Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study

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Summary

Background Psilocybin is a serotonin receptor agonist that occurs naturally in some mushroom species. Recent studies have assessed the therapeutic potential of psilocybin for various conditions, including end-of-life anxiety, obsessive-compulsive disorder, and smoking and alcohol dependence, with promising preliminary results. Here, we aimed to investigate the feasibility, safety, and efficacy of psilocybin in patients with unipolar treatment-resistant depression.

Methods In this open-label feasibility trial, 12 patients (six men, six women) with moderate-to-severe, unipolar, treatment-resistant major depression received two oral doses of psilocybin (10 mg and 25 mg, 7 days apart) in a supportive setting. There was no control group. Psychological support was provided before, during, and after each session. The primary outcome measure for feasibility was patient-reported intensity of psilocybin's effects. Patients were monitored for adverse reactions during the dosing sessions and subsequent clinic and remote follow-up. Depressive symptoms were assessed with standard assessments from 1 week to 3 months after treatment, with the 16-item Quick Inventory of Depressive Symptoms (QIDS) serving as the primary efficacy outcome. This trial is registered with ISRCTN, number ISRCTN14426797.

Findings Psilocybin's acute psychedelic effects typically became detectable 30–60 min after dosing, peaked 2–3 h after dosing, and subsided to negligible levels at least 6 h after dosing. Mean self-rated intensity (on a 0–1 scale) was 0·51 (SD 0·36) for the low-dose session and 0·75 (SD 0·27) for the high-dose session. Psilocybin was well tolerated by all of the patients, and no serious or unexpected adverse events occurred. The adverse reactions we noted were transient anxiety during drug onset (all patients), transient confusion or thought disorder (nine patients), mild and transient nausea (four patients), and transient headache (four patients). Relative to baseline, depressive symptoms were markedly reduced 1 week (mean QIDS difference –11·8, 95% CI –9·15 to –14·35, p=0·002, Hedges' g=3·1) and 3 months (–9·2, 95% CI –5·69 to –12·71, p=0·003, Hedges' g=2) after high-dose treatment. Marked and sustained improvements in anxiety and anhedonia were also noted.

Interpretation This study provides preliminary support for the safety and efficacy of psilocybin for treatment-resistant depression and motivates further trials, with more rigorous designs, to better examine the therapeutic potential of this approach.

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Introduction

Psilocybin is a naturally occurring plant alkaloid found in the *Psilocybe* genus of mushrooms. Psilocybe mushrooms have been used for millennia for healing purposes, but were only discovered by modern science in the late 1950s.[1,2] Psilocybin is a prodrug of psilocin (4-hydroxy-dimethyltryptamine), a serotonin receptor agonist and classic psychedelic drug whose principal psychoactive effects are mediated by serotonin 2A (5-HT_{2A}) receptor agonism.[3] Psilocybin therefore has a novel pharmacology in the context of currently available antidepressant medications, because selective serotonin-reuptake inhibitors are not direct 5-HT_{2A} receptor agonists.

Enhanced cognitive flexibility,[4] associative learning,[5] cortical neural plasticity,[6] and antidepressant responses have been reported with 5-HT_{2A} receptor agonism in animals,[7] and increased and sustained improvements in wellbeing[8] and optimism[9] have been observed after psychedelic experiences in human beings. Findings from human imaging studies with psilocybin have supplemented these discoveries, showing changes in brain activity suggestive of antidepressant potential; for example, a range of effective antidepressant treatments have been found to normalise hyperactivity in the medial prefrontal cortex and we found reduced blood flow in this region with intravenous psilocybin.[10] Moreover, data obtained from large-scale population studies have recently challenged the view that psychedelics negatively affect mental health,[11–13] with one study's findings showing lower rates of psychological distress and suicidality among people who had used

Research in context

Evidence before this study

We searched PubMed up to Jan 30, 2016, using the terms "psilocybin", "hallucinogens", "psychedelics", and "depression". We did not find any clinical trials assessing psilocybin as a treatment for depression, but we did find population analyses, review articles, and imaging studies lending support to this approach. We also found one report documenting enduring decreases in depressive symptoms after a single dose of psilocybin in a randomised controlled trial of psilocybin-assisted psychotherapy for end-of-life anxiety, one report on an open-label trial showing rapid decreases in depressive symptoms that endured for up to 21 days after a single dose of ayahuasca, and two early reports or case studies on the effects of lysergic acid diethylamide on "neurotic" and depressive symptoms describing "improvements", albeit without validated measures of symptom severity.

Added value of this research

To our knowledge, this is the first investigation of the safety and efficacy of psilocybin as a treatment for major depression. Our findings imply that psilocybin might have value as a treatment option in the management of treatment-resistant depression. Single oral administrations of 10 mg (safety dose) and 25 mg (treatment dose) psilocybin were well tolerated and led to enduring reductions in symptom severity after the two sessions.

Implications of all the available evidence

The results of this small-scale feasibility study should help to motivate further research into the efficacy of psilocybin with psychological support for major depression. Larger-scale randomised controlled trials are warranted to better examine the potential of psilocybin as a treatment option for this highly prevalent, disabling, costly, and difficult-to-treat disorder. More broadly, the present study should help to catalyse the re-emergence of a promising research area in psychiatry.

psychedelics within their lifetime than among those who used no psychedelics but an equivalent amount of other drugs.[11] In modern trials, psychedelics have been found to reduce anxious,[14,15] depressive,[15,16] and obsessive-compulsive symptoms,[17] as well as addictive behaviours,[18,19] often for several months after just one or two exposures. Extensive historical and modern evidence now supports the view that, administered in a controlled environment with appropriate support, psychedelics have a favourable safety profile.[20]

Depression is a major public health problem; it is a leading contributor to the global burden of disease, affecting hundreds of millions of people worldwide, and costing the USA alone more than US$200 billion each year.[21] Antidepressant medications and cognitive behavioural therapy can be effective for some patients, but around 20% do not respond to any intervention, and many of those who do respond, eventually relapse.[22] We aimed to investigate the safety and feasibility of psilocybin in patients with treatment-resistant depression, and to establish an initial impression of its efficacy. We postulated that the treatment would be well tolerated and depressive symptoms would be substantially reduced from baseline at all assessment points, for up to 3 months after treatment.

Methods

Study design and participants

This was an open-label feasibility study in patients with treatment-resistant depression; there was no control group. Patients, investigators, raters, and statisticians were not masked to treatment assignment, and all participants received the study intervention (psilocybin administered in two dosing sessions; an initial safety [low] dose and a subsequent treatment [high] dose). The inclusion criteria were major depression of a moderate to severe degree (17+ on the 21-item Hamilton Depression Rating scale [HAM-D]), and no improvement despite two adequate courses of antidepressant treatment of different pharmacological classes lasting at least 6 weeks within the current depressive episode.[23] Exclusion criteria were: current or previously diagnosed psychotic disorder; immediate family member with a diagnosed psychotic disorder; medically significant condition rendering unsuitability for the study; history of serious suicide attempts (requiring hospitalisation); history of mania; blood or needle phobia; positive pregnancy test at screening or during the study; and current drug or alcohol dependence.

Information about the study's recruitment was sent to general practitioners via the North West London Clinical Research Network. However, patients were also allowed to self-refer to the study if they were UK residents. In every case, patients initiated contact with the research team (via email, letter, or telephone), were sent a study information sheet, and a subsequent telephone screening was arranged, during which the lead psychiatrist on the trial (MBo) obtained information about the patient's demographics, medical and psychiatric history, and other key inclusion or exclusion criteria. The patient's general practitioner or psychiatrist provided written documentation of the patient's diagnosis and mental health background in every case.

This trial received a favourable opinion from the National Research Ethics Service London—West London, was sponsored and approved by Imperial College London's Joint Research and Compliance Office (JRCO), and was adopted by the National Institute for Health Research Clinical Research Network. The National Institute for Health Research/Wellcome Trust Imperial Clinical Research Facility gave site-specific approval for the study.

The study was reviewed and approved by the Medicines and Healthcare products Regulatory Agency (MHRA). All participants provided written informed consent. Study and data monitoring was carried out independently by the Imperial Clinical Research Facility and JRCO.

Procedures

Psilocybin was obtained from THC-pharm (Frankfurt, Germany) and formulated into the investigational medicinal product (5 mg psilocybin in size 0 capsules) by Guy's and St Thomas' Hospitals' Pharmacy Manufacturing Unit (London, UK). A Home Office Licence for storage and dispensing of Schedule One drugs was obtained.

Screening consisted of written informed consent, a thorough evaluation of the patient's physical and mental health background, a psychiatric interview (Mini-International Neuropsychiatric Interview), clinician assessments of depression severity (the 21-item HAM-D and the Montgomery-Åsberg Depression Rating Scale [MADRS], and Global Assessment of Functioning [GAF]; all assessed by MBo), and additional patient-rated scales (16-item Quick Inventory of Depressive Symptoms [QIDS], Beck Depression Inventory [BDI—original version], Spielberger's State-Trait Anxiety Inventory [form 2, trait version only; STAI-T], and the Snaith-Hamilton Pleasure Scale [SHAPS]). Patients also received a thorough physical health check, consisting of an electrocardiogram, routine blood tests, blood pressure, heart rate, and physical examination. At the end of screening, eligible patients were given an opportunity to meet with the two clinical psychiatrists who would support them through the remainder of the trial.

Eligible patients attended a subsequent visit involving a baseline functional MRI (fMRI) scanning session lasting 60 min, followed by an extensive preparatory session with their allocated psychiatrists; fMRI data will be reported elsewhere. This preparatory session involved inviting the patient to talk openly about their personal history (including thoughts on the origins of their depression), a discussion of psilocybin's psychological effects, and simulation of aspects of the dosing session itself, such as listening to a sample of the session music while wearing eyeshades. The preparatory session typically lasted for 4 h, with lunch and breaks provided.

Patients enrolled in the study attended two subsequent dosing sessions that were separated by 7 days. No more than one patient was dosed on any given day. Patients arrived at the research facility (Imperial Clinical Research Facility) at 0900 h, gave a urine sample for drugs of abuse (including amphetamines, benzodiazapines, opiates, and cannabinoids), performed a breathalyser test for alcohol use, and completed interim QIDS, BDI, and STAI-T assessments to ensure no substantial deviation from baseline measures. They were then taken to a dosing room that was pre-decorated (eg, with low lighting). Patients were invited to relax on a ward bed in a supine or reclined position and music was played through high-quality stereo speakers and earphones. The two psychiatrists sat on either side of the bed. Patients were supervised at all times by at least two staff members.

Dosing commenced at 1030 h in every case. Patients received a low oral dose of psilocybin 10 mg (two 5 mg capsules) on a first dosing day and a high oral dose of psilocybin 25 mg (five 5 mg capsules) on a second dosing day, separated by 1 week. Blood pressure, heart rate, and observer ratings of the intensity of psilocybin's acute psychoactive effects (0–4, with 0 signifying no effects and 4 signifying extreme effects[8]) were measured at baseline (typically 5 min before dosing) and 30, 60, 120, 180, 240, 300, and 360 min after dosing. Subjective ratings of the acute altered state of consciousness using the revised

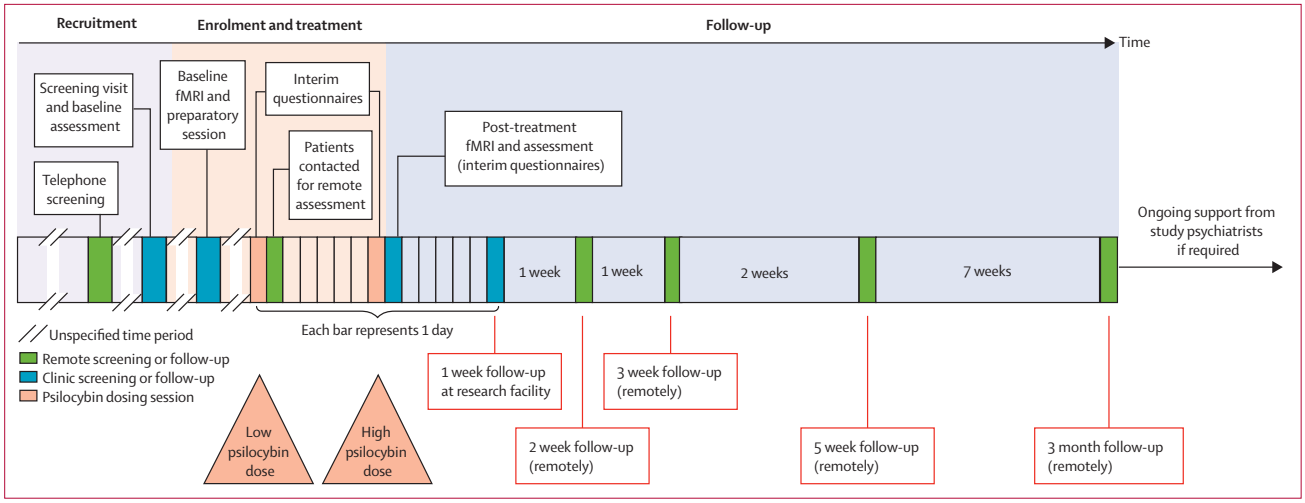


Figure 1: **Schedule of study interventions**

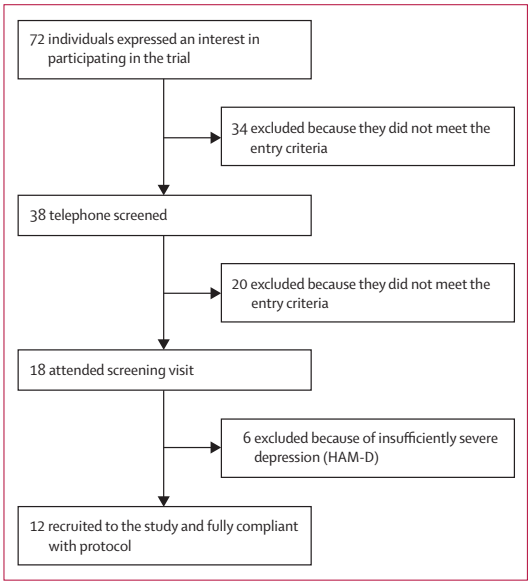
11 dimension altered states of consciousness questionnaire (11D ASC)[24] were completed 6–7 h after dosing.

Psychiatrists adopted a non-directive, supportive approach, allowing the patient to experience a mostly uninterrupted inner "journey". Check-ins (ie, asking the patient how they are feeling) occurred at the same timepoints as the physiological recordings. Tranquilising medications (oral lorazepam and risperidone) were available if necessary. The phenomenology of the acute experience, including accounts of the nature of the therapeutic support provided before, during, and after the experience, and considerations related to the music selection and other aspects of the clinical setting, will be discussed in separate publications.

Return transport from the research facility was organised ahead of dosing sessions. Patients were taken to and from the sessions accompanied by a close friend or relative, and had the option of staying overnight in accommodation adjacent to the hospital. Emergency contact details were provided, and patients confirmed their safe return from the research facility.

Patients were contacted via telephone 1 day after their low-dose session to check on their wellbeing and monitor for any adverse events. Patients returned to the research facility 1 day after their high-dose session for a post-treatment fMRI scan lasting 60 min. After the fMRI scan, patients completed interim questionnaires (QIDS, STAI-T, and HAM-D), and were invited back to the research facility where they were met by their psychiatrists to discuss their experience the previous day.

Patients attended one further study visit to the research facility 1 week after their high-dose session, during which all baseline questionnaires and assessments were repeated and an opportunity was provided for further psychological debriefing (the 1 week follow-up visit). Assessments of HAM-D, MADRS, and GAF were again done by MBo. Subsequent assessments of clinical progress were done via email 2, 3, and 5 weeks after the high-dose session; we assessed only QIDS during subsequent follow-up, so as not to overload the patient. Final follow-up was done remotely at 3 months after the high-dose session, and included QIDS, BDI, STAI-T, and SHAPS. Patients were made aware that they could contact the study psychiatrists at any time if their depression deteriorated. Figure 1 summarises the screening, intervention, and follow-up procedures in this study.



See Online for appendix

Figure 2: **Trial profile**

Outcomes

The main objective of this study is to optimise the protocol for the administration of oral psilocybin in this patient group, while gaining an initial impression of treatment efficacy. The primary outcome measure to assess feasibility was patient-rated subjective intensity of psilocybin's effects, which we report on a 0–1 scale. We assessed the safety of the intervention through clinical monitoring during and after dosing sessions, and during 3 months of face-to-face and remote follow-up. We also aimed to assess the preliminary efficacy of psilocybin in patients with treatment-resistant depression; the primary outcome measure for this endpoint was mean change in the severity of self-reported depressive symptoms (with the 16 item QIDS) from baseline to 1 week after the high-dose psilocybin session. The QIDS was chosen as the primary outcome measure due to its brevity, increasingly widespread use, and validity at 1 week intervals.[25] We chose to assess the primary efficacy endpoint at 1 week after the high-dose session to allow comparison with previous studies of ketamine infusion for treatment-resistant depression;[26] the low-dose session was conceived a priori as a safety session rather than a treatment session. We also assessed change in BDI, STAI-T, and SHAPS between baseline and 1 week and 3 months of follow-up, and change in HAM-D, MADRS, and GAF between baseline and 1 week of follow-up.

Statistical analysis

In this feasibility study, we did not perform a formal power calculation. We planned to recruit 12 patients to provide an initial impression of the tolerability and efficacy of this novel treatment approach. A subsequent protocol amendment (Oct 6, 2015) increased the recruitment to 20 patients to provide statistical power for fMRI imaging. Here, we report findings for the 12 patients initially enrolled; outcome and fMRI data for all 20 patients will be reported separately.

Due to the small population, two-tailed Wilcoxon signed ranks tests were performed for non-parametric data. Two-tailed *t* tests were also performed and the relevant *t* values are provided in the appendix. We provide 95% CIs around the mean differences. We calculated

	Sex	Age, years	Ethnic origin	Employment status	Estimated illness duration, years	Baseline scores			Past unsuccessful medications*	Past psychotherapy	Education	Weekly alcohol intake, units	Previous psilocybin use (time since last use)
						BDI	HAM-D	STAI-T					
1	Female	43	Black Caribbean	Employed	30	36	19	72	SSRI (two), SNRI (two), NDRI, NSSRI, MAOI	None	Postgraduate	1	None
2	Male	40	Hispanic	Unemployed	25	33	28	76	SSRI (two), SNRI, NDRI, NSSRI, Na^+ channel blocker (two), ketamine infusion, TCA	Cognitive narrative therapy	Postgraduate	0	None
3	Male	37	White	Employed	17	22	18	63	SSRI (two), SNRI	Cognitive behavioural therapy, group therapy	Postgraduate	0	None
4	Female	30	White	Studying	10	26	18	67	NDRI, NSSRI	Cognitive behavioural therapy	Postgraduate	0	One use (6 months)
5	Male	34	White	Unemployed	12	38	25	71	SSRI (three), TCA	Cognitive and mindfulness behavioural therapy	Undergraduate	0	None
6	Female	57	White	Unemployed	29	39	23	78	SSRI (four), SNRI, SARI	Counselling	Secondary education	2	Two uses (45 years)
7	Male	52	White	Unemployed	27	33	22	57	TCA, SARI	Counselling, mindfulness	Secondary education	0	Three uses (30 years)
8	Female	37	White	Employed	17	39	17	71	SSRI (two), TCA	Counselling	Undergraduate	2	None
9	Male	37	White	Unemployed	15	32	26	71	SSRI (three), SNRI	Counselling, cognitive behavioural therapy	Postgraduate	6	None
10	Female	36	Black Caribbean	Unemployed	8	47	28	75	SSRI (two), NSSRI	Counselling	Undergraduate	18	Three uses (14 years)
11	Female	64	White	Employed	15	24	17	72	SSRI (four), SNRI (two), NDRI, MAOI, Na^+ channel blocker, SARI, DRI	Cognitive behavioural therapy	Postgraduate	1	Three uses (48 years)
12	Male	45	White	Employed	8	35	17	68	SSRI, TCA	Cognitive behavioural therapy	Undergraduate	0	None

BDI=Beck Depression Inventory. HAMD-D=Hamilton Depression Rating scale. STAI-T=State-Trait Anxiety Inventory. SSRI=selective serotonin-reuptake inhibitor. SNRI=serotonin–noradrenaline reuptake inhibitor. NDRI=noradrenaline–dopamine-reuptake inhibitor. NSSRI=noradrenaline and specific serotonin-reuptake inhibitor. MAOI=monoamine oxidase inhibitor. TCA=tricyclic antidepressant. SARI=serotonin antagonist and reuptake inhibitor. DRI=dopamine-reuptake inhibitor. *One medication from each class, unless otherwise stated.

Table 1: **Baseline and demographic characteristics, by patient**

effect sizes using the Hedges' g formula, which is more appropriate for small sample sizes. Hedges' g values are very similar to Cohen's d values for dependent data.

This trial is registered with the ISRCTN registry, number ISRCTN14426797. The registration was initiated on March 30, 2015, and finalised on July 7, 2015 (delay caused by administrative issues); recruitment started on April 21, 2015, after initiation of public registration.

Role of the funding source

The study funder had no role in the design, data collection, analysis, interpretation, or writing of the report. The corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

Results

Enrolment started on May 1, 2015, and finished on Aug 25, 2015. 72 people were initially considered for the study, most of whom self-referred after hearing about this trial through public outreach work (eg, public presentations by the investigators and media reports). 38 were considered appropriate for a telephone screen, from which 18 were invited for a formal screening visit, and 12 were ultimately recruited for the trial (figure 2), of whom ten were self-referrals. Patients' demographic and clinical characteristics are shown in table 1. Nine of the 12 patients met criteria for severe or very severe depression at baseline (BDI score ≥30), with the remaining three patients meeting criteria for moderate depression (BDI score 19 to <30). 11 patients had received some form of psychotherapy before participation in the study.

The acute effects of psilocybin were well tolerated by all of the patients and no serious or unexpected adverse events occurred. Mean self-rated intensity of psilocybin experience was 0·51 (SD 0·36) for the low-dose session and 0·75 (0·27) for the high-dose session (difference 0·24 [95% CI 0·06–0·41], Z –2·4, p=0·019).

	Severity	Timing or onset	Duration
Patient 1			
Transient anxiety	Mild	Onset of both sessions	60 min
Transient headache	Mild	Day after high-dose session	One day only
Transient confusion	Mild (core drug effect)	Peak of both sessions	60–120 min
Patient 2			
Transient anxiety	Mild	Anticipatory anxiety only (both sessions)	30 min
Patient 3			
Transient anxiety	Mild	Anticipatory anxiety only (both sessions)	30 min
Transient confusion	Mild (core drug effect)	Peak of both sessions	60–180 min
Patient 4			
Transient anxiety	Mild (low dose), moderate (high dose)	Onset of both sessions and peak of high dose	60 min (low dose), 120 min (high dose)
Transient nausea	Moderate	Onset phase of high-dose session	Arose and subsided within 60 min
Transient confusion	Mild (core drug effect)	Peak of both sessions	60–180 min
Transient paranoia	Mild	Peak of high-dose session	Arose and subsided within 30 min
Patient 5			
Transient anxiety	Moderate (low dose), severe (high dose)	Onset of both sessions and peak of high dose	60 min (low dose), 150 min (high dose)
Transient headache	Mild	Day after high-dose session	One day only
Transient confusion	Mild (core drug effect)	Peak of both sessions	60–120 min
Patient 6			
Transient anxiety	Mild	Anticipatory anxiety only (both sessions)	30 min
Patient 7			
Transient anxiety	Mild	Anticipatory anxiety only (both sessions)	30 min
Transient confusion	Mild (core drug effect)	Peak of both sessions	60–180 min
Patient 8			
Transient anxiety	Mild or negligible	Anticipatory anxiety only (both sessions)	30 min
Patient 9			
Transient anxiety	Mild (low dose), moderate (high dose)	Onset of low-dose and high-dose session	60 min (low dose), 150 min (high dose)
Transient headache	Mild	Day after high-dose session	One day only
Transient confusion	Mild (core drug effect)	Peak of both sessions	60–180 min
Patient 10			
Transient anxiety	Mild	Onset of both sessions	60 min
Transient nausea	Mild	Onset and peak of low-dose session	Subsided after 90 min
Transient headache	Mild or moderate	Day after high-dose session	2 days
Transient confusion	Mild (core drug effect)	Peak of both sessions	60–180 min
Patient 11			
Transient anxiety	Moderate (both sessions)	Onset phase and peak of both sessions	150 min (both sessions)
Transient nausea	Mild (high dose)	Onset phase of high-dose session	Arose and subsided within 60 min
Transient confusion	Mild (core drug effect)	Peak of both sessions	60–180 min
Transient paranoia	Mild	Peak of low-dose session	Arose and subsided within 60 min
Patient 12			
Transient anxiety	Mild	Anticipatory anxiety only (both sessions)	30 min
Transient confusion	Mild (core drug effect)	Peak of both sessions	60–180 min

Table 2: **Adverse events by patient**

No patients required tranquilising medications (oral lorazepam and risperidone) during the dosing sessions. Psilocybin's acute psychedelic effects typically became detectable between 30 min and 60 min after dosing, peaked between 2 h and 3 h after dosing, and subsided to negligible levels at which the patient could be assessed for discharge at least 6 h after dosing (appendix). Self-rated experiences on the 11D-ASC questionnaire from the two sessions are shown in the appendix. Results from interim patient questionnaires (QIDS, BDI, and STAI-T), done immediately before the low-dose session to monitor for substantial changes since enrolment, did not differ from baseline (data not shown). Interim questionnaires done the day after the high-dose session showed some reduction in depressive symptoms (data for HAM-D in appendix; data for QIDS and STAI-T not shown).

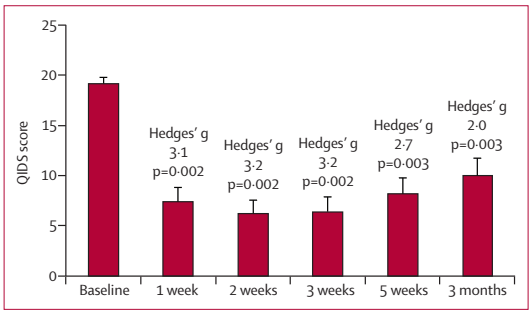


Figure 3: **Mean depression severity (QIDS) over time**
Depression severity determined by self-rated 16-item QIDS. QIDS scores of 16–20 are considered to reflect severe depression, scores of 11–15 are considered moderate depression, scores of 6–10 are considered mild depression, and scores of 5 and less are considered absent depression. All post-treatment assessments were obtained after the high-dose session (ie, 1 week post-treatment refers to 1 week after the high-dose session). Hedges' g values versus baseline are shown. QIDS=Quick Inventory of Depressive Symptoms.

The most common adverse events were transient anxiety (mostly mild) during drug onset (n=12), transient confusion or thought disorder (n=9), mild and transient nausea (n=4), and transient headache (n=4; table 2). These adverse events were expected psychological effects of psilocybin. Subacute headache typically presented 1 day after the psilocybin session, and subsided after 1–2 days. Paranoia presented in only one patient, but this was mild and transient. No prolonged psychotic symptoms were observed in any of the patients. One patient contacted the study psychiatrists during the 3 months of follow-up due to deterioration of their depression, and was referred to their general practitioner.

QIDS depression scores were significantly reduced from baseline to 1 week and 3 months post-treatment, with the maximum effect at 2 weeks (figure 3, table 3). BDI and clinician-administered ratings confirmed these results (figure 4, table 3). All patients showed some reduction in depression severity at 1 week that was sustained in the majority for 3 months (appendix). According to standard criteria for determining remission (eg, a score of ≤9 on the BDI), eight (67%) of the 12 patients achieved complete remission at 1 week and seven patients (58%) continued to meet criteria for response (50% reduction in BDI score relative to baseline) at 3 months, with five of these (42%) still in complete remission (figure 4, table 3). STAI-T anxiety scores were also significantly reduced at 1 week and 3 months post-treatment, as were SHAPS anhedonia scores for 1 week and 3 months post-treatment (table 3).

Discussion

In this open-label, single-arm pilot study, we sought to examine the feasibility of administering psilocybin to patients with treatment-resistant depression as a prelude to a larger randomised controlled trial. Our results support

	QIDS						BDI			STAI-T			SHAPS			HAM-D		MADRS		GAF	
	Baseline	1 week	2 weeks	3 weeks	5 weeks	3 months	Baseline	1 week	3 months	Baseline	1 week	3 months	Baseline	1 week	3 months	Baseline	1 week	Baseline	1 week	Baseline	1 week
Mean (SD)	19·2 (2·0)	7·4 (4·9)	6·3 (4·6)	6·4 (5·1)	8·2 (5·4)	10·0 (6·0)	33·7 (7·1)	8·7 (8·4)	15·2 (11·0)	70·1 (5·8)	40·6 (14·2)	54·8 (14·5)	7·5 (3·7)	1·4 (2·7)	2·8 (3·7)	21·4 (4·5)	7·4 (6·9)	31·0 (5·0)	9·7 (9·8)	50·3 (9·2)	77·7 (13·0)
Difference versus baseline (95% CI)	..	−11·8 (−9·15 to −14·35)	−12·9 (−10·64 to −15·16)	−12·8 (−9·9 to −15·6)	−11·0 (−7·7 to −14·2)	−9·2 (−5·69 to −12·71)	..	−25·0 (−20·1 to −29·9)	−18·5 (−11·8 to −25·2)	..	−29·5 (−22·03 to −36·97)	−15·3 (−7·77 to −22·83)	..	−6·1 (−4·46 to −7·74)	−4·7 (−3·29 to −6·11)	..	−14·0 (−9·6 to −18·4)	..	−23·3 (−17·1 to −29·5)	..	27·3 (18·0 to 36·6)
Z	..	−3·1	−3·1	−3·06	−2·9	−3·0	..	−3·1	−3·1	..	−3·1	−2·9	..	−3·1	−3·1	..	−3·0	..	−3·1	..	3
Hedges' g*	..	3·1	3·2	3·2	2·7	2·0	..	3·2	2·0	..	2·7	1·4	..	1·9	1·3	..	2·4	..	2·7	..	2·4
p value*	..	0·002	0·002	0·002	0·003	0·003	..	0·002	0·002	..	0·002	0·004	..	0·002	0·002	..	0·003	..	0·002	..	0·003

Follow-up refers to the period starting after the second (high-dose) administration of psilocybin. Clinician-administered ratings (HAM-D, MADRS, and GAF) were completed only at baseline and 1 week after the high-dose session. QIDS=Quick Inventory of Depressive Symptoms. BDI=Beck Depression Inventory. STAI-T=State-Trait Anxiety Inventory. SHAPS=Snaith-Hamilton Pleasure Scale. HAM-D=Hamilton Depression Rating Scale. MADRS=Montgomery-Åsberg Depression Rating Scale. GAF=Global Assessment of Functioning. *Compared with baseline.

Table 3: **Clinical ratings at baseline and follow-up**

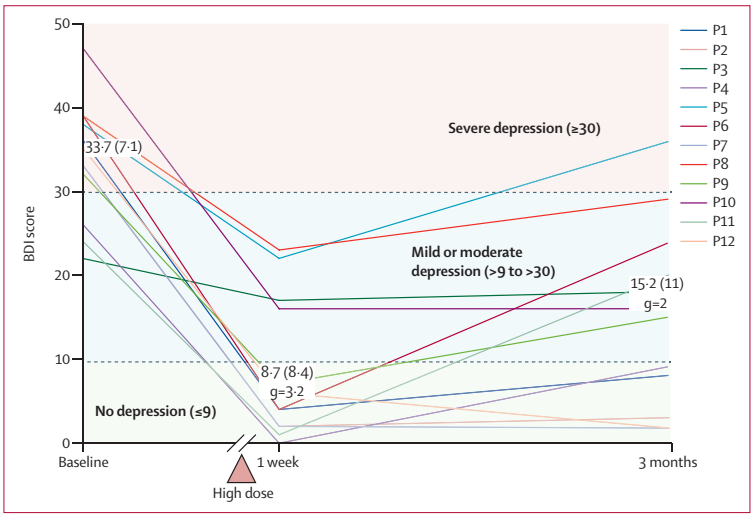


Figure 4: **Depression severity (BDI) over time, by patient**
Figure shows depression severity (BDI) over time plotted for each of the 12 patients. Mean values (SD) are shown as well as the relevant effect sizes (Hedges' g) versus baseline. BDI=Beck Depression Inventory.

the view that, done with appropriate safeguards (eg, careful screening and adequate therapeutic support), psilocybin can be safely administered to this patient group.

Because this was a small-scale feasibility study with an open-label design, strong inferences cannot be made about the treatment's therapeutic efficacy. However, the data do suggest that further research is warranted. The response rate to psilocybin was 67% (n=8) at 1 week after treatment (HAM-D and BDI), and seven of these eight patients also met criteria for remission. Moreover, 58% (n=7) of the patients maintained their response for 3 months, and 42% (n=5) remained in remission. It is also worth noting that psilocybin has a favourable toxicity profile and is not associated with compulsive drug-seeking behaviours in animals or human beings. The side-effects that we noted were minor, and expected in light of previous studies of psilocybin.[27]

Spontaneous recovery in refractory depression is rare, and many of the patients in the present study reported having depression for much of their adult lives (mean estimated illness duration 17·8 years [SD 8]). Key questions for future research therefore should address why the therapeutic effect observed in the present study is so large, and if it can be replicated when tighter experimental controls are introduced. Because the treatment in our study consisted of not just two psilocybin administrations but also psychological support before, during, and after these sessions, as well as a positive therapeutic environment for the sessions, the relative effects of these factors need to be determined, which can only be done by conducting further trials with appropriate control conditions.

A logical next step would be to carry out a placebo-controlled randomised trial in which the level of therapist contact is consistent between conditions. This would enable any between-group differences in clinical outcomes to be attributed to psilocybin rather than the psychological support provided. However, a positive interaction between these variables seems likely, and inert placebo-based blinds are known to be ineffective in studies involving conspicuous experimental interventions, because patients can easily discern whether they are in the active condition or not. Use of an active placebo for the control condition might therefore be worth considering. Additionally, randomised comparative efficacy trials (eg, with an optional crossover component) incorporating another treatment for refractory depression (eg, ketamine infusion) could also be explored.

The magnitude and persistence of the antidepressant effects observed here are not incongruent with what has been observed previously with psilocybin in chronic psychiatric conditions. For example, 80% of long-term heavy tobacco smokers demonstrated abstinence from smoking 6 months after two treatment sessions with psilocybin.[18] Alcohol-dependent patients demonstrated significantly reduced drinking behaviours over 8 months after one or two psilocybin sessions.[19] Significantly decreased anxiety and depression scores were observed 3 and 6 months after a single dose of psilocybin in patients with anxiety related to end-stage cancer,[15] and improvements in wellbeing lasting for more than 1 year were observed in healthy individuals given a single dose of psilocybin.[8] Rapid and enduring decreases in depressive symptoms were also recently found in a small-scale feasibility trial involving the psychedelic brew, ayahuasca.[16]

It is important to consider the limitations of this pilot study; for example, although all patients showed some clinical improvements for at least 3 weeks after treatment, and no serious or unexpected adverse reactions were observed, enduring improvements beyond 3 weeks were not observed universally, and five of the 12 patients showed a degree of relapse at 3 months.

One should be cautious of the potential for inflated effect sizes in early trials, particularly when the sample size is small. That all patients showed some improvement in their depressive symptoms for up to 3 weeks after treatment could be suggestive of an expectancy bias. It may also be relevant that most patients in this trial were self-referring and, thus, actively sought this treatment. Psychedelics are known to promote suggestibility,[28] which might have further enhanced positive outcomes. Future double-blind randomised controlled trials could address the role of expectancy and suggestibility by measuring and controlling these variables. For example, patients could be asked about their pre-treatment expectations, suggestions could be controlled between conditions, and outcomes from self-referred patients could be compared with those from patients referred via clinicians. From a more pragmatic perspective, if expectancy or suggestibility are found to be influential in the context of psychedelic therapy, they could be treated as exploitable components of the treatment model rather than confounding variables.

Serotonergic antidepressants have been found to down-regulate the primary receptor target of psilocybin (the 5-HT_{2A} receptor) and attenuated subjective responses to psychedelics have previously been reported in individuals chronically medicated with serotonergic antidepressants.[29] Thus, patients may be required to withdraw from concurrent antidepressant medication before receiving psilocybin and this should only ever be done with care.

In conclusion, we sought to assess the safety and tolerability of psilocybin plus psychological support in patients with unipolar treatment-resistant depression. Our findings support the feasibility of this approach and the magnitude and duration of the post-treatment reductions in symptom severity motivate further controlled research. Psilocybin has a novel pharmacological action in comparison with currently available treatments for depression (ie, 5-HT_{2A} receptor agonism) and thus could constitute a useful addition to available therapies for the treatment of depression.

Contributors

RLC-H and DJN designed the study and RLC-H wrote the report. RLC-H coordinated the study, and collected and analysed the data. MBo was the lead psychiatrist on the trial. MBo, JR, CMJD, DE, and MBl provided psychological support for the patients. All authors critically revised the report or contributed important intellectual content.

Declaration of interests

DT has received research funding and lecture honoraria from Servier, and lecture honoraria from Lundbeck. The other authors declare no competing interests.

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