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Single-Dose Psilocybin Treatment for Major Depressive Disorder
A Randomized Clinical Trial

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IMPORTANCE Psilocybin shows promise as a treatment for major depressive disorder (MDD).

OBJECTIVE To evaluate the magnitude, timing, and durability of antidepressant effects and safety of a single dose of psilocybin in patients with MDD.

DESIGN, SETTING, AND PARTICIPANTS In this phase 2 trial conducted between December 2019 and June 2022 at 11 research sites in the US, participants were randomized in a 1:1 ratio to receive a single dose of psilocybin vs niacin placebo administered with psychological support. Participants were adults aged 21 to 65 years with a *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* diagnosis of MDD of at least 60 days' duration and moderate or greater symptom severity. Exclusion criteria included history of psychosis or mania, active substance use disorder, and active suicidal ideation with intent. Participants taking psychotropic agents who otherwise met inclusion/exclusion criteria were eligible following medication taper. Primary and secondary outcomes and adverse events (AEs) were assessed at baseline (conducted within 7 days before dosing) and at 2, 8, 15, 29, and 43 days after dosing.

INTERVENTIONS Interventions were a 25-mg dose of synthetic psilocybin or a 100-mg dose of niacin in identical-appearing capsules, each administered with psychological support.

MAIN OUTCOMES AND MEASURES The primary outcome was change in central rater–assessed Montgomery-Asberg Depression Rating Scale (MADRS) score (range, 0-60; higher scores indicate more severe depression) from baseline to day 43. The key secondary outcome measure was change in MADRS score from baseline to day 8. Other secondary outcomes were change in Sheehan Disability Scale score from baseline to day 43 and MADRS-defined sustained response and remission. Participants, study site personnel, study sponsor, outcome assessors (raters), and statisticians were blinded to treatment assignment.

RESULTS A total of 104 participants (mean [SD] age, 41.1 [11.3] years; 52 [50%] women) were randomized (51 to the psilocybin group and 53 to the niacin group). Psilocybin treatment was associated with significantly reduced MADRS scores compared with niacin from baseline to day 43 (mean difference,−12.3 [95% CI, −17.5 to −7.2]; P <.001) and from baseline to day 8 (mean difference, −12.0 [95% CI, −16.6 to −7.4]; P < .001). Psilocybin treatment was also associated with significantly reduced Sheehan Disability Scale scores compared with niacin (mean difference, −2.31 [95% CI, 3.50-1.11]; P < .001) from baseline to day 43. More participants receiving psilocybin had sustained response (but not remission) than those receiving niacin. There were no serious treatment-emergent AEs; however, psilocybin treatment was associated with a higher rate of overall AEs and a higher rate of severe AEs.

CONCLUSIONS AND RELEVANCE Psilocybin treatment was associated with a clinically significant sustained reduction in depressive symptoms and functional disability, without serious adverse events. These findings add to increasing evidence that psilocybin—when administered with psychological support—may hold promise as a novel intervention for MDD.

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Visual Abstract

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Multimedia

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Interest in the therapeutic potential of the psychedelic psilocybin has skyrocketed in recent years, spurred in part by increasing awareness of the limitations of currently approved pharmacological treatments for major depressive disorder (MDD)[1-5] and in part by recent studies suggesting that psilocybin engenders a rapid antidepressant response that far outlasts the presence of the drug in the body.[6-15] However, recent critiques highlight notable limitations in many of these studies,[16-19] including small sample sizes, assessments by raters likely to be functionally unblinded, an open or waitlist comparator design, and an inadequate assessment of adverse events (AEs). Larger recent studies have addressed these issues to various degrees, but report primary end points of short duration,[14,15] leaving open the question of the long-term clinical utility of psilocybin for an often chronic condition such as MDD.

The current study seeks to address these issues using a randomized, multiblinded design that compared a single dose of psilocybin with an active placebo comparator (niacin), with outcome assessments conducted by blinded centralized raters to examine the timing of onset of action, durability of benefit, and safety profile of psilocybin over a 6-week period.

Key Points

Question What are the efficacy and safety of psilocybin in patients with major depressive disorder?

Findings In a randomized, placebo-controlled, 6-week trial in 104 adults, a 25-mg dose of psilocybin administered with psychological support was associated with a rapid and sustained antidepressant effect, measured as change in depressive symptom scores, compared with active placebo. No serious treatment-emergent adverse events occurred.

Meaning A 25-mg dose of psilocybin was well tolerated and may hold promise as a treatment for major depressive disorder when combined with psychological support.

Methods

Study Design Overview and Oversight

This randomized, 2-group, phase 2 clinical trial was designed to evaluate the efficacy of psilocybin vs niacin (active placebo) administered with psychological support in patients with MDD. The trial was conducted at 11 US sites from December 2019 to June 2022 (list of sites provided in eTable 1 in Supplement 3). The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice Guideline. Participants provided written informed consent before engaging in study-specific procedures. The protocol was approved by a central institutional review board (Western Institutional Review Board Copernicus Group) and/or site institutional review boards. The trial protocol is available in Supplement 1 and the statistical analysis plan is available in Supplement 2.

Participants

Recruitment occurred through a study-specific website, clinical programs at participating institutions, advertisements, and national clinician-focused and patient-advocate listservs. Eligible participants were medically healthy adults aged 21 to 65 years who met *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*) criteria for MDD with a current depressive episode of at least 60 days assessed by the *Structured Clinical Interview for DSM-5 Disorders Clinical Version*.[20] Participants were required to have a central rater–assessed Montgomery-Asberg Depression Rating Scale (MADRS) total score greater than or equal to 28 at screening, with less than or equal to 30% improvement in MADRS score during a 7- to 35-day period to allow for a psychiatric medication taper if indicated (including not receiving antidepressants for ≥2 weeks or 5 half-lives, whichever was longer), to ensure randomized participants met criteria for moderate to severe MDD at the baseline assessment. Additional exclusion criteria included personal or first-degree family history of psychosis or mania, moderate/severe alcohol or drug use disorder, being unable/unwilling to discontinue prohibited psychotropic medications, use of a psychedelic drug in the past 5 years or more than 10 lifetime uses, active suicidal ideation with intent or plan, or suicidal behavior in the past 12 months. There were no exclusions for number of prior depressive episodes, length of current episode, maximum symptom severity, or number of previous pharmacological or behavioral treatments, with the exception of history of deep brain or vagus nerve stimulation, which were exclusionary as a proxy for severe treatment resistance. See the study protocol in Supplement 1 for a full list of inclusion and exclusion criteria. Participants were queried regarding demographic information by site personnel; race and ethnicity were collected in accordance with the US Food and Drug Administration guidance document *Collection of Race and Ethnicity Data in Clinical Trials*.[21]

Study Procedures

Following the 7- to 35-day screening period to allow for a medication taper if needed, participants who continued to meet eligibility criteria completed baseline assessments followed by 6 to 8 hours of preparation. On the day of dosing (ie, receipt of the intervention), eligible participants were randomized in a 1:1 ratio using permuted blocks with random block sizes of 2, 4, and 6, with randomization stratified by site, to receive a single 25-mg oral dose of psilocybin or 100-mg dose of niacin. Randomization was administered centrally by the study's clinical research organization via the Advantage eClinical data system. Statistical programs generated for randomization by unblinded statistical staff at the clinical research organization included a master medication list program that generated a random blinded bottle number code and associated treatment for each bottle and a treatment assignment program that assigned participants to a treatment. Bottles were labeled by the drug distributor with a blinded bottle number prior to distribution to sites. On the day of dosing, after participants were confirmed to be eligible, the data system identified the participant's treatment assignment based on the treatment table.

The data system then identified a bottle shown to be available on site containing the appropriate treatment. Only the blinded bottle number was then displayed to site staff for treatment administration.

Niacin was used as an active placebo that produces an acute physiological response (flushing) thought to aid in blinding.[8,22] Study drug administration occurred on the same day as randomization (day 1), no later than 7 days following the baseline assessment. Postdosing assessments were conducted on days 2, 8, 15, 29, and 43. Participants, study sponsor, and study site personnel were blinded to treatment group until unblinding following data lock.

Study drugs were administered within a "set and setting" protocol[23] that was identical for participants randomized to receive either psilocybin or niacin placebo and that included (1) 6 to 8 hours of preparatory sessions with 2 facilitators between the baseline assessment and the day of dosing, (2) a 7- to 10-hour dosing session conducted in a comfortable room under the supervision of the same facilitators, and (3) 4 hours of postdose integration sessions during which participants were invited to discuss their dosing experience with the facilitators. All set and setting sessions (eg, preparatory, dosing, integration) were protocolized and communicated via instructions in a manual for clinical facilitators. During the dosing session, participants were encouraged to wear eyeshades and listen to a curated playlist on headphones. Lead facilitators were doctoral-level psychologists or physicians with MDD treatment experience and co-facilitators held a minimum of a bachelor's degree in a mental health–related field. All facilitators completed study-specific training prior to engaging with participants.

Efficacy Assessments

The primary study outcome was between-group difference in mean change of central rater–assessed MADRS score from baseline to day 43. MADRS is a 10-item scale with a scoring range of 0 to 60, with higher scores indicating more severe depression.[24] A minimal clinically important difference (MCID) in change in MADRS score was not prespecified, although depression trial literature supports a placebo-adjusted change in score as low as 2 and as high as 9 and an absolute change from pretreatment of 6 as clinically meaningful and a change of 12 as clinically substantial.[25,26] To reduce the risk of functional unblinding of raters, all MADRS assessments, including those at screening and baseline, were conducted via telephone[27,28] by trained, remote central raters who maintained interrater reliability and were blinded to participant treatment assignment, study visit, and the specifics of the protocol and study design.

The key secondary outcome was change in total MADRS score from baseline to day 8. Additional secondary outcomes included change in Sheehan Disability Scale (SDS) score from baseline to day 43 and proportion of participants with a sustained depressive symptom response, defined a priori as at least a 50% reduction from baseline MADRS score at days 8, 15, 29, and 43, and sustained depressive symptom remission, defined a priori as MADRS score less than or equal to 10 at days 8, 15, 29, and 43. The SDS comprises self-rated items that measure the extent to which psychiatric symptoms have impaired functioning in patients' work/school, social, and family/home responsibilities. Scores for each section range from 0 to 10,[29] and the total score was calculated as the mean score of all 3 sections. No MCID is defined for active vs control interventions. If the work/school section was not applicable, the mean score was calculated as the mean of social life and family/home responsibilities. Administration of the SDS at baseline and postdosing assessments was overseen by trained and blinded site raters.

Exploratory outcomes included scores on the Clinical Global Impressions Scale, Hamilton Anxiety Rating Scale, Quality of Life Enjoyment and Satisfaction Questionnaire, Symptoms of Major Depressive Disorder Scale, and the Oxford Depression Questionnaire (to assess emotional blunting). These exploratory assessments were completed by self-report overseen by blinded and trained site raters at baseline and all postdosing assessments.

Safety Assessments

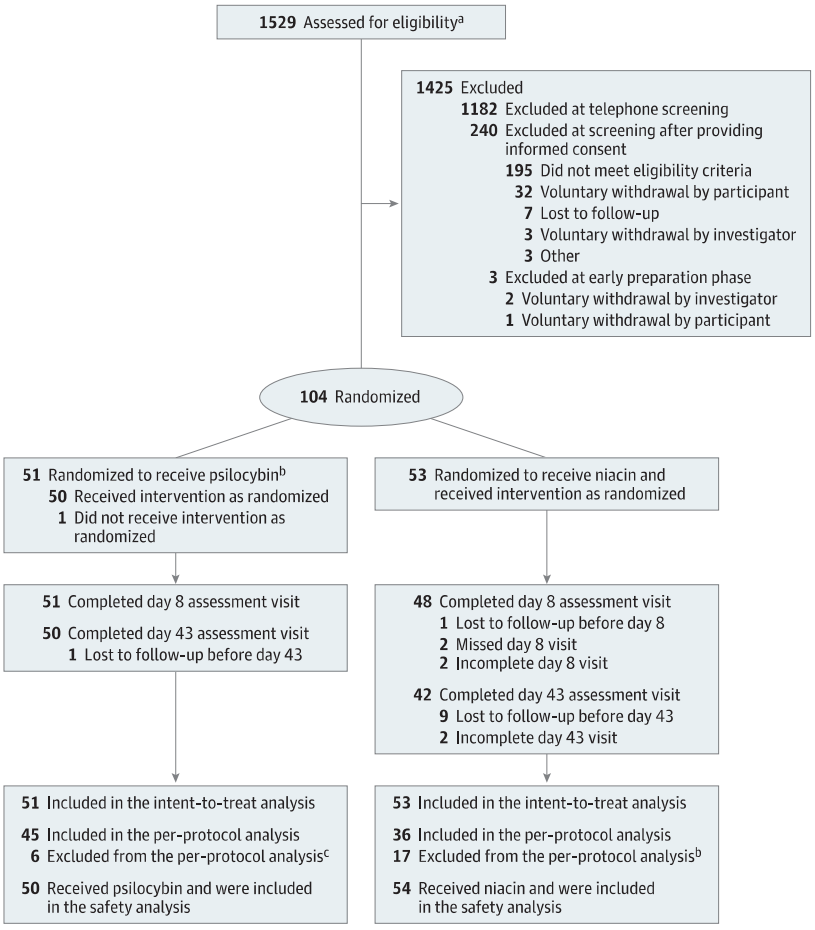
AEs were collected from enrollment through the end of study and were graded for severity, seriousness, and relationship to study product by site principal investigators. Treatment-emergent AEs (TEAEs) were considered any AE that occurred after drug administration. Among TEAEs, an AE was classified as "related" if there was a reasonable possibility that the study drug caused the event as judged by site principal investigators. Solicited adverse events included (1) active suicidal ideation assessed with the Columbia Suicide Severity Rating Scale (C-SSRS) administered by site personnel or MADRS item 10 and verified by clinical assessment, (2) elevated blood pressure or heart rate requiring medication, (3) drug overdose with suicidal intent, (4) headache, (5) nausea, and (6) visual perceptual effects. Serious AEs were classified as those resulting in any of a list of negative health outcomes (eg, death, inpatient hospitalization, significant or persistent incapacity, congenital birth defect/abnormality) following the standard definition.[30]

Statistical Analysis

The US Food and Drug Administration initially recommended day 8 as the primary end point, so the study was powered on the assumption of a mean change in MADRS score from baseline to day 8 of 18 points and from baseline to day 43 of 17 points in the psilocybin group. In the niacin group, a mean change in MADRS score of 10 points was assumed for all postdosing assessments. An SD of 10 points was assumed for both groups. With the expectation of a 5% dropout rate by day 8 and an additional 7.5% dropout rate by day 43 and 2-sided α of .05, a sample size of 100 participants resulted in 92% power for the primary day 43 end point and 98% power for the key secondary day 8 end point. The US Food and Drug Administration subsequently recommended changing the primary end point to day 43; in response, the sample size was increased from 80 to 100 to account for additional dropout expected with the longer-term primary outcome follow-up.

The primary efficacy analysis was a de facto estimand conducted on the intent-to-treat (ITT) population that included all randomized participants analyzed according to randomized

Figure 1. Participant Flow in a Study of Single-Dose Psilocybin Treatment for Major Depressive Disorder



[a] Includes all potential participants from the point of telephone screening.

[b] One participant randomized to receive psilocybin received niacin and was included in the niacin group for the safety population.

[c] Reasons for exclusion included missing day 8 or day 43 central rater Montgomery-Asberg Depression Rating Scale assessments or major protocol deviations.

See eFigure 1 in Supplement 3 for additional details.

treatment group. Analyses of other efficacy outcomes used a similar approach. The per-protocol (PP) population included a subset of the ITT population that received study drug, completed day 8 and day 43 MADRS assessments, and had no major protocol deviations affecting the primary or secondary outcomes. The safety population included all randomized participants who received a study drug. Safety data were analyzed according to the intervention received.

Analysis of continuous outcomes used a mixed-effects model for repeated measures with an unstructured covariance matrix, adjusted for the baseline score of the relevant outcome assessment, site, sex, and treatment-resistant depression (TRD) status as fixed effects with no imputation of missing data. Time was included as a categorical variable, and a treatment × time effect was included to evaluate between-group differences in mean scores at each point. Sensitivity analyses using multiple imputation methods were run for the primary and key secondary outcomes. Sustained depressive symptom response and remission were assessed using logistic regression models adjusted for sex and TRD, with site excluded due to low participant counts at some sites resulting in model convergence issues. In addition to odds ratios (ORs) with 95% CIs, absolute differences with 95% CIs were also calculated.

A sequential significance testing procedure was used to control the overall α level at .05 for primary and secondary end points. Two-sided tests were used in the following prespecified order with testing halted the first time the null hypothesis is not rejected (ie, first *P* value ≥.05): change in MADRS score from baseline to day 43, change in MADRS score from baseline to day 8, change in SDS score from baseline to day 43, sustained depressive symptom response, and sustained depressive symptom remission. No procedure for α-level control was applied for exploratory end points, therefore *P* values reported for these outcomes in eTables 4-8 in Supplement 3 should be considered nominal (ie, not adjusted for multiple comparisons).

Incidence of AEs was summarized using counts, percentages, and Clopper-Pearson 95% CIs for the following protocol-defined study periods: enrollment through day 43, dosing (day 1) through day 9, and day 10 through day 43. Relative incidence for TEAEs was calculated by dividing the percentage of participants experiencing an event in the psilocybin treatment group by the percentage in the niacin group and were presented with Wald 95% CIs. Percent difference in AEs between groups with 95% CIs were also calculated.

All statistical analyses were performed using SAS, version 9.4 (SAS Institute). See the statistical analysis plan in Supplement 2 for additional details.

Results

Participants

Among 1529 potential participants who completed prescreening, 347 signed informed consent, 240 were excluded at screening, 3 were excluded prior to randomization, and 104 were randomized, received the study drug, and comprised the ITT population (51 in the psilocybin group and 53 in the niacin group) (**Figure 1**). Median (IQR) time between enrollment and randomization on the morning of dosing was comparable for the 2 groups (28 [21-36] days for psilocybin and 28 [20-35] days for niacin). Enrollment by study site is detailed in eTable 1 in Supplement 3.

One participant randomized to receive psilocybin received the incorrect treatment, resulting in 50 participants receiving psilocybin and 54 receiving niacin. Baseline characteristics of the ITT population are provided in **Table 1**. Mean (SD) participant age was 40.4 (10.9) years in the psilocybin group and 41.8 (11.7) years in the niacin group; half were men and the majority (89%) were White. Ten participants (19.6%) in the psilocybin group and 13 (24.5%) in the niacin group reported previous lifetime use of a psychedelic. Median (IQR) length of the current depressive episode was 53 (25-135) weeks for psilocybin vs 81 (26-145) weeks for niacin; 4 participants (8%) in the psilocybin group vs 10 (19%) in the niacin group were experiencing a first episode (the remainder were experiencing a recurrent disorder). Seven participants in the psilocybin group vs 6 in the niacin group (12.5% of the ITT sample) met criteria for TRD. The median (IQR) number of prior pharmacologic treatments in the current episode was 1 (0-2) for both groups. Fifteen participants (29%) in the psilocybin group and 8 (15%) in the niacin group completed a medication taper prior to dosing. By 6 weeks, 1 participant in the psilocybin group and 9 in the niacin group had withdrawn or been lost to follow-up; 3 participants in the psilocybin group and 3 in the niacin group started antidepressant medication prior to study completion at day 43, of whom 2 participants in the psilocybin group and 1 in the niacin group also commenced psychotherapy prior to study completion. No participants withdrew due to an AE.

Efficacy

The psilocybin-treated group showed greater change vs niacin in central rater-assessed MADRS score from baseline to day 43 (mean difference, −12.3 [95% CI, −17.5 to −7.2]; P <.001) (**Table 2** and **Figure 2**) and from baseline to day 8 (key secondary end point) (mean difference, −12.0 [95% CI, −16.6 to −7.4]; P < .001). Similar results were observed for day 15 and day 29 (Figure 2) and in multiple imputation sensitivity analyses accounting for missing data (1 psilocybin and 9 niacin participant measures missing and imputed at day 43 and 0 psilocybin and 3 niacin participant measures missing and imputed at day 8; see eTable 2 and eAppendix in Supplement 3 for full details). More participants receiving psilocybin than niacin had sustained depressive symptom response (20/48 [42%] vs 5/44 [11%]; adjusted absolute difference, 30.3 [95% CI, 13.5-47.1]; P = .002; OR, 5.6 [95% CI, 1.9-16.7]; P = .002) (Table 2). Sustained depressive symptom remission rate appeared greater

Table 1. Baseline Participant Characteristics

Characteristic	Psilocybin (n = 51)	Niacin (n = 53)
Sex, No. (%)		
Men	27 (53)	25 (47)
Women	24 (47)	28 (53)
Age, mean (SD), y	40.4 (10.9)	41.8 (11.7)
Ethnicity, No. (%)	n = 50	
Hispanic or Latino	4 (8)	12 (23)
Not Hispanic or Latino	46 (92)	41 (77)
Race, No. (%)		n = 51
Black or African American	3 (6)	0
White	44 (86)	49 (96)
Multiracial	4 (8)	2 (4)
Annual income, No. (%), $	n = 45	n = 44
≤24 999	8 (18)	6 (14)
25 000-49 999	3 (7)	8 (18)
50 000-74 999	5 (11)	3 (7)
75 000-99 999	6 (13)	8 (18)
≥100 000	23 (51)	19 (43)
Treatment-resistant depression, No. (%)[a]	7 (14)	6 (11)
Underwent a medication taper prior to randomization, No./total No. (%)[b]	15 (29)	8 (15)
Baseline MADRS score, mean (SD)[c]	35.5 (5.7)	35.0 (4.5)
Baseline SDS score, mean (SD)[c]	6.69 (1.99)	7.14 (1.61)
Length of current depressive episode, median (IQR), wk[d]	53 (25-135)	81 (26-145)
Prior depressive episodes, No. (%)[d]		
0	4 (8)	10 (19)
1	10 (20)	5 (9)
2	8 (16)	15 (28)
3	9 (18)	3 (6)
4	6 (12)	9 (17)
5	4 (8)	6 (11)
>5	10 (20)	5 (9)
Prior pharmacological treatments for current depressive episode, median (IQR)[e]	1 (0-2)	1 (0-2)

[a] Based on Massachusetts General Hospital Antidepressant Treatment History Questionnaire as meeting the following criteria: self-report of receiving treatment with ≥2 antidepressant medications (or 1 antidepressant with ≥1 augmenting agent) for this current depressive episode for ≥8 weeks, dose of medication is equal to or greater than minimally adequate dose, and response to these medications is <50% improvement.

[b] Participants underwent medication taper if they met all other study inclusion/exclusion criteria, except for use of a prohibited psychotropic medication, and were willing to undergo tapering.

[c] Score from the Montgomery-Asberg Depression Rating Scale (MADRS) assessment completed at the baseline visit. For participants with a repeated baseline visit, the score from the repeated visit was used for analysis. The median value is based on all participants in the intent-to-treat population. The total sample median score of 35.5 is consistent with a severe major depressive episode. Maximal change score on the MADRS is 60 points; maximal change score on the Sheehan Disability Scale (SDS) is 10 points, with lower scores indicating clinical improvement. Minimal clinically important difference (MCID) from baseline is a 6-point improvement for the MADRS and a 1.33-point improvement on the SDS as scored in this study.

[d] Length of current depressive episode and number of unique lifetime depressive episodes were determined via the clinician-administered Structured Interview for *DSM-5* Disorders-Clinical Trials Version.

[e] Pharmacological treatments taken for ≥8 weeks reported on the Massachusetts General Hospital Antidepressant Treatment History Questionnaire.

Table 2. Overall Summary of Primary, Secondary, and Select Exploratory Efficacy Outcomes

Outcome	Mean change from baseline (95% CI)[a]		Mean difference (95% CI)[a]	
	Psilocybin (n = 51)	Niacin (n = 53)	Psilocybin vs niacin	*P* value
MADRS total score[b]				
Day 2	−2.7 (−4.1 to −1.3)	−2.7 (−4.1 to −1.3)	−0.1 (−2.1 to 1.9)	.95
Day 8 (key secondary outcome)	−17.8 (−21.1 to −14.6)	−5.8 (−9.1 to −2.6)	−12.0 (−16.6 to −7.4)	<.001[c]
Day 15	−18.0 (−21.3 to −14.7)	−6.9 (−10.3 to −3.5)	−11.1 (−15.8 to −6.3)	<.001
Day 29	−19.2 (−22.6 to −15.8)	−5.5 (−9.0 to −2.0)	−13.7 (−18.6 to −8.8)	<.001
Day 43 (primary outcome)	−19.1 (−22.7 to −15.5)	−6.8 (−10.5 to −3.1)	−12.3 (−17.5 to −7.2)	<.001[c]
SDS mean score[b]				
Day 8	−3.85 (−4.60 to −3.10)	−1.49 (−2.27 to −0.72)	−2.36 (−3.46 to −1.26)	<.001
Day 15	−3.97 (−4.73 to −3.21)	−1.76 (−2.56 to −0.97)	−2.21 (−3.33 to −1.09)	<.001
Day 29	−4.26 (−5.08 to −3.45)	−1.78 (−2.64 to −0.93)	−2.48 (−3.68 to −1.28)	<.001
Day 43 (secondary outcome)	−4.07 (−4.88 to −3.26)	−1.76 (−2.62 to −0.91)	−2.31 (−3.50 to −1.11)	<.001[c]
Other secondary outcomes	**No./total No. (%)**[d]	**No./total No. (%)**[d]	**Difference (95% CI)**[e]	
Sustained depressive symptom response[f]	20/48 (41.7)	5/44 (11.4)	30.3 (13.5 to 47.1)[g]	.002[c,d]
Sustained depressive symptom remission[h]	12/48 (25.0)	4/44 (9.1)	15.9 (1.0 to 30.8)[i]	.05[d]

Abbreviations: MADRS, Montgomery-Asberg Depression Rating Scale; SDS, Sheehan Disability Scale.

[a] Mixed model for repeated measures with an unstructured covariance structure adjusted for baseline score, site, sex, and treatment-resistant depression. Negative values indicate an improvement in symptom severity. For additional information, see footnote c in Table 1.

[b] All outcomes are exploratory unless otherwise noted.

[c] Statistically significant based on sequential testing procedure.

[d] Restricted to participants in the intent-to-treat population with MADRS assessments at baseline, and days 8, 15, 29, and 43 after baseline.

[e] *P* value from logistic regression model adjusted for sex and treatment-resistant depression, predicting odds of response or remissions for psilocybin compared with niacin. Wald 95% CIs are provided for difference in difference in response and remission rates.

[f] Sustained depressive symptom response is defined as ≥50% reduction from baseline central rater MADRS total score at each of the postdose assessments on days 8, 15, 29, and 43.

[g] Odds ratio, 5.60 (95% CI, 1.87-16.74).

[h] Sustained depressive symptom remission is defined as a central rater MADRS total score ≤10 at each of the postdose assessments on days 8, 15, 29, and 43.

[i] Odds ratio, 3.37 (95% CI, 0.99-11.47).

with psilocybin, but the difference was not statistically significant (12/48 [25%] for psilocybin vs 4/44 [9.1%] for niacin; adjusted absolute difference, 15.9 [95% CI, 1.0-30.8]; *P* = .05; OR, 3.4 [95% CI, 1.0-11.5]) (Table 2). Rates of response and remission at each postdosing assessment are shown in eTable 3 in Supplement 3. Mean change difference in SDS-assessed functional disability score from baseline to day 43 was greater in the psilocybin vs niacin group (−2.31 [95% CI, 3.50-1.11]; *P* < .001) (Table 2). Psilocybin treatment was associated with improvements in various exploratory end points, including reductions in global disease severity, self-reported depressive and anxiety symptoms, and improvement in quality of life, while having no effect on emotional blunting (eTables 4-8 in Supplement 3).

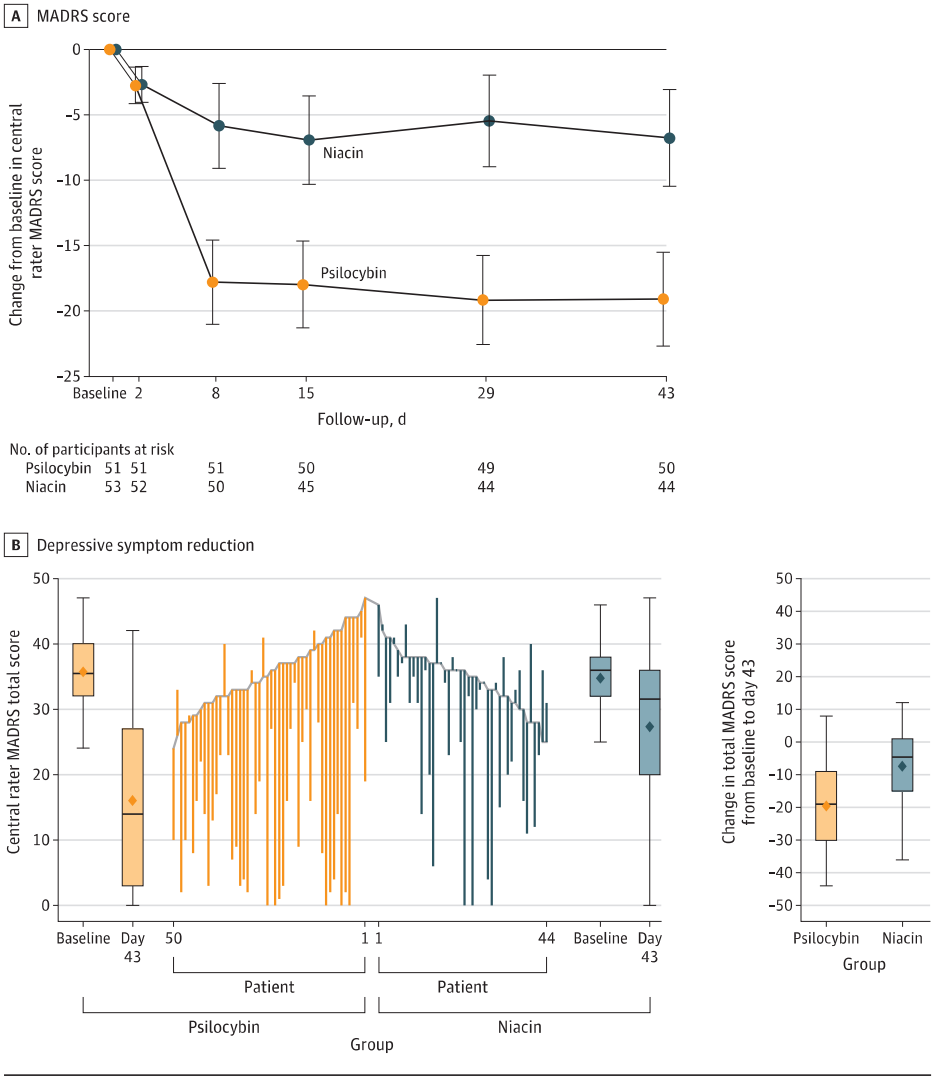
Results in the PP population of 81 participants (45 in the psilocybin group and 36 in the niacin group, excluding 5 [10%] in the psilocybin and 8 [15%] in the niacin group, due to major protocol deviations likely to impact primary or secondary outcomes; see eAppendix and eFigure 1 in Supplement 3 for details) were similar in direction, magnitude, and significance to results in the ITT population, with the exception that the difference in sustained remission between psilocybin- and niacin-treated participants became statistically significant (12/44 [27%] with psilocybin vs 3/36 [8%] with niacin; adjusted absolute difference, 18.9% [95% CI, 3.0%-34.9%]; OR, 4.0 [95% CI, 1.0-15.7]; *P* = .04) (eTable 9 in Supplement 3).

Safety

In the safety population (Figure 1), 44 of 50 participants (88%) receiving psilocybin and 33 of 54 (61%) receiving niacin reported at least 1 AE through day 43. Three serious AEs occurred between enrollment and randomization (nephrolithiasis; incisional hernia, obstructive; and appendicitis; **Table 3**). From randomization on the day of dosing (day 1) through day 9, a total of 41 of 50 participants (82%) in the psilocybin group experienced at least 1 drug-related TEAE vs 24 of 54 (44%) in the niacin group (difference, 38% [95% CI, 20.6%-41.3%]; relative incidence [RI], 1.8 [95% CI, 1.3-1.8]). Severe related AEs through day 9 were reported by 4 of 50 participants (8%) receiving psilocybin (migraine in 1 participant, headache in 1 participant, illusion in 1 participant [all solicited], and panic attack and paranoia in 1 participant) vs 0 in the niacin group. The rates of mild and moderate drug-related TEAEs in the same period were higher for psilocybin vs niacin (mild: difference, 35% [95% CI, 17.9%-52.9%]; RI, 1.8 [95% CI, 1.1-1.8]); moderate: difference, 18% [95% CI, 5.8%-30.8%]; RI, 2.3 [95% CI, 1.0-5.7]). From day 10 through day 43, related TEAEs were reported by 2 of 50 participants (4%) in the psilocybin group vs 1 of 53 (2%) receiving niacin (difference, 2% [95% CI, −4.4% to 8.7%]; RI, 2.1 [95% CI, 0.2-22.7]) (Table 3).

Solicited AEs were reported by 38 of 50 participants (76%) receiving psilocybin vs 16 of 54 (30%) receiving niacin (difference, 46% [95% CI, 29.4%-63.4%]; RI, 2.6 [95% CI, 1.7-4.0]).

Figure 2. Change in Montgomery-Asberg Depression Rating Scale (MADRS) Score by Treatment Group



A, Results from mixed model for repeated measures adjusted for baseline score, site, sex, and treatment-resistant depression. Error bars represent 95% CIs; point labels are *P* values for treatment difference for primary (day 43) and key (day 8) secondary end points in the intent-to-treat population. B, Raw value participant change values with means indicated with diamonds and medians indicated by the bar in the boxes. The boxes show the IQR and the whiskers extend from the boxes to indicate the most extreme point that is less than or equal to 1.5 times the IQR. See eFigure 2 in Supplement 3 for additional details.

The majority of solicited events were mild (73 of 91 total events [80%] in the psilocybin group and 22 of 23 total events [96%] in the niacin group). Severe solicited events were reported by 3 participants receiving psilocybin (2 headaches and 1 visual perceptual effects) and 1 headache was reported in a participant receiving niacin. The most common solicited AE was headache in 33 of 50 participants (66%) receiving psilocybin and 13 of 54 participants (24%) receiving niacin (difference, 42% [95% CI, 27.3%-57.6%]; RI, 2.7 [95% CI, 1.6-4.6]), followed by nausea in 24 of 50 participants (48%) receiving psilocybin and 3 of 54 participants (6%) receiving niacin (difference, 42% [95% CI, 24.5%-59.3%]; RI, 8.6 [95% CI, 2.8-26.9]). Visual perceptual effects (assessed following resolution of acute drug effects) were reported by 22/50 (44%) psilocybin participants on the day of dosing and by 3/50 (6%) after the dosing day, all resolved by study conclusion (See Table 3 for details). Based on C-SSRS or MADRS Item 10 scores and confirmed by clinical assessment, no suicidal or self-injurious behavior occurred during the trial and all instances of suicidal ideation were considered passive. One participant receiving psilocybin and 5 in the niacin group had an increase in C-SSRS suicidal ideation score from baseline to end of trial (eTables 10 and 11 in Supplement). No clinically significant changes in vital signs or clinical laboratory tests were observed.

Discussion

In this phase 2 study, treatment with a 25-mg dose of psilocybin administered with psychological support was associated with a statistically and clinically significant reduction in depressive symptoms compared with a niacin placebo, assessed as change in total MADRS score and as rates of sustained response. The 15.9% difference in sustained remission rates between the groups was not significantly different. Improvements in depression were apparent within 8 days of psilocybin dosing, consistent with a rapid onset of action, and were maintained across the 6-week follow-up period, without

Table 3. Summary of Safety Events in the Safety Population

Adverse event (AE)[a]	Enrollment through day 43, No. (%)		Randomization through day 9			Day 10 through day 43		
	Psilocybin (n = 50)	Niacin (n = 54)	Psilocybin (n = 50), No. (%)	Niacin (n = 54), No. (%)	Difference (95% CI), %[b]	Psilocybin (n = 50), No. (%)	Niacin (n = 53), No. (%)	Difference (95% CI), %[b]
At least 1 AE	44 (88)	33 (61)	42 (84)	32 (59)	25 (8.2 to 41.3)	18 (36)	13 (25)	11 (−6.2 to 29.1)
At least 1 related AE[c]	41 (82)	24 (44)	41 (82)	24 (44)	38 (20.6 to 54.6)	2 (4)	1 (2)	2 (−4.4 to 8.7)
At least 1 serious AE	1 (2)	2 (4)			NC			NC
Drug-related AE severity[c]								
Mild	39 (78)	23 (43)	39 (78)	23 (43)	35 (17.9 to 52.9)	1 (2)	1 (2)	0 (−5.2 to 5.5)
Moderate	11 (22)	2 (4)	11 (22)	2 (4)	18 (5.8 to 30.8)	1 (2)		NC
Severe	4 (8)		4 (8)		NC	1 (2)		NC
At least 1 solicited AE[d]	38 (76)	16 (30)	38 (76)	16 (30)	46 (29.4 to 63.4)			NC
Headache[e]	33 (66)	13 (24)	33 (66)	13 (24)	42 (27.3 to 57.6)	NA	NA	NA
Nausea[e]	24 (48)	3 (6)	24 (48)	3 (6)	42 (24.5 to 59.3)	NA	NA	NA
Visual perceptual effects on dosing day	22 (44)	3 (6)	22 (44)	3 (6)	38 (23.4 to 53.5)	NA	NA	NA
Visual perceptual effects after dosing day	3 (6)		3 (6)		NC			NC
At least 1 AE requiring psychiatric attention	2 (4)	1 (2)		1 (2)	NC	2 (4)	1 (2)	2 (−4.4 to 8.7)
At least 1 psychiatric concomitant medication reported[f]	8 (16)	7 (13)	3 (6)	4 (7)	−1 (−11.0 to 8.2)	5 (10)	4 (8)	2 (−8.5 to 13.4)

Abbreviations: NA, not applicable (event not solicited during period); NC, not calculable.

[a] Participants are counted once for each category regardless of the number of events.

[b] Wald 95% CIs for difference in incidences between treatment groups (psilocybin – niacin).

[c] An AE was classified as "related" if there was a reasonable possibility that the study drug or procedure caused the event. Severity and relationship to study drug or procedure were determined by the site principal investigator.

[d] Only solicited events with any occurrences during the study are summarized. See eTable 2 in Supplement 3 for a full list of events solicited during the study.

[e] Headache and nausea were only collected as solicited events during randomization through postdose day 9.

[f] Defined as concomitant medications with WHODRUG ATC2 codes N05 – Psycholeptics or N06 – Psychoanaleptics.

attenuation of the effect, and with higher point prevalence rates of MADRS-defined response and remission than has been observed in recent psilocybin studies of TRD.[10,14] Although an MCID was not specified a priori for this study, the 12.3-point difference in change in score between the psilocybin and niacin groups is larger than the upper limit active placebo difference in the literature of 9 points and the 19.1-point reduction in MADRS score from baseline to day 43 in the psilocybin group is larger than the 12-point difference shown to reflect substantial clinical improvement in patients with TRD.[25] In contrast to prior psilocybin trials for depression,[8,14,15] there was not a significant reduction in depressive symptoms or a psilocybin/placebo difference in depressive symptom status at the day 2 assessment (ie, 1 day after dosing) (Figure 2 and Table 2). This may reflect the fact that to maintain central rater blinding, the 7-day recall period used for all other MADRS assessments was maintained at day 2, with the result that the majority of recall period for the day 2 assessment covered the predosing period during which depressive symptoms remained elevated, based on results from the Symptoms of Major Depressive Disorder Scale (eTable 7 in Supplement 3).

Psilocybin also improved psychosocial functioning compared with niacin as shown by mean difference in SDS score change. Similar results were observed in the per-protocol population and in sensitivity analyses. Psilocybin treatment was associated with improvement in various exploratory end points, including reduced overall disease severity, anxiety and self-reported depressive symptoms, and improved quality of life (eTables 4-7 in Supplement 3). Psilocybin treatment did not evince the type of emotional blunting reported with standard antidepressant medicines (eTable 8 in Supplement 3).[31]

Psilocybin was generally well-tolerated, with most AEs being of mild or moderate severity and generally limited to the acute dosing period. The 8% rate of severe adverse events in participants receiving psilocybin was similar to the 10% rate reported in the study by Goodwin et al in participants with TRD treated with a single 25-mg dose of psilocybin.[14] However, in contradistinction to the study by Goodwin et al, no clinically confirmed active suicidal ideation or suicidal behavior occurred in either randomized group. No serious TEAEs were reported in the current study; however, psilocybin treatment was associated with a higher rate of overall AEs and a higher rate of severe AEs compared with niacin, with these severe AEs being known effects of psilocybin.[17] Moreover, psychedelics may produce AEs not captured by standard rating scales or may induce unrecognized new psychiatric conditions even as they improve target syndromes.[32]

Limitations

Several limitations in this study warrant consideration. First, the success of allocation blinding was not assessed, and it is likely that the acute psychoactive effects of psilocybin produced some degree of functional unblinding that may have contributed to the observed effect in psilocybin-treated

participants and the increased dropout rate in niacin-treated participants.[33] To help address this issue, the current study used off-site centralized raters to reduce the potential impact of unblinding on the assessment of outcomes. Nonetheless, recent data demonstrating high rates of functional unblinding in a randomized, placebo-controlled trial of psilocybin for alcohol use disorder highlight a possible role for measuring blinding effectiveness in future studies of agents with acute psychoactive effects.[33]

Second, the use of niacin as active placebo may have increased believability of the comparator condition and enhanced the placebo response, given that placebo response rates in the current study were equivalent to those seen in response to a low-dose psilocybin comparator in participants with TRD and larger than the effect of an inactive placebo in a recent study in participants with MDD.[14,15] Nonetheless, placebo response rates in the current study are smaller than are typically observed with daily placebo pills,[34] which may have inflated the placebo-adjusted effect size compared with studies of standard antidepressants in patients with MDD. As a complement to traditional placebo-controlled trials, a better understanding of the contribution that placebo effects make to the antidepressant efficacy of psilocybin might be gained via use of novel comparators (eg, ketamine) that induce acute effects to aid with blinding while failing to generally produce the type of sustained antidepressant response observed with psilocybin.

Third, relevant to the important question of durability of effect with time-limited treatments, the 6-week (day 43) postdosing primary end point in the current study is longer than primary end points in recent randomized, double-blind, placebo-controlled trials of single-dose psilocybin for TRD (3 weeks) or MDD (2 weeks),[14,15] although one of these studies included a longer, 12-week, overall follow-up period during which the antidepressant effect of psilocybin waned in the TRD study group.[14] Whether the sustained antidepressant effect observed in the current study reflects the low rate of treatment resistance (13%) or some other factor is unknown. Similarly, the current study does not allow inferences to be drawn regarding whether the antidepressant effect would have diminished over subsequent weeks or been maintained, although it is intriguing that a small open trial of two doses of psilocybin in MDD—as opposed to TRD—found evidence for maintenance of effect in many participants out to a year post-dosing.[12] Regardless, it will be essential to conduct rigorous, large-scale, longer-term, follow-up studies to better understand how to best use psilocybin in often chronic conditions such as MDD or TRD.

Fourth, that psilocybin and niacin were administered within an identical, fully protocolized program of psychological support is a strength of the current study. All study facilitators received extensive training; however, fidelity to the psychological support protocol by study facilitators was not assessed, leaving open the possibility that at least some degree of between-participant variability in response may be attributable to unknown differences in psychological support provided by facilitators, rather than direct biological effects of psilocybin per se. This study limitation highlights the importance of better understanding potential benefits and harms that may be engendered by the psychological/psychotherapeutic components of psilocybin assisted therapy.

Fifth, as with the majority of recent clinical trials of psychedelics,[35] a major limitation of the current study is a lack of participant ethnic and racial diversity. The current study sample was predominantly White, non-Hispanic, and from upper socioeconomic echelons. Whether psilocybin would be more, less, or equivalently effective in a more ethnically, racially, and socioeconomically diverse sample is an urgent question that must be addressed in future studies by actively employing strategies shown to increase recruitment and retention of racial and ethnic minoritized populations and other underrepresented groups in clinical trials of psychedelic agents.[36]

Conclusions

In this randomized trial, a single 25-mg dose of psilocybin administered with psychosocial support was associated with clinically and statistically significant reductions in depressive symptoms and improvement in measures of functional disability compared with a 100-mg dose of niacin placebo administered under an identical protocol. No serious TEAEs occurred during the study, but psilocybin treatment was associated with an increase rate of overall, solicited, and severe TEAEs, most of which occurred during or immediately after the dosing period. These findings add to evidence that psilocybin—when administered with psychological support—may hold promise as a novel intervention for MDD.

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