint ($p = 0.012$, $pFDR = 0.021$), 3-month follow-up ($p = 0.009$,

Psilocybin		Escitalopram		p
FU medications (yes)	FU medications (no)	FU medications (yes)	FU medications (no)	–
8 (30.7%)	18 (69.3%)	10 (43.5%)	13 (56.5%)	0.53
FU psychedelics (yes)	FU psychedelics (no)	FU psychedelics (yes)	FU psychedelics (no)	–
8 (30.8%)	18 (69.2%)	4 (17.4%)	19 (82.6%)	0.45
FU therapy (yes)	FU therapy (no)	FU therapy (yes)	FU therapy (no)	–
12 (46.2%)	14 (53.8%)	9 (40.9%)	13 (59.1%)	0.94

Chi-square tests were used to analyze differences between the groups. No significant differences were found, as indicated by the associated p-values.

Table 2: **The table displays the follow-up use of medications, psychedelics, and therapy in both the psilocybin and escitalopram groups.**

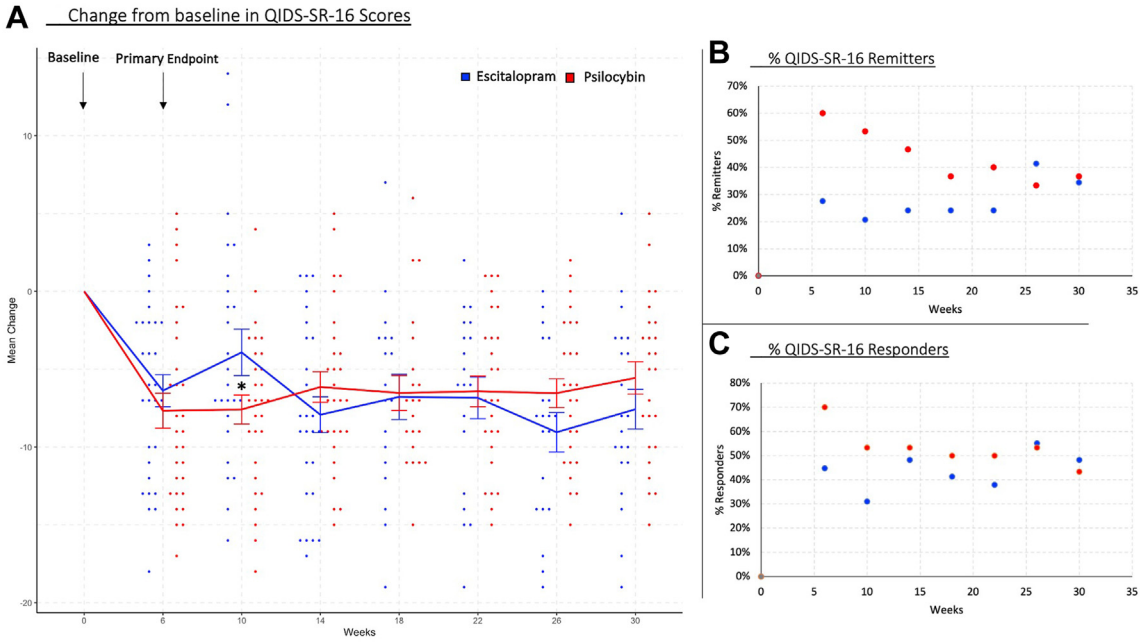

Fig. 2: **Changes in depressive symptomatology during the follow-up period** (A) Mean change from baseline in the score on the 16-item Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR-16; on which scores range from 0 to 27, with higher scores indicating greater depression). No significant between-condition differences between Psilocybin Therapy and Escitalopram Treatment were found, except for 1-month (10 weeks) follow-up, both groups appeared to present sustained improvements. I bars indicate standard errors and dots individual change scores in the two arms. (B) QIDS-SR-16 remitters (QIDS-SR-16 scores ≤5) over the follow-up period. (C) QIDS-SR-16 responders (≥50% QIDS-SR-16 reduction). FDR-corrected p values, * indicates a superiority of PT over ET, ‘p < 0.05, *p < 0.01, **p < 0.005.

pFDR = 0.018) and 6-month follow-up (p = 0.021, *pFDR* = 0.034), indicating greater improvements in meaning in life between baseline and all follow-up timepoints for PT versus ET (ET mean difference at 3-month follow-up: 1.59, p = 0.32, d = 0.10, at 6-month follow-up: 2.12, p = 0.16, d = 0.31, PT mean difference at 3-month follow-up: 7.51, p < 0.001, d = 0.95, at 6-month follow-up: 6.98, p < 0.001, d = 1.02). Full results of both between-condition differences and single arm analyses can be found in Table 3, Fig. 3, and Supplementary Tables S3–S5.

Connectedness

Without adjustments for missing data, a significant Time × Condition interaction was found (F (3,147) = 5.93, p < 0.001, *pFDR* = 0.003) for WCS scores, indicating the presence of a significant between-condition difference for at least one timepoint. Subsequent post-hoc comparisons observed significant Time × Condition interactions at 6-week endpoint (p < 0.001, pFDR < 0.001), 3-month follow-up (p = 0.007, *pFDR* = 0.02) and 6-month follow-up (p = 0.03, *pFDR* = 0.04), indicating greater improvements in connectedness between baseline and all follow-up timepoints for PT versus ET (ET mean difference at 3-month follow-up: 8.15, p = 0.005, d = 0.42, at 6-month follow-up: 10.95, p = 0.003, d = 0.74, PT mean difference at 3-month follow-up: 22.22, p < 0.001, d = 1.29, at 6-month follow-up: 21.99, p < 0.001, d = 1.22). Full results of both between-condition differences and single arm analyses can be found in Table 3, Fig. 4, and Supplementary Tables S3–S5.

Flourishing

Without adjustments for missing data, no significant Time × Condition interaction was found (F (3,147) = 1.79, p = 0.15, *pFDR* = 0.21) for FS, indicating the absence of between-condition differences in flourishing across the follow-up period. Follow-up analyses examining within-subject changes in the ET and the PT conditions revealed comparable significant improvements in flourishing at all follow-up timepoints (ET mean difference at 3-month follow-up: 7.50, p < 0.001, d = 0.8, at 6-month follow-up: 8.89, p < 0.001, d = 1.08, PT mean difference at 3-month follow-up: 13.75, p < 0.001, d = 1.55, at 6-month follow-up: 12.72, p < 0.001, d = 1.38). Full results can be found in Table 3, Fig. 4, and Supplementary Tables S3–S5. As a note, this result deviates from the results from Carhart-Harris et al., 2021 and for this reason we conducted pairwise

1A) Between-condition differences in outcomes between baseline and subsequent timepoints

Outcome	Timepoint compared to baseline	B (SE)	95% CI	*d*
Depressive symptoms (QIDS-SR-16)	Week 6	−1.28 (1.37)	−3.93, 1.36	–
	Month 1	−3.58 (1.41)*	−6.31, −0.85	–
	Month 2	1.02 (1.42)	−1.71, 3.77	–
	Month 3	0.13 (1.57)	−2.89, 3.16	–
	Month 4	0.93 (1.51)	−1.97, 3.84	–
	Month 5	1.80 (1.47)	−1.04, 4.64	–
	Month 6	1.51 (1.49)	−1.35, 4.38	–
Work and Social Functioning (WSAS)	Week 6	−7.53 (2.37)*	−12.1, −2.94	–
	Month 3	−10.29 (2.69)**	−15.5, −5.08	–
	Month 6	−7.46 (2.58)*	−12.4, −2.47	–
Connectedness (WCS)	Week 6	19.35 (4.71)**	10.25, 28.46	–
	Month 3	14.18 (5.25)*	4.04, 24.36	–
	Month 6	11.02 (5.06)*	1.25, 20.83	–
Meaning in Life (MLQ)	Week 6	5.01 (1.96) *	1.23, 8.80	–
	Month 3	5.90 (2.23)*	1.59, 10.23	–
	Month 6	4.86 (2.17)*	0.67, 9.05	–

1B) Differences in outcomes between baseline and subsequent timepoints in the psilocybin therapy condition only

Outcome	Timepoint compared to baseline	B (SE)	95% CI	*d*
Depressive symptoms (QIDS-SR-16)	Week 6	−7.66 (0.88)**	−9.37, −5.95	1.53
	Month 1	−7.63 (0.89)**	−9.36, −5.90	1.55
	Month 2	−6.21 (0.90)**	−7.95, −4.46	1.18
	Month 3	−6.48 (0.98) **	−8.39, −4.57	1.24
	Month 4	−6.18 (0.92)**	−7.97, −4.39	1.24
	Month 5	−6.42 (0.91)**	−8.19, −4.66	1.33
	Month 6	−5.27 (0.93)**	−7.08, −3.46	1.33
Work and Social Functioning (WSAS)	Week 6	−10.70 (1.7)**	−14.19, −7.20	1.16
	Month 3	−12.09 (1.9)**	−15.90, −8.27	1.41
	Month 6	−12.73 (1.9)**	−16.47, −9.03	1.69
Connectedness (WCS)	Week 6	29.04 (3.89)**	21.46, 36.62	1.56
	Month 3	22.22 (4.25)**	13.95, 30.52	1.29
	Month 6	21.99 (4.08)**	14.06, 29.98	1.22
Meaning in Life (MLQ)	Week 6	7.50 (1.40)**	4.77, 10.22	0.94
	Month 3	7.51 (1.53)**	4.53, 10.51	0.95
	Month 6	6.98 (1.53)**	3.99, 9.97	1.02
Flourishing (FS)	Week 6	14.43 (1.87)**	10.40, 18.46	1.58
	Month 3	13.75 (2.20)**	9.48, 18.04	1.55
	Month 6	12.72 (2.18)**	8.45, 17.02	1.38

1C) Differences in outcomes between Baseline and subsequent timepoints in the escitalopram treatment condition only

Outcome	Timepoint compared to baseline	B (SE)	95% CI	*d*
Depressive symptoms (QIDS-SR-16)	Week 6	−6.37 (0.98)**	−9.94, −2.45	1.27
	Month 1	−4.04 (1.03)*	−9.39, −1.62	0.74
	Month 2	−7.24 (1.03)**	−13.28, −5.51	1.59
	Month 3	−6.59 (1.24)**	−11.76, −2.35	1.33
	Month 4	−7.13 (1.22)**	−13.88, −5.50	1.48
	Month 5	−8.23 (1.18)**	−14.58, −6.53	1.70
	Month 6	−6.83 (1.18)**	−11.90, −3.53	1.35
Work and Social Functioning (WSAS)	Week 6	−3.17 (1.51)*	−6.12, −0.21	0.42
	Month 3	−1.80 (1.79)	−5.28, 1.68	0.18
	Month 6	−5.26 (1.69)*	−8.56, −1.96	0.66

(Table 3 continues on next page)

1C) Differences in outcomes between Baseline and subsequent timepoints in the escitalopram treatment condition only

Outcome	Timepoint compared to baseline	B (SE)	95% CI	*d*
(Continued from previous page)				
Connectedness (WCS)	Week 6	9.69 (2.52)**	4.77, 14.60	0.66
	Month 3	8.15 (2.87)*	2.53 13.73	0.42
	Month 6	10.95 (3.69)*	5.53, 16.35	0.74
Meaning in Life (MLQ)	Week 6	2.48 (1.36)	−0.17, 5.13 5.27, 12.58	0.30
	Month 3	1.59 (1.61)	−1.55, 4.72	0.10
	Month 6	2.12 (1.52)	−0.84, 5.09	0.31
Flourishing (FS)	Week 6	8.93 (1.87)**	5.27, 12.58	1.16
	Month 3	7.50 (2.20)**	3.21, 11.76	0.80
	Month 6	8.89 (2.08)**	4.84, 12.95	1.08

Note. B = unstandardized coefficient estimate; SE, Standard Error; CI, Confidence Interval; *d* = Cohen's *d*. 'p < 0.05, *p < 0.01, **p < 0.001. Unstandardized (B) coefficients indicate the mean differences between PT and ET in pre-post change, FDR-corrected p values,* indicates a superiority of PT over ET, 'p < 0.05, *p < 0.01, **p < 0.001. Flourishing (FS) results are not displayed as the scale did not reach significance in the omnibus test performed in the first set of analyses. **B/C)** Single arm analyses for Psilocybin and Escitalopram Treatment conditions showing linear mixed model with QIDS-SR16, WSAS, WCS, MLQ and FS as outcome variables, and time as predictor variable (measured monthly for QIDS-SR-16, and every three months for the other variables). Single arm analyses are not corrected for multiple comparisons as the main focus of the present study was on the between-condition differences in outcomes over the follow-up period.

Table 3: **A) Between-condition differences (measured monthly for QIDS-SR-16, and every three months for the other variables WSAS, WCS, MLQ) between psilocybin therapy and escitalopram treatment.**

comparisons to investigate a possible discrepancy between the effect of time on flourishing in the two analyses. We indeed observed that the confidence intervals associated with the differences between baseline and week 6 did not overlap with zero, converging with previously reported trial findings. This suggests that our ANOVA test was not powerful enough to detect these differences but was retained as a more conservative approach.

Impact of attrition bias and potentially confounding variables on the results

We repeated our uncorrected analyses utilizing a conservative imputation for missing data favoring ET over

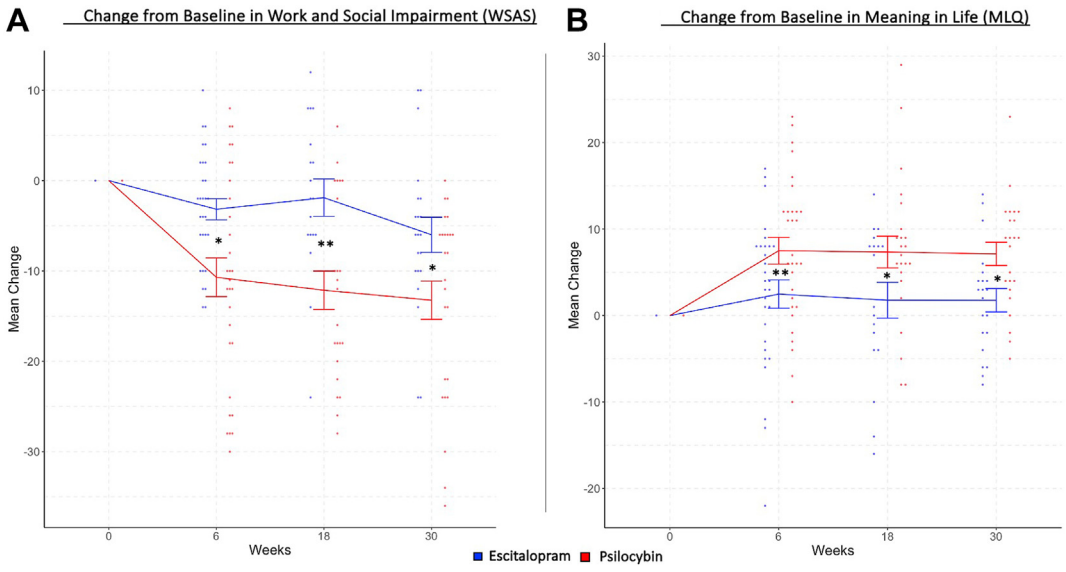

Fig. 3: **Changes in work and social impairment and meaning in life during the follow-up period** (A) Mean change from baseline in the scores of work and social impairment (WSAS), with lower scores indicating lower impairment. (B) Mean change from baseline in the scores of meaning in life (MLQ), with higher scores indicating higher meaning in life. (FDR-corrected p values, * indicates a superiority of PT over ET, 'p < 0.05, *p < 0.01, **p < 0.005. I bars indicate standard errors and dots individual change scores in the two arms.

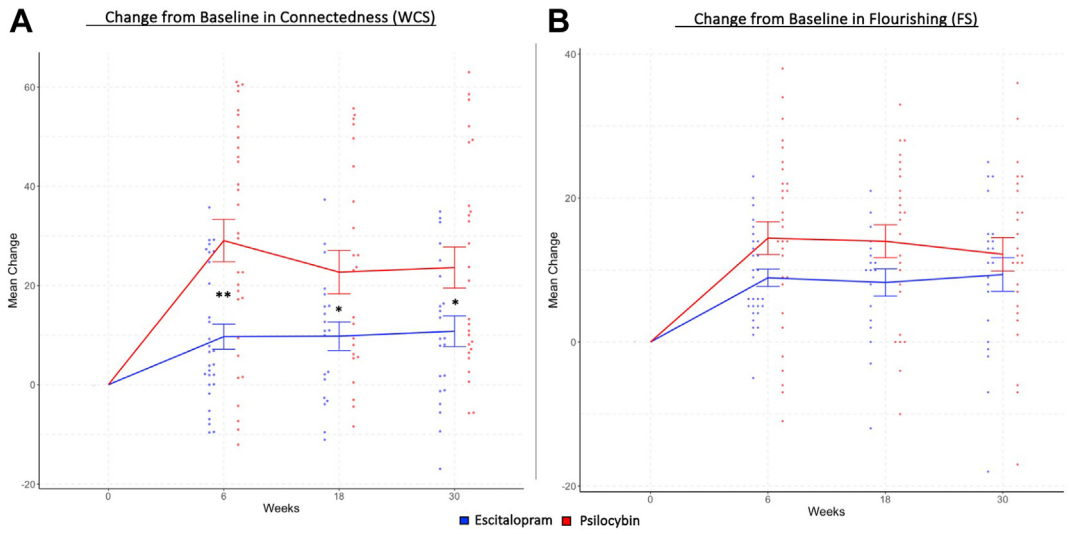

Fig. 4: **Changes in connectedness and flourishing during the follow-up period** (A) Mean change from baseline in the scores of connectedness (WCS), with higher scores indicating higher connectedness. (B) Mean change from baseline in the scores of flourishing (FS), with higher scores indicating higher flourishing. FDR-corrected p values, * indicates a superiority of PT over ET, 'p < 0.05, *p < 0.01, **p < 0.005. I bars indicate standard errors and dots individual change scores in the two arms.

PT, with and without controlling for potential confounding variables (Supplementary Tables S8 and S9). These two sets of analyses generated results that were consistent with our uncorrected results for all the included measures. The pattern of results from uncorrected models survived while controlling for use of medication, psychedelics, and non-pharmacological therapy in the follow-up period.

Discussion

The present study expands upon results from Carhart-Harris and colleagues[5] by examining the long-term therapeutic profile of psilocybin versus escitalopram with matched psychological support through a 6-month naturalistic follow-up. The previous trial report included only outcomes at the 6-week endpoint, whereas the present paper presents data through the six-month follow-up. Results from six months of follow-up show similarly sustained reductions in depressive symptoms for PT and ET interventions on the QIDS-SR-16. However, in the present data, patients in the PT versus the ET condition exhibited significantly greater sustained improvements work and social functioning (WSAS), connectedness (WCS) and meaning in life (MLQ) throughout six months of naturalistic follow-up. Overall, the results suggest that although PT and ET may have comparable long-term effects in depression symptomatology, PT might be linked to sustained higher levels of global mental health beyond mere symptom reduction.

However, these results should be qualified by suboptimal visibility into treatment seeking behaviour within the follow-up period. Although there was no observed disparity in treatment uptake in the follow-up period between groups, 63% of patients in the PT arm still reported some form of additional treatment during the six months of follow-up, aligning with previous studies.[42] Moreover, treatment uptake was not granularly measured beyond the presence or absence of psychedelic use, medication, and psychotherapy. As such, we cannot rule out the involvement of these adjunct treatments in having a causal role in the observed between-condition differences. Nevertheless, establishing the absence of disparity between groups on the measured treatment behaviour is a meaningful prerequisite for countenancing the present results and forming preliminary interpretation and hypotheses.

Notwithstanding this serious limitation, few modern studies have investigated the long-term effects of PT administered in a clinical trial of depression. Previously, Gukasyan and colleagues[42] found sustained antidepressant effects up to 12 months following PT and Carhart-Harris and colleagues[43] demonstrated sustained antidepressant effects up to 6 months in a treatment-resistant cohort. To the degree that the pattern of results observed here are causally related to the experimental treatment conditions and replicate in future work, a number of causal explanations are conceivable. The antidepressant effects of PT may arise from a combination of neurobiological, psychological, and social factors. By promoting neuroplasticity, engendering transformative experiences, and administering psychotherapy, psilocybin might offer unique opportunities for (re)learning mechanisms that can generate a healthy recalibration of an individual's psychological state.[44] Accordingly, the active influence of psychotherapy on the therapeutic

effect of psilocybin is important to consider in the present trial. Psychological support is regarded by the authors as an ethical standard, though the amount and type of support/psychotherapy provided remains variable and subject to considerations of population and disorder type.[45] Furthermore, as in the case of combined antidepressant psycho- and pharmacotherapy, psychotherapy may produce greater sustained efficacy and lower relapse.

Unlike the current study, the single-group or crossover methodologies of previous studies did not allow for long-term parallel group comparisons[42,43] and entry into a non-psychedelic waitlist or inert placebo arm could cause disappointment effects that exaggerate between-condition differences.[46]

Thirty four percent (34%) of patients in the ET reported continuation or resumption of medication in the follow-up, yet ET patients exhibited sustained rates of response around 50% and remission around 30% at six months. Given that a successful course of SSRI therapy is typically associated with a relapse rate of around 40% six months after discontinuation (Kato et al., 2021), we conjecture that the trial's intensive psychological support might have contributed to the observed benefits in the ET condition post trial. Such an inference is equally applicable to the PT group. However, standard PT includes psychological support by default,[45] a practice not always paralleled in SSRI treatment protocols, where medication is often prescribed without accompanying therapy (16).

In meta-analysis, the odds of depression relapse following psychotherapy alone are approximately half of those associated with medications alone[47]—meaning patients are more likely to relapse after pharmacotherapy. While patients in the ET condition received psychological support only during the six *weeks* trial treatment phase (versus 18–24 weeks of psychotherapy for a conventional course of CBT[48]), they received around 20 h of psychological support during this time—often from two trained mental health professionals. In other words, this was a relatively standard "dose" of psychotherapeutic hours but administered over a treatment period approximately 75% shorter, including two prolonged sessions of 6–8 h each. To our knowledge, outside of psychedelic therapy, no prior study has investigated such a high-intensity psychotherapeutic intervention for depression in combination with escitalopram. Indeed, additive benefits have been observed with conventional psychotherapy–psychopharmacological combinations, with previous meta-analyses finding that combined interventions are more effective than either treatment alone in both the short- and the long-term.[49] Given that antidepressant effects can begin as early as one week after treatment (and approach peak efficacy at 6 weeks[50,51]), even the brief course of escitalopram of the ET condition might have potentiated psychotherapeutic interventions by, for instance, reducing depressive symptoms like amotivation and hopelessness that can impede progress. We present this possible accounting for the durability of therapeutic effects in the ET while recognizing the potential confounding influence of treatment seeking behaviour in the follow-up period.

Should such results replicate in future work, one possibility is that a brief course of escitalopram can exert neuroplasticity-enhancing effects that, like psilocybin, enhance intensive psychotherapy. Escitalopram has recently been shown to augment neuroplasticity and facilitate learning, especially emotional relearning.[52] It is at least plausible therefore that neuroplasticity-related mechanisms are at work in both ET and PT conditions of this trial, though future study is required to confirm such hypotheses and evaluate whether they may also underlie more conventional treatment rhythms (e.g., weekly psychotherapy). A final consideration is that the two 1 mg doses of psilocybin administered could have played a role in the antidepressant effects observed in this arm. This dosage aligns with the quantities used in previous research on microdosing of magic mushrooms.[53,54] Although recent research has sparked interest in the benefits of microdosing psychedelics for mental health and wellbeing, existing studies have yet to demonstrate substantive or reliable long-term positive effects.[55] Moreover, microdosing typically involves ingesting small amounts of psychedelics at least 2–3 times a week over numerous weeks, unlike the regimen employed in our study, which involved two 1 mg doses separated by three weeks. Therefore, we submit that these doses were unlikely to significantly contribute to the results.

Compared with ET, patients in the PT condition reported overall greater improvements in other study outcomes measures assessed in the follow-up period; general functioning, connectedness and meaning in life. The superior enhancements in functioning in the PT condition carry potential importance, as clinical guidelines for MDD prioritize the restoration of functioning as a key objective (e.g.,[48]), and symptom remission frequently does not coincide with functional recovery.[56] As such, functioning may be of at least equal importance for adjudicating the relative efficacy of the therapies presently under study as functioning might lead to improved quality-adjusted life years (QALYs;[57]) over time, a metric usually used for assessing the cost-effectiveness of new treatments.[58] An item-level analysis was conducted to probe the most responsive domains of functioning to PT versus ET, revealing that domains linked to home management, social and private leisure activities, and meaningful relationships, but not the ability to work, responded more strongly to PT than ET (Supplementary Table S7).

PT was also notably associated with superior enhancements in connectedness and meaning in life. These outcomes are not commonly measured in clinical research, but we chose to include them in view of their

clinical relevance to symptom components of depression involving deficits in reward function (e.g., anhedonia, amotivation,[59,60]), and their relevance to the novel therapeutic profile of PT. Connectedness to others and society has been previously hypothesized as a transdiagnostic factor for mental health and well-being[33] and beyond mental health, chronic loneliness has been associated with significant increases in medical morbidity and overall mortality.[61,62] Finally, connectedness and meaning may be particular important to patients with MDD as patients tend to rate outcomes such as well-being, quality of life, and functioning as more significant than reductions in negative mood.[63] This distinction is especially pertinent given the potential discordance between physicians and patients in their perceptions of recovery from depression. While physicians prioritize the absence of negative mood symptoms (negative valence), patients tend to emphasize the degree to which their lives are meaningful and enjoyable (positive valence).[64]

One main limitation in our comparison of PT's and ET's sustained efficacy concerns the presence of missing data and the use of extraneous interventions in the follow-up period. Treatment seeking behaviour in the follow-up period might have confounded our ability to attribute differences between conditions to our experimental manipulation. We strove to mitigate potential biases from missing data favoring PT using a conservative statistical approach involving imputation and adjustment for potential confounds. Nevertheless, comprehensive details regarding the exact methods and frequencies of antidepressant/psychedelic administration and therapy during the follow-up period were not collected. We underscore the necessity of replicative future research to guide a more confident interpretation concerning the long-term therapeutic outcomes of PT and ET combined with psychological support.

The presence of missing data was partly a consequence of the coronavirus pandemic, which overlapped with follow-up timepoints for many participants. The pandemic might have influenced outcomes, though research on its impact on mental health has been mixed, showing either increased prevalence and burden of mental disorders[65] or no changes or minimal changes.[66] We believe our randomised design insulated the study from impacts on pre-post estimates of change in the case of the former.

An additional limitation concerns the degree to which ET truly reflects a gold-standard SSRI course of treatment. As ET entailed escitalopram for a relatively short duration (6 weeks), and patients are typically prescribed SSRIs for a longer period to prevent relapse of depressive symptoms, a better comparison would arguably have involved prolonged use of escitalopram throughout the follow-up period. Nevertheless, the ET comparator entailed a large amount of psychological support within a six-week intervention.[7,8] See also some recent neuroimaging evidence of the neurobiological action of ET in this trial.[67]

Although we interpret no difference between conditions in antidepressant response, we note recent evidence of potential psychometric problems with our primary outcome measure (QIDS-SR-16) and how the QIDS-SR-16 data assessed at the 6 week end-point differed from three other measures (BDI, MADRS, and HAM-D) as well as a post-hoc generated depression factor using factors from all four measures.[27] These problems and psychometric differences may have contributed to a null between-condition difference at 6 weeks and during follow-up.[27] Relatedly, we also recognize the potential for Type II error due to our study's sample size at follow-up, which was not optimally powered to detect small but meaningful differences between treatments.

A further limitation is the reliance on retrospective and self-reported treatment assessments. This methodological approach may introduce recall bias, as participants' memories of their symptoms and behaviours can be subject to inaccuracy over time.[68] Moreover, the retrospective nature of self-reporting could be influenced by participants' current state of mind and social expectations.[69] These factors should be carefully considered when interpreting the results.

Another factor that is important to discuss is that daily escitalopram (43 doses in the present study) versus two doses of psilocybin implies assumptions regarding the need for a steady state drug action with the former and a quite distinct longer-tailed action with the latter—implying a carryover action with PT that endures well after the psilocybin/psilocin itself has been metabolized from the body. This 'carryover' type action is exactly how the potential mechanisms of PT have previously been characterized[44,70] and differentiated from the action of SSRIs.[71] This is important as it implies that whereas PT is assumed to have a long-tailed causal action, a 6-week course of an SSRI is not generally assumed to act in this way, e.g., with guidelines advising sustained use to avoid relapse and evidence showing shorter time-to-relapse than psychotherapy. In other words, whereas causal connections between PT and enduring psychological changes have previously been inferred (e.g.,[72,73])—the same precedent does not exist for escitalopram. Thus, one is left either inferring that any causal connection to the intervention in the ET arm was caused by the unusual intensity of psychotherapy in that condition, or that the justification for inferring any causal connection at all is not strong. Regarding this latter possibility, the implication would be that other spurious factors such as post-trial interventions, spontaneous improvement and/or regression to the mean may have contributed to the observed 6-month improvements in this condition. We attempted to understand this further by examining the correlational relationships of early treatment response at 6 weeks with subsequent follow-ups, i.e., correlating

change between baseline and 6 weeks with change between baseline and subsequent follow-ups. We found that distinct patterns emerge for the PT and ET conditions. The PT group indeed exhibited correlations that tended to be larger than the ET group and consistently moderate, e.g., exceeding $r = 0.30$ (Supplementary Table S11). These results indicate that the order of individuals who responded most robustly at the 6-week mark maintained moderate stability through the first 5 months of the follow-up period, and suggest that early processes of change–elicited during PT–may have exerted a sustained influence throughout this period. In contrast, the ET did not exhibit the same level of stability. Although there were sporadic instances of large correlation, the pattern was not consistent, suggesting that the effects observed at follow-ups in ET may be less attributable to the original treatment and more attributable to alternative interventions or stochastic changes in the follow-up period.

Finally, this study did not incorporate a systematic assessment of side effects during the follow-up period. This constitutes a limitation of our research and we suggest that future studies consider including longitudinal side effect profiles to enhance the evaluation of therapeutic interventions' safety over time. We also note that response rates in the PT arm at the 6-month follow-up in the current study (43%) were lower than those reported previously in[42]—which were 79% at 6 months for MDD. This difference could suggest that the longevity of the effects of PT may vary among individuals or may depend on other factors, such as the open-label study design in,[42] the severity of the depression at baseline or the type of therapeutic support used.

More limitations inherent to the main trial can be found in.[5]

Overall, while PT and ET interventions were both associated with improvements in depressive symptom severity at 6-month follow-up, we observed greater benefits for psychological connectedness, general functioning, and existential meaning among PT patients. In view of missing data and limitations on visibility into treatment-seeking behaviour within the follow-up period, these results are considered preliminary but useful for informing hypotheses in future replicative research.

Contributors

DE. and TB, were responsible for conceptualization, formal analysis, investigation, and methodology. They also supervised the project, validated findings, and played significant roles in writing the original draft and reviewing and editing the manuscript. BW played a critical role in conceptualization, supervision, formal analysis, and methodology. He also acquired resources, validated results, and was integral in writing both the original draft and subsequent reviews and edits of the manuscript. KG formulated the research questions, interpreted the results, and reviewed the literature, in addition to writing the initial draft of the manuscript. RM, BG, JM, and CT each contributed to the conceptualization, investigation, and methodology of the study. They were involved in reviewing and editing the manuscript, with CT specifically focusing on formal analysis. AMB and MBJ managed the project administration and were involved in the investigation and methodology, also contributing to writing and reviewing the manuscript. DN and RCH were involved in investigation, supervision, and validation of the study, alongside acquiring funding and editing the manuscript. DE, TB, BW and KG have access to and verify the underlying study data.

Data sharing statement

The data from this study will be made available upon publication of the associated research article. The complete de-identified patient dataset can be accessed by approved researchers for academic purposes. Access to the dataset will be granted following the approval of a proposal and is contingent upon the execution of a signed data access agreement. The data will be accessible for an indefinite period, allowing for continued academic inquiry and analysis. Supporting documents, including the informed consent form, will be made available under the same criteria. Further details regarding the mechanism of data sharing will be determined and communicated in due course.

Declaration of interests

RCH is a scientific advisor to Mindstate Design Lab. DE is a paid advisor for Aya Biosciences, Clerkenwell Health, Lophora Aps, and Mindstate Design Lab and had a role on Data Safety Monitoring Board on SmallPharma Ltd DMT depression trial. DJN has received consulting fees from Algernon and H. Lundbeck and Beckley Psytech, advisory board fees from COMPASS Pathways and lecture fees from Takeda and Otsuka and Janssen plus owns stock in Alcarelle, Awakn, and Psyched Wellness. B.W. owns Axial Therapeutic Research, Inc., a company investigating the safety and effectiveness of alternative treatments for military veteran health. BG and MBJ have received consulting fees from Cybin Inc. TB has received consulting fees from Adamo Biosciences. KTG received grants/contracts from Northern Ontario Academic Medicine Association: Clinical Innovation Opportunities Fund (2022/1–2023/1), Sir Mortimer B. Davis-Jewish General Hospital Foundation (The): JGH Québec Network on Suicide, Mood Disorders and Related Disorders. None of the other authors reported conflicts of interest. Compass Pathways delivered the study drug (psilocybin COMP360) and via contract agreement with Imperial Collge (study sponsor and IP holder) were granted access to safety data from the study.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102799.

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