Review Article

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Psilocybin for anorexia nervosa: efficacy, safety, and durability of clinical effects: a systematic review of clinical trials

Psilocibina para anorexia nervosa: eficácia, segurança e durabilidade dos efeitos clínicos: uma revisão sistemática de ensaios clínicos

Psilocibina para la anorexia nerviosa: eficacia, seguridad y durabilidad de los efectos clínicos: una revisión sistemática de ensayos clínicos

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ABSTRACT:
Introduction: Anorexia nervosa is a severe psychiatric disorder with substantial morbidity and limited pharmacological treatment options. Psilocybin-assisted interventions have emerged as a potential novel approach, but evidence specific to anorexia nervosa remains limited. **Objective:** To evaluate the efficacy, safety, tolerability, and durability of psilocybin-based interventions in adults with anorexia nervosa. **Methods:** Registered in the International Prospective Register of Systematic Reviews (PROSPERO number CRD420261479321). The review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. PubMed, Scopus, Web of Science, and the Cochrane Library were systematically searched. Prospective clinical trials evaluating psilocybin in adults with anorexia nervosa were eligible. Outcomes included eating-disorder psychopathology, associated psychiatric symptoms, weight-related outcomes, safety, acceptability, and durability. Findings were synthesized narratively according to study design and outcome domain. **Results:** Two independent uncontrolled prospective trials involving 31 participants met the inclusion criteria. Psilocybin administration was associated with improvements in global and domain-specific eating-disorder psychopathology, motivation for recovery, body-image anxiety, anxiety symptoms, eating-related preoccupations, and functional impairment, although findings were heterogeneous across outcomes. Some improvements persisted beyond the immediate treatment period, with follow-up extending to 12 months in one study. Acute tolerability was generally acceptable, although serious psychiatric events and hypoglycemia were reported. The absence of randomized comparators and the small, highly selected samples precluded causal inference and quantitative meta-analysis. **Conclusion:** Psilocybin-assisted interventions show promising preliminary clinical signals in anorexia nervosa, including improvements in eating-disorder psychopathology and selected associated outcomes. However, current evidence remains insufficient to establish efficacy or generalizable safety. Well-powered randomized controlled trials with rigorous medical monitoring and longer follow-up are warranted.

Keywords: eating-disorder psychopathology, psychedelic-assisted therapy, recovery motivation, body-image disturbance, clinical tolerability.

RESUMO:
Introdução: A anorexia nervosa é um transtorno psiquiátrico grave, associado a significativa morbidade e a opções limitadas de tratamento

farmacológico. As intervenções assistidas por psilocibina têm emergido como uma possível nova abordagem terapêutica, mas as evidências específicas para a anorexia nervosa ainda são limitadas. **Objetivo:** Avaliar a eficácia, a segurança, a tolerabilidade e a durabilidade dos efeitos das intervenções baseadas em psilocibina em adultos com anorexia nervosa. **Métodos:** Registrada no *International Prospective Register of Systematic Reviews* (PROSPERO número CRD420261479321). A revisão foi conduzida e relatada em conformidade com a declaração *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) 2020. Foram realizadas buscas sistemáticas nas bases de dados PubMed, Scopus, Web of Science e Cochrane Library. Foram elegíveis ensaios clínicos prospectivos que avaliaram a psilocibina em adultos com anorexia nervosa. Os desfechos incluíram psicopatologia dos transtornos alimentares, sintomas psiquiátricos associados, desfechos relacionados ao peso, segurança, aceitabilidade e durabilidade dos efeitos. Os achados foram sintetizados narrativamente, de acordo com o delineamento dos estudos e os domínios dos desfechos. **Resultados:** Dois ensaios prospectivos independentes, não controlados, envolvendo 31 participantes, atenderam aos critérios de inclusão. A administração de psilocibina foi associada a melhorias na psicopatologia global e específica dos transtornos alimentares, na motivação para a recuperação, na ansiedade relacionada à imagem corporal, nos sintomas de ansiedade, nas preocupações relacionadas à alimentação e no comprometimento funcional, embora os resultados tenham sido heterogêneos entre os desfechos. Algumas melhorias persistiram além do período imediato de tratamento, com acompanhamento de até 12 meses em um dos estudos. A tolerabilidade aguda foi geralmente aceitável, embora tenham sido relatados eventos psiquiátricos graves e episódios de hipoglicemia. A ausência de grupos comparadores randomizados e o tamanho reduzido das amostras, altamente selecionadas, impediram a inferência causal e a realização de metanálise quantitativa. **Conclusão:** As intervenções assistidas por psilocibina apresentam sinais clínicos preliminares promissores na anorexia nervosa, incluindo melhorias na psicopatologia dos transtornos alimentares e em determinados desfechos associados. Entretanto, as evidências atuais ainda são insuficientes para estabelecer sua eficácia ou segurança generalizável. São necessários ensaios clínicos randomizados, com poder estatístico adequado, monitoramento médico rigoroso e acompanhamento de longo prazo.

Palavras-chave: psicopatologia dos transtornos alimentares, terapia assistida por psicodélicos, motivação para a recuperação, alterações da imagem corporal, tolerabilidade clínica.

RESUMEN:
Introducion: La anorexia nerviosa es un trastorno psiquiátrico grave, asociado con una morbilidad considerable y opciones limitadas de tratamiento farmacológico. Las intervenciones asistidas por psilocibina han surgido como un posible nuevo enfoque terapéutico, pero la evidencia específica sobre la anorexia nerviosa sigue siendo limitada. **Objetivo:** Evaluar la eficacia, la seguridad, la tolerabilidad y la durabilidad de los efectos de las intervenciones basadas en psilocibina en adultos con anorexia nerviosa. **Métodos:** Registrada en el International Prospective Register of Systematic Reviews (PROSPERO, número CRD420261479321). La revisión se llevó a cabo y se informó de conformidad con la declaración Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020. Se realizaron búsquedas sistemáticas en las bases de datos PubMed, Scopus, Web of Science y Cochrane Library. Se consideraron elegibles los ensayos clínicos prospectivos que evaluaron la psilocibina en adultos con anorexia nerviosa. Los desenlaces incluyeron la psicopatología de los trastornos alimentarios, los síntomas psiquiátricos asociados, los desenlaces relacionados con el peso, la seguridad, la aceptabilidad y la durabilidad de los efectos. Los hallazgos se sintetizaron narrativamente según el diseño de los estudios y los dominios de los desenlaces. **Resultados:** Dos ensayos prospectivos independientes, no controlados, que incluyeron a 31 participantes, cumplieron los criterios de inclusión. La administración de psilocibina se asoció con mejoras en la psicopatología global y específica de los trastornos alimentarios, la motivación para la recuperación, la ansiedad relacionada con la imagen corporal, los síntomas de ansiedad, las preocupaciones relacionadas con la alimentación y el deterioro funcional, aunque los resultados fueron heterogéneos entre los desenlaces. Algunas mejoras persistieron más allá del período inmediato de tratamiento, con un seguimiento de hasta 12 meses en uno de los estudios. La tolerabilidad aguda fue generalmente aceptable, aunque se notificaron acontecimientos psiquiátricos graves y episodios de hipoglucemia. La ausencia de grupos comparadores aleatorizados y el tamaño reducido de las muestras, altamente seleccionadas, impidieron la inferencia causal y la realización de un metaanálisis cuantitativo. **Conclusión:** Las intervenciones asistidas por psilocibina muestran señales clínicas preliminares prometedoras en la anorexia nerviosa, incluidas mejoras en la psicopatología de los trastornos

alimentarios y en determinados desenlaces asociados. Sin embargo, la evidencia actual sigue siendo insuficiente para establecer su eficacia o seguridad generalizable. Se necesitan ensayos clínicos aleatorizados con potencia estadística adecuada, seguimiento médico riguroso y seguimiento a largo plazo.

Palavras clave: psicopatología de los trastornos alimentarios, terapia asistida por psicodélicos, motivación para la recuperación, alteraciones de la imagen corporal, tolerabilidad clínica.

INTRODUCTION

Anorexia nervosa (AN) is a severe eating disorder characterized by persistent restriction of energy intake, intense fear of weight gain, and disturbances in weight or body-image perception. Beyond its substantial psychiatric burden, AN is associated with serious medical complications and one of the highest mortality rates among psychiatric disorders, underscoring the need for effective and durable interventions [1, 2]. Current management relies primarily on multidisciplinary care combining nutritional rehabilitation, medical monitoring, and eating-disorder-focused psychotherapy; however, substantial proportions of patients experience persistent illness, relapse, or incomplete recovery, and no pharmacological treatment is currently approved specifically for AN [3, 4, 5].

This therapeutic gap has increased interest in interventions targeting mechanisms that are difficult to modify with conventional approaches, including cognitive rigidity, maladaptive self-referential processing, anxiety, and persistent eating-disorder cognitions [6, 7]. Psilocybin, a serotonergic psychedelic primarily acting through 5-HT2A receptor signaling, has emerged as a potential candidate for addressing some of these processes [8]. Experimental evidence suggests that psilocybin can influence cognitive flexibility and emotional processing, while psychedelic-assisted interventions typically incorporate psychological preparation and integration that may contribute to therapeutic change [9].

Clinical interest in psilocybin-assisted interventions for eating disorders is emerging, but the evidence base remains limited. A systematic review examining psilocybin across eating disorders found that anorexia-nervosa-specific clinical evidence was sparse and emphasized the need for larger, controlled studies [10]. Accordingly, the efficacy, safety, and durability of psilocybin-assisted interventions for anorexia nervosa remain uncertain.

Given the scarcity of anorexia-nervosa-specific evidence, several important questions remain unresolved. In particular, it remains unclear whether observed improvements represent reproducible treatment effects rather than uncontrolled within-participant change, whether psychological and eating-disorder outcomes persist beyond the immediate treatment period, and whether psilocybin can be administered safely across the physiologically heterogeneous AN population. These questions are especially relevant because AN may involve nutritional compromise, cardiovascular abnormalities, and metabolic vulnerability that require careful clinical monitoring [3]. The purpose of this systematic review was therefore to synthesize prospective clinical-trial evidence on the efficacy, safety, tolerability, acceptability, and durability of psilocybin in adults with AN, with particular emphasis on changes in eating-disorder psychopathology, recovery-related and associated psychiatric outcomes, adverse events, and persistence of clinical effects beyond the immediate post-treatment period.

METHODS

Protocol and registration

This systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD420261479321) before study selection and data extraction. The review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The review question, eligibility criteria, outcomes, and synthesis strategy were specified a priori. The study-selection process is presented in Figure 1, and the complete database-specific search strategies are provided in Supplementary Table S1.

Eligibility criteria

Eligible studies were prospective human clinical trials evaluating psilocybin as a therapeutic intervention in adults (≥18 years) with a clinically established diagnosis of anorexia nervosa (AN). AN had to be defined according to recognized diagnostic criteria, including DSM or ICD criteria or validated diagnostic procedures based on these systems. Studies enrolling participants with current AN, chronic or treatment-resistant AN, AN subtypes, or AN in partial remission were eligible. Participants with psychiatric comorbidities were permitted provided that AN remained the defined target population and AN-specific outcomes could be identified.

Studies involving mixed eating-disorder populations were eligible only when outcomes for participants with AN were separately reported or the

investigators explicitly defined AN as the target population. Studies limited to other eating disorders, pediatric populations, healthy volunteers without an identifiable AN cohort, or populations in which AN could not be distinguished were excluded.

The intervention was psilocybin administered therapeutically, irrespective of dose, number of administrations, treatment setting, or the presence and intensity of psychological support. Eligible preparations included adequately characterized synthetic or pharmaceutical-grade psilocybin. Psilocybin-assisted interventions incorporating psychological preparation, therapist support, structured psychotherapy, integration sessions, or treatment as usual were eligible. Uncharacterized recreational psychedelic or mushroom exposure was excluded, as were interventions involving other psychedelic or psychoactive substances when psilocybin-specific data were unavailable.

Both controlled and uncontrolled prospective studies were eligible. Eligible comparator conditions included placebo, active placebo, low-dose psilocybin, treatment as usual, standard care, psychotherapy, nutritional treatment, pharmacological treatment, or wait-list controls. Prospective single-arm and open-label studies were also eligible because of the anticipated paucity of clinical evidence; these studies were prespecified to be synthesized separately from comparative trials and were not considered equivalent in evidentiary strength to randomized studies.

The primary efficacy domain was change in AN eating-disorder psychopathology, preferentially assessed using the Eating Disorder Examination (EDE), EDE Questionnaire (EDE-Q), or another validated eating-disorder measure. Secondary outcomes included clinical response or remission, eating-disorder symptom domains, body weight and BMI, motivation and readiness for recovery, body-image outcomes, depressive and anxiety symptoms, obsessive-compulsive symptoms, quality of life, functional status, and suicidality. Safety outcomes included adverse events, serious adverse events, treatment discontinuation, psychiatric events, cardiovascular and metabolic abnormalities, laboratory abnormalities, and other clinically relevant physiological effects. Treatment acceptability, feasibility, retention, and durability of clinical effects were also prespecified outcomes.

Studies were excluded if they were retrospective, cross-sectional, case-control, case-report or case-series publications; reviews or meta-analyses; protocols without clinical results; conference abstracts without sufficient

full-text data; editorials or commentaries; preclinical or animal studies; or reports lacking sufficient information to establish an eligible AN population or therapeutic psilocybin exposure.

Information sources and search strategy
A comprehensive electronic literature search was conducted in PubMed, Scopus, Web of Science, and the Cochrane Library to identify eligible clinical studies. Search strategies combined controlled vocabulary and free-text terms relating to anorexia nervosa, psilocybin, and therapeutic or psychedelic interventions. Database-specific syntax and indexing were adapted for each information source. The complete search strategies are provided in Supplementary Table S1.

No restriction based on publication date was applied. Full-text peer-reviewed publications and full-text preprints reporting original eligible clinical data were considered. Reference-list screening and clinical-trial registry searching were also used to identify potentially eligible studies, ongoing studies, and additional reports of included trials where applicable.

Study selection
All retrieved records were imported into the screening workflow and duplicate records were removed before screening. Two reviewers independently screened titles and abstracts, followed by independent full-text assessment of potentially eligible reports according to the prespecified eligibility criteria. Disagreements were resolved by discussion and consensus. Studies judged eligible after full-text assessment were linked at the clinical-trial level so that multiple publications, registry records, preprints, or companion reports originating from the same trial were counted as one independent study.

When multiple reports represented the same underlying trial, the report containing the most comprehensive clinical data was used as the primary report, while companion publications were used to supplement additional efficacy, safety, or follow-up information. The reasons for full-text exclusion were documented, and the study-selection process is summarized in Figure 1.

The search yielded 184 records: 42 from PubMed, 74 from Scopus, 61 from Web of Science, and 7 from the Cochrane Library. After removal of 80 duplicates, 104 records underwent title/abstract screening. Two reports underwent full-text assessment, and both met the eligibility criteria, resulting in two independent clinical trials being included in the review.

Data extraction

Data were extracted independently by two reviewers using a prespecified standardized extraction framework. Extracted variables included study characteristics, participant demographics and clinical characteristics, AN diagnostic and remission status, illness duration and treatment resistance, baseline BMI and nutritional status, psychiatric comorbidity, background treatment and medication changes, psilocybin formulation and dosing regimen, psychological preparation and support, psychotherapy and integration procedures, comparator characteristics, follow-up duration, efficacy outcomes, safety outcomes, treatment adherence and discontinuation, acceptability and feasibility, durability of clinical effects, funding, conflicts of interest, and trial registration information.

For efficacy outcomes, the reviewers extracted the measurement instrument, assessment time point, sample size, baseline and follow-up values, change from baseline, effect estimates, confidence intervals where reported, P values, and statistical methods. For safety outcomes, participant-level adverse-event incidence was distinguished from the number of adverse-event episodes whenever both were available. Study-level and publication-level information were also reconciled to avoid double-counting participants.

Values not reported in the source publications were recorded as not reported (NR) rather than inferred. Where a relevant outcome was presented only in a source supplement that was unavailable in the extracted material, the missing numerical information was not reconstructed. Discrepancies between reports within the same publication were retained and flagged rather than silently reconciled.

Outcome assessment and timing

The principal efficacy assessment focused on change in eating-disorder psychopathology following completion of the planned psilocybin intervention. Outcomes were categorized according to follow-up duration as acute/immediate (during dosing or within 7 days), early post-treatment (>7 days to 4 weeks), short-term (>4 weeks to 12 weeks), intermediate-term (>12 weeks to 6 months), long-term (>6 to 12 months), and extended long-term (>12 months).

Where several assessments were available within the same follow-up category, the prespecified or primary study endpoint was prioritized. Longer-term assessments were examined separately to characterize maintenance or attenuation of clinical change. Community-norm proximity

was retained as reported by the investigators but was not considered equivalent to formal diagnostic remission.

Methodological quality and risk-of-bias considerations
Methodological quality was assessed according to the final designs of the included studies. Both eligible trials were ultimately single-arm, uncontrolled prospective studies, meaning that the Cochrane Risk of Bias 2 tool was not applicable. Rather than assigning inappropriate randomized-trial risk-of-bias scores, methodological limitations were evaluated narratively across prespecified domains relevant to uncontrolled psychedelic intervention studies.

These domains included absence of randomization and comparator groups, participant and assessor blinding, fixed-order dosing, selection and self-referral, expectancy and functional-unblinding effects, sample size and statistical precision, attrition and missing data, multiplicity of outcome testing, concomitant psychological treatment, background medication changes, and generalizability. Particular attention was given to features that could affect causal attribution of observed changes to psilocybin itself.

The resulting methodological considerations are summarized in Table 1.

Data synthesis
Because the final evidence base consisted of only two heterogeneous, uncontrolled prospective studies, no quantitative meta-analysis was performed. The studies differed materially in design, sample size, baseline clinical characteristics, psilocybin exposure, psychological support, outcome reporting, and duration of follow-up. In particular, neither study included a concurrent comparator, and within-participant changes could not validly be interpreted as between-group treatment effects.

Accordingly, findings were synthesized narratively and organized by the prespecified domains of eating-disorder psychopathology, motivation and psychiatric symptoms, weight/BMI, safety, acceptability and feasibility, and durability. Randomized or controlled evidence, had it been identified, would have been distinguished from uncontrolled evidence; in the final dataset, both included studies were uncontrolled and were therefore interpreted primarily as evidence regarding within-participant change, tolerability, feasibility, and potential durability signals.

Where numerical effect estimates were reported by the original studies, these were presented as reported rather than transformed into pooled

comparative effects. Cohen's d values from the individual studies were retained where available to describe the magnitude of within-participant change. Clinical and methodological heterogeneity were considered alongside statistical significance, and no formal heterogeneity or publication-bias analyses were undertaken because fewer than two clinically comparable comparative studies were available.

The direction and persistence of findings across outcome domains and follow-up periods are summarized in Figure 2. Detailed efficacy, safety, durability, and methodological findings are presented in Tables 1, 2, 3, 4, respectively, with expanded participant, intervention, adverse-event, outcome-by-timepoint, and funding/conflict-of-interest data provided in Supplementary Tables S2, S3, S4, S5, S6. The database-specific search strategies are provided in Supplementary Table S1.

Ethics

This review used data exclusively from previously published clinical research reports and did not involve collection of new human-subject data. Accordingly, institutional ethical approval and informed consent were not required.

RESULTS

Study selection

The database search identified 184 records, comprising 42 records from PubMed, 74 from Scopus, 61 from Web of Science, and 7 from the Cochrane Library. After removal of 80 duplicate records, 104 records underwent title and abstract screening. Of these, 102 were excluded, leaving 2 reports for full-text retrieval and eligibility assessment. Both reports met all predefined eligibility criteria and represented two independent clinical trials, yielding a final evidence base of 2 studies comprising 31 participants. The study-selection process is presented in the PRISMA flow diagram (Figure 1).

Characteristics of included studies

The two included studies were prospective, single-arm, uncontrolled clinical trials conducted in the United Kingdom and United States, respectively. Douglass et al. [11] was a single-blind, within-participant, fixed-order pilot study conducted in 21 adult women, whereas Knatz Peck et al [12]. was an open-label, phase 1 feasibility study involving 10 adult women (Table 5). Both studies evaluated synthetic psilocybin administered within structured psychological-support frameworks, but their dosing schedules differed substantially: Douglass et al. [11] administered 1 mg

followed by two 25-mg doses at 2-week intervals, whereas Knatz Peck et al. [12] evaluated a single 25-mg dose. Follow-up extended to 12 months in Douglass et al. [11] and 3 months in Knatz Peck et al. [12].

All participants were women. The Douglass [11] cohort had a mean age of 32.0 years and a mean baseline BMI of 16.4 kg/m², and participants were characterized by chronic illness and failure to achieve remission despite prior treatment. The Knatz Peck [12] cohort was younger on average (mean age, 28.3 years) and had a higher mean BMI of 19.7 kg/m²; importantly, 5 of 10 participants had current AN and 5 were in partial remission, including 4 with current restricting-type AN, 1 with current binge-purge-type AN, and 5 with restricting-type AN in partial remission. Psychiatric comorbidity was common in both cohorts, although ascertainment differed, with clinician-administered MINI assessment in Douglass et al. and self-report in Knatz Peck et al [11, 12].

Both studies incorporated psychological preparation, therapist support during dosing, and post-session integration. Douglass et al. [11] used a more extensive psychotherapy framework incorporating emotion-focused family therapy, compassion-focused therapy, and systemic-therapy-informed approaches, alongside continued eating-disorder treatment as usual. Knatz Peck et al. [12] similarly provided therapist-led preparation, in-session support, and integration sessions, although the specific psychotherapy framework was not reported. One participant withdrew from the Douglass [11] study after the second dose because of the time and emotional burden of study participation; no treatment-period dropout occurred in Knatz Peck et al. [12].

Detailed participant and intervention characteristics are provided in Supplementary Tables S2 and S3, respectively.

Efficacy and clinical outcomes

Eating-disorder psychopathology

Eating-disorder psychopathology represented the principal efficacy domain. In Douglass et al. [11], the global Eating Disorder Examination (EDE) score decreased from 3.2 (SD 1.0) at baseline to 2.2 (SD 0.9) at the 6-week final visit, corresponding to a within-participant change of −1.0 and Cohen's d=1.08 (P=0.0001). The reduction was maintained at 3 months (mean EDE, 2.0 [SD 1.3]; change, −1.2; d=1.09; P<0.0001) and 6 months (2.1 [SD 1.3]; change, −1.1; d=0.98; P<0.0001). The overall longitudinal effect of time was statistically significant (F(3,60)=15.5, P<0.0001) (Table 2, Panel A).

The EDE subscales in Douglass et al. [11] also demonstrated significant longitudinal changes. Significant overall time effects were observed for dietary restraint ($F(3,60)=15.0$, $P<0.0001$), eating concern ($F(3,60)=15.7$, $P<0.0001$), shape concern ($F(3,60)=7.9$, $P=0.0001$), and weight concern ($F(3,60)=3.4$, $P=0.02$). However, the improvement in weight concern did not remain statistically significant at the 6-month assessment, whereas the other three subscales showed sustained improvement through 6 months. Exact per-time-point effect estimates for the EDE subscales were not available in the extracted material.

Global EDE-Q scores also demonstrated a significant longitudinal effect in Douglass et al. [11] ($F(10,200)=6.6$, $P<0.0001$), with the largest reported numerical reduction of approximately 1.1 points at 3 and 12 months. The available data therefore suggested persistence of self-reported eating-disorder psychopathology improvement over the 12-month observation period, although exact means and standard deviations at individual time points were not reported in the extracted material.

In Knatz Peck et al. [12], EDE subscale findings were more heterogeneous. Dietary restraint decreased numerically at 1 month (2.18 to 1.38) and 3 months (2.18 to 1.46), but neither change was statistically significant ($P=0.107$ and 0.169, respectively). Eating concern likewise decreased from 2.10 at baseline to 1.24 at 1 month and 1.00 at 3 months, without reaching conventional statistical significance ($P=0.075$ and 0.051, respectively). Shape concern decreased from 3.68 to 2.43 at 1 month ($d=0.78$; $P=0.036$) but this finding was not maintained at 3 months (2.43; $d=0.62$; $P=0.081$). Weight concern decreased from 3.64 at baseline to 2.76 at 1 month and 2.30 at 3 months, with statistically significant within-participant changes at both assessments ($d=0.78$; $P=0.036$ at each time point).

The overall pattern of eating-disorder psychopathology findings is summarized visually in Figure 2, which illustrates the direction, magnitude where estimable, and persistence of observed changes across follow-up.

Motivation, psychiatric symptoms, and functional outcomes

In Douglass et al. [11], motivation/readiness improved significantly, as assessed by the precontemplation subscale of the Readiness and Motivation Questionnaire (RMQ). Reductions were observed after the second dose ($\beta=-9.71$; $d=0.89$; $P=0.01$), reached near-maximal magnitude at 2 months ($\beta=-13.3$; $d=0.86$; $P=0.0001$) and 3 months ($\beta=-13.4$; $d=0.88$; $P<0.0001$), attenuated at 4 months ($\beta=-8.36$; $d=0.58$; $P=0.065$), and remained statistically significant at 12 months

(d=0.65; P=0.0017). The overall longitudinal effect was significant (F(10,200)=3.99, P<0.0001).

In Knatz Peck et al. [12], the 1-month RMQ result was not statistically significant, with exact numerical estimates unavailable in the extracted material. Conversely, significant improvements were observed at 1 month in trait anxiety measured by the STAI-T (d=0.78; P=0.036), body-image anxiety measured by PASTAS (d=0.76; P=0.04), eating-related preoccupations and rituals measured by the YBC-EDS (d=0.75; P=0.043), and eating-disorder-related functional impairment measured by the CIA (d=0.75; P=0.041). Depressive symptoms assessed with the QIDS were not statistically significantly changed, although exact numerical estimates were unavailable in the extracted material.

Clinical response and weight-related outcomes

Both studies reported exploratory response information based on proximity to community EDE norms rather than formal diagnostic remission. In Douglass et al. [11], 6/21 participants (28.6%) were within the community-norm range at the final visit, increasing to 10/21 (47.6%) at 3 months and 8/21 (38.1%) at 6 months. Two participants were already within the normative range at baseline. In Knatz Peck et al. [12], 4/10 participants (40%) were within 1 standard deviation of community norms for the global EDE at 3 months. These measures were descriptive and should not be interpreted as formal remission rates.

BMI findings were limited. In Douglass et al. [11], BMI was monitored primarily as a safety parameter rather than as a preregistered efficacy endpoint, and numerical longitudinal BMI values were not available in the extracted material. In Knatz Peck et al. [12], mean BMI change was not statistically significant at 3 months; nevertheless, 5 of 10 participants experienced an increase in BMI, ranging from 0.4 to 1.2 kg/m², and no correlation between BMI change and EDE response was reported.

Safety and Tolerability

Safety findings are presented in Table 3, with the complete event-level dataset provided in Supplementary Table S4. Both studies reported generally manageable acute tolerability, although all 21 participants in Douglass et al. experienced at least one adverse event. Across that study, 107 adverse-event reports were recorded, comprising 49 mild, 43 moderate, and 15 severe reports. Headache was the most frequently

reported event (18/21 participants; 41 reports), followed by nausea (12/21; 27 reports).

Knatz Peck et al. [12] similarly reported headache in 8/10 participants and fatigue in 7/10, while nausea, dizziness, migraine, and other transient symptoms occurred less frequently. No serious adverse events were reported in that study. Two participants experienced asymptomatic hypoglycemia after dosing, both episodes resolving within 24 hours without intervention. No clinically significant ECG or vital-sign abnormalities were reported.

A clinically important safety signal emerged during longer-term follow-up in Douglass et al. [11]. One participant experienced two suicide attempts, occurring approximately 7 and 9 months after the final treatment visit; both events were judged unlikely to be related to psilocybin. A separate suicidal-ideation adverse event was also reported. In Knatz Peck et al. [12], no clinically significant increase in C-SSRS scores was observed, although one participant with pre-existing major depressive disorder and suicidal ideation reported increased suicidal ideation at 3 months, which investigators judged unrelated to study participation.

Neither study required anxiolytic rescue medication. One participant discontinued the Douglass study after the second dose because of the time and emotional burden of participation rather than a pharmacological adverse event; no treatment-period discontinuation occurred in Knatz Peck et al [12].

Durability of clinical outcomes

Durability represented a major distinguishing feature of the evidence base and is summarized in Table 4 and Figure 2. In Douglass et al. [11], the global EDE improvement remained statistically significant through 6 months, representing the last reported EDE assessment. The global EDE-Q showed significant longitudinal improvement through 12 months, while RMQ precontemplation scores remained significantly reduced at 12 months despite attenuation from the maximum improvement observed at approximately 2–3 months. However, the investigators noted substantial inter-individual variability in the magnitude and persistence of clinical improvement, with some participants showing less sustained benefit or movement toward baseline.

In Knatz Peck et al. [12], durability was more limited because follow-up ended at 3 months. Weight concern remained significantly reduced at 3

months, whereas the significant reduction in shape concern observed at 1 month was no longer statistically significant at 3 months. Other outcomes, including anxiety, body-image anxiety, eating-related preoccupations, and functional impairment, were reported primarily at 1 month, limiting conclusions regarding their longer-term persistence.

Methodological quality and risk-of-bias considerations

Methodological considerations are summarized in Table 1. Both studies were uncontrolled, non-randomized, single-arm investigations, precluding separation of psilocybin-specific effects from expectancy, temporal effects, regression to the mean, concomitant psychological treatment, and other sources of within-participant change. Douglass et al. [11] used a single-blind, fixed-order design, but participants knew that psilocybin would be administered and the EDE interviewer was not blinded to the dosing regimen. The 1-mg and 25-mg administrations therefore cannot be interpreted as a conventional placebo-controlled dose comparison.

Both studies were small pilot/feasibility investigations and did not employ correction for multiple comparisons, increasing the possibility of chance findings across the numerous outcomes and follow-up assessments. Concomitant psychological treatment was substantial in both studies, and medication changes represented an additional potential source of confounding. In Douglass et al. [11], 10 of 21 participants underwent antidepressant withdrawal before psilocybin treatment, while one participant remained on low-dose citalopram. The study also used last observation carried forward for missing longitudinal observations.

Generalizability was further constrained by the demographic characteristics of the samples. Both trials enrolled women exclusively, with predominantly White participants, and the cohorts differed substantially in baseline BMI and AN clinical status. Particularly, the inclusion of participants with partial-remission AN in Knatz Peck et al. [12] limits direct comparability with the chronic, non-remitted population studied by Douglass et al. [11]. These methodological considerations preclude strong causal inference regarding the efficacy of psilocybin and support interpreting the available evidence as preliminary uncontrolled evidence of within-participant clinical change rather than definitive evidence of treatment efficacy.

Overall synthesis of the included evidence

The two included trials provided preliminary evidence of reductions in eating-disorder psychopathology and several associated psychological outcomes following psilocybin administration, with the strongest

longitudinal evidence arising from the 21-participant Douglass study. Improvements in global EDE scores were sustained through 6 months, while changes in EDE-Q and recovery-motivation measures extended into 12 months. The smaller Knatz Peck [12] study demonstrated significant short-term improvements in selected domains, particularly weight concern, body-image anxiety, trait anxiety, eating-related preoccupations, and functional impairment, but findings across EDE subdomains were heterogeneous and longer-term follow-up was limited. The direction and durability of the available findings across outcome domains are summarized in Figure 2.

Across both trials, safety findings were generally manageable during active treatment, but the occurrence of serious psychiatric events during later follow-up in Douglass et al. [11]. underscores the importance of continued safety surveillance in this clinically vulnerable population. Overall, the evidence base remains limited by the absence of randomized comparators, very small sample sizes, expectancy and blinding limitations, concurrent psychological interventions, medication changes, and multiplicity of outcome testing. Accordingly, the observed improvements should be interpreted as signals of potential clinical benefit and feasibility rather than confirmation of psilocybin efficacy in anorexia nervosa.

DISCUSSION

This systematic review identified two independent prospective clinical trials involving 31 adults with anorexia nervosa, both of which evaluated psilocybin in uncontrolled single-arm designs and therefore provide preliminary rather than comparative evidence. Across the trials, psilocybin administered with psychological support was associated with reductions in eating-disorder psychopathology and improvements in selected recovery-oriented and psychiatric outcomes, with generally manageable short-term tolerability and evidence of persistence for some outcomes beyond the immediate post-treatment period. The longer-term findings were most evident in the study with 12-month follow-up, although substantial inter-individual variability was reported. These findings are encouraging but should not be interpreted as demonstrating psilocybin efficacy, because neither study included a randomized comparator and both were vulnerable to expectancy effects, concomitant psychological treatment, and other sources of uncontrolled within-participant change [11, 12].

The most consistent signal concerned eating-disorder psychopathology, the prespecified primary efficacy domain. Douglass et al. reported

substantial reductions in global EDE scores that remained statistically significant through 6 months, together with significant longitudinal improvement in EDE-Q scores extending to 12 months [11]. Knatz Peck et al. similarly observed improvements in selected EDE domains, particularly weight concern, while dietary restraint and eating concern did not reach conventional statistical significance and improvement in shape concern was not maintained at 3 months [12]. This pattern suggests that psilocybin-assisted treatment may influence clinically relevant cognitive and affective components of AN rather than producing a uniform effect across all symptom domains. Such findings are mechanistically plausible given the proposed role of psychedelic-assisted therapy in modifying maladaptive cognitive and emotional processes, although the present evidence cannot determine whether these changes result from psilocybin itself, the accompanying therapeutic context, or their interaction. Previous work has similarly highlighted the rationale for investigating psilocybin in eating disorders while emphasizing that the clinical evidence remains preliminary [10, 13].

The observed effects also extended beyond core eating-disorder symptoms to motivation for recovery, body-image anxiety, trait anxiety, eating-related preoccupations and rituals, and functional impairment, particularly in the Knatz Peck study. In contrast, depressive symptoms and BMI showed less consistent evidence of improvement. This divergence is clinically relevant because psychological recovery from AN cannot be reduced to weight restoration alone; nevertheless, BMI remains an important component of clinical recovery and medical safety, and the absence of a clear aggregate weight effect reinforces the need to distinguish improvement in psychopathology from nutritional recovery. The finding that psychological outcomes may improve without parallel weight restoration is therefore hypothesis-generating rather than evidence that psilocybin can independently address the full multidimensional syndrome of AN.

No major acute safety signal emerged across the two included trials, and treatment completion was high; however, these findings should be interpreted cautiously. Headache, nausea, fatigue, dizziness, and transient anxiety were among the most frequently reported adverse events, while no serious adverse events occurred in the Knatz Peck trial and no clinically significant ECG or vital-sign abnormalities were reported. In contrast, the Douglass trial recorded two suicide attempts in one participant during later follow-up, although both were judged unlikely to be related to psilocybin.

The occurrence of hypoglycemia in two participants in the Knatz Peck study further illustrates why physiological monitoring is particularly important in AN, where malnutrition and medical instability may overlap with the cardiovascular and metabolic effects of psychedelic administration [3, 14]. Importantly, both trials were conducted in highly selected, closely monitored research settings, and neither provides sufficient evidence to establish the safety of psilocybin in medically unstable, severely malnourished, or otherwise high-risk patients with AN. This distinction is clinically important because AN management requires ongoing assessment of vital signs, electrolytes, nutritional status, and, when indicated, ECG abnormalities [3].

The durability of the observed changes represents a potentially important signal. In the longer study, reductions in global EDE scores persisted through 6 months, while improvements in EDE-Q and recovery motivation extended to 12 months; however, the investigators also reported substantial inter-individual variability. In the shorter trial, weight concern remained improved at 3 months, whereas shape concern no longer met conventional statistical significance at that time point. Thus, the available evidence suggests that some psychological changes may persist beyond the immediate post-treatment period, but the durability of benefit remains uncertain because these observations derive entirely from uncontrolled cohorts and may reflect concurrent psychotherapy, expectancy, regression to the mean, or natural symptom fluctuation rather than a sustained pharmacological effect. The limited duration of follow-up in one of the two trials also leaves long-term relapse and maintenance insufficiently characterized [10, 11, 12].

Limitations

The principal limitation lies in the evidence base itself. Only two independent clinical trials involving 31 participants met the prespecified criteria, and both were single-arm, uncontrolled studies. Consequently, the observed improvements cannot be separated from expectancy effects, the therapeutic context, concomitant psychological treatment, background treatment, medication changes, regression to the mean, and temporal variation in AN symptoms. The small samples also limit statistical precision and the detection of uncommon adverse events, while the exclusive enrollment of women and the demographic homogeneity of the cohorts constrain generalizability. Differences in baseline BMI, remission status, treatment intensity, dosing schedule, and follow-up further limit direct cross-study comparison. These limitations are consistent with the broader

literature, which has characterized the evidence for psilocybin in eating disorders as preliminary and has emphasized the absence of adequately powered controlled trials [10].

Implications for practice and future research

At present, psilocybin should be regarded as an investigational intervention for AN rather than an established treatment. The current findings are sufficient to support continued clinical research but not routine therapeutic adoption, particularly in patients with substantial nutritional or cardiovascular instability. Future trials should prioritize adequately powered randomized designs with credible placebo or active-control conditions, standardized psychological support, prespecified AN-specific primary outcomes, systematic cardiovascular and metabolic monitoring, and sufficiently long follow-up to distinguish transient responses from durable recovery. Studies should also recruit more representative populations, including men and patients across a broader range of illness severity and remission status, and should incorporate standardized definitions of response and remission together with strategies to assess expectancy and functional blinding. These design features would allow the field to determine whether the promising within-participant changes observed to date represent reproducible psilocybin-specific effects or primarily reflect the broader therapeutic context in which psychedelic treatment is delivered.

CONCLUSION

In conclusion, psilocybin-assisted interventions show promising preliminary signals of improvement in anorexia nervosa psychopathology and selected recovery-related outcomes, with generally manageable short-term tolerability and some evidence of sustained benefit beyond treatment.

However, the current evidence remains insufficient to establish causal efficacy or generalizable safety because only two small, uncontrolled clinical trials are available. Larger randomized controlled trials with standardized psychological support, rigorous safety monitoring, and longer follow-up are needed before psilocybin can be considered an established treatment for anorexia nervosa.

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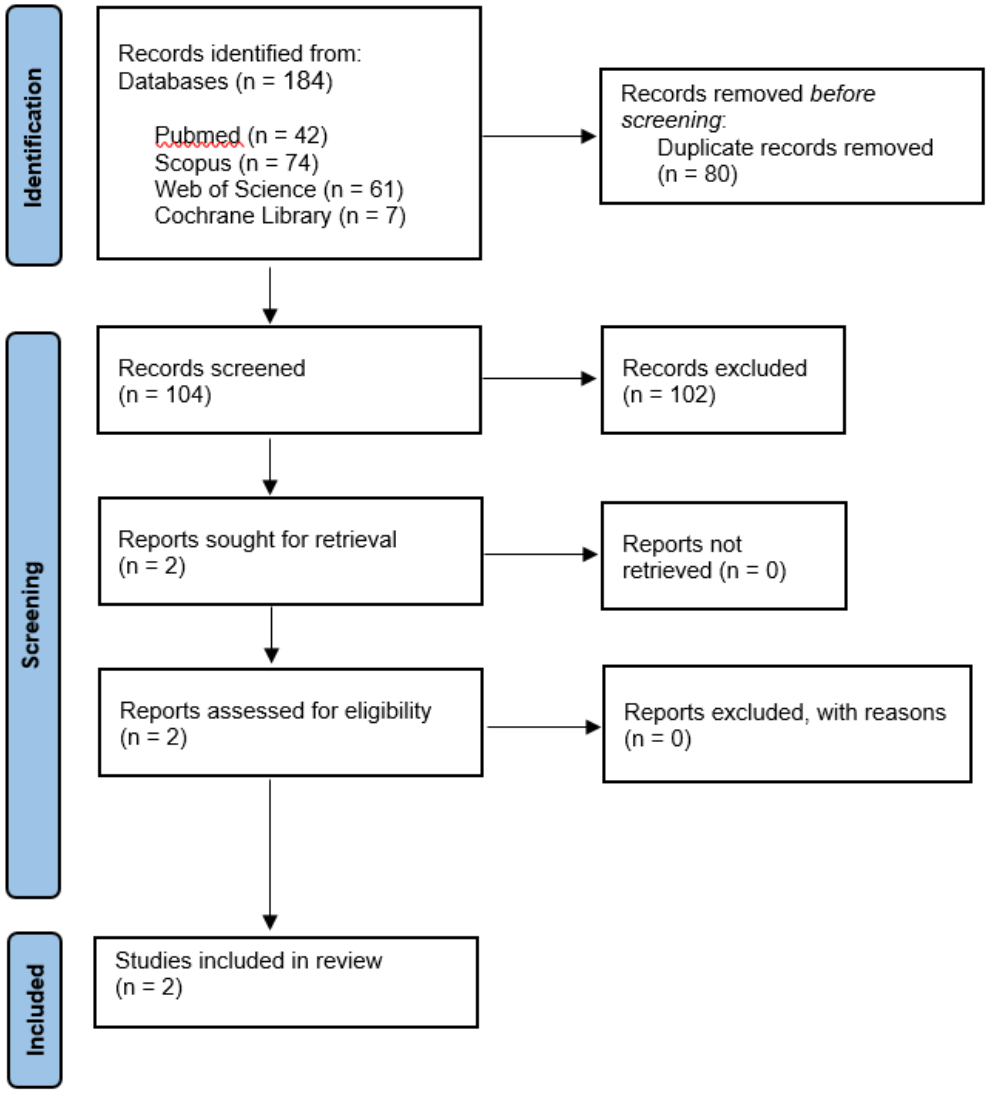


Figure 1. PRISMA Flow Diagram
Source: The authors.

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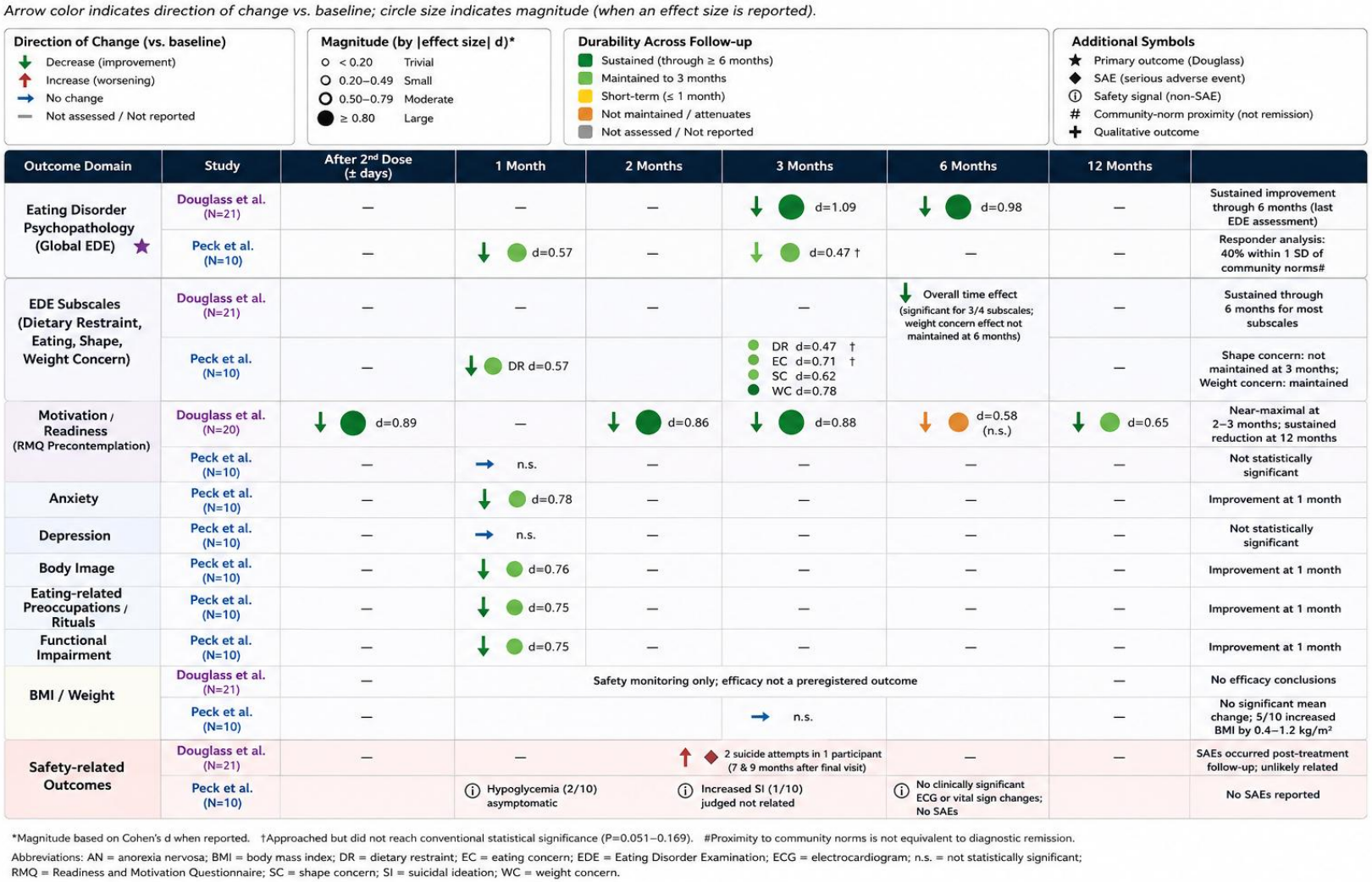


Figure 2. Conceptual Evidence Map: Direction and Durability of Findings Across Two Uncontrolled Psilocybin Trials in Anorexia Nervosa
Source: The authors

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Table 1. Methodological quality and risk-of-bias considerations

Domain	Douglass et al.	Knatz Peck et al.	Implication for interpretation
Study design	Single-arm, single-blind, within-participant, fixed-order pilot study	Single-arm, open-label, phase 1 feasibility study	Neither study permits strong causal inference regarding psilocybin-specific efficacy
Randomization	None	None	Baseline differences and temporal effects cannot be separated from intervention-associated change
Comparator	None; the 1-mg dose was not an inert placebo	None	Within-participant changes cannot be attributed specifically to psilocybin
Participant blinding	Partial; participants knew psilocybin was being administered and that the maximum dose was 25 mg, but were not informed of dose order/strength	None; open-label	Expectancy and functional-unblinding effects may influence reported outcomes
Outcome-assessor blinding	EDE interviewer was not blinded to the dosing regimen	NR	Detection bias cannot be excluded, particularly for clinician-rated outcomes
Fixed-order dosing	1 mg → 25 mg → 25 mg; fixed ascending sequence	NA; single dose	Dose-specific effects cannot be isolated; null dose comparisons in Douglass et al. do not establish dose equivalence
Selection/self-referral	Recruitment through specialist eating-disorder services and online self-referral; stringent eligibility requirements	Self-referral and community recruitment; highly selected sample	Selection may limit representativeness of the broader AN population
Expectancy/suggestibility	Explicitly discussed; participants knew they would receive psilocybin	Explicitly discussed; self-referral, psychedelic media exposure, and treatment setting may have influenced expectations	Pharmacological effects cannot be separated from expectancy effects

Sample size and statistical precision	n=21 enrolled; pilot study; exploratory analyses	n=10; phase 1 feasibility study; no power analysis reported	Small samples limit precision and increase susceptibility to unstable estimates
Missing data/attrition	1 withdrawal after dose 2; LOCF used; intention-to-treat analysis	No treatment-period dropout reported; n=10 completed	LOCF and small-sample attrition may affect longitudinal estimates in Douglass et al.
Multiplicity	No correction for multiple comparisons	No correction for multiple comparisons	Increased possibility of chance findings across multiple outcomes and follow-up assessments
Concurrent psychological treatment	Talk therapy, including emotion-focused family therapy, compassion-focused therapy and systemic-therapy elements, plus treatment as usual	Psychological preparation, dosing support and integration therapy	Observed changes cannot be attributed specifically to psilocybin independent of psychological support
Background medication changes	Antidepressant withdrawal in 10/21 (47.6%); 1 participant remained on citalopram	Serotonergic medication titration before baseline; exact number withdrawn NR	Medication changes may contribute to outcome trajectories
Generalizability	Female-only sample; predominantly White British; highly educated; treatment-resistant/chronic population	Female-only; 90% White/Caucasian; included current and partial-remission AN; limited gender, racial and cultural diversity	Findings may not generalize to male patients, more diverse populations, or patients with different illness severity/remission status
Causal attribution	No comparator, no randomization, partial blinding, concurrent treatment and fixed-order dosing	No comparator, open-label design, concurrent psychological treatment and expectancy concerns	Strong causal attribution of observed clinical change to psilocybin is not possible
Overall methodological concern	Major limitations for causal efficacy inference	Major limitations for causal efficacy inference	Evidence should be interpreted as preliminary uncontrolled evidence of within-participant change rather than definitive evidence of efficacy

Source: The authors

Tabela 2. Efficacy and clinical outcomes (Panel A, B, C and D)

Panel A. Eating-disorder psychopathology

Study	Outcome	Time point	n	Baseline, mean (SD)	Follow-up, mean (SD)	Change from baseline	Cohen's d	P value
Douglass et al.	Global EDE Interview	Final visit (6 weeks)	21	3.2 (1.0)	2.2 (0.9)	−1.0	1.08	0.0001
Douglass et al.	Global EDE Interview	3 months	21	3.2 (1.0)	2.0 (1.3)	−1.2	1.09	<0.0001
Douglass et al.	Global EDE Interview	6 months	21	3.2 (1.0)	2.1 (1.3)	−1.1	0.98	<0.0001
Douglass et al.	Global EDE-Q	Longitudinal follow-up	21	NR	NR	Maximal numerical reduction: 1.1 points at 3 and 12 months	NR	<0.0001 overall
Peck et al.	EDE dietary restraint	1 month	10	2.18 (1.76)	1.38 (1.56)	NR	0.57	0.107
Peck et al.	EDE dietary restraint	3 months	10	2.18 (1.76)	1.46 (1.84)	NR	0.47	0.169
Peck et al.	EDE eating concern	1 month	10	2.10 (1.75)	1.24 (1.50)	NR	0.64	0.075
Peck et al.	EDE eating concern	3 months	10	2.10 (1.75)	1.00 (1.32)	NR	0.71	0.051
Peck et al.	EDE shape concern	1 month	10	3.68 (1.30)	2.43 (1.84)	NR	0.78	0.036
Peck et al.	EDE shape concern	3 months	10	3.68 (1.30)	2.43 (1.95)	NR	0.62	0.081
Peck et al.	EDE weight concern	1 month	10	3.64 (1.65)	2.76 (1.81)	NR	0.78	0.036
Peck et al.	EDE weight concern	3 months	10	3.64 (1.65)	2.30 (2.00)	NR	0.78	0.036

Overall longitudinal effects: For Douglass et al., global EDE showed a significant effect of time ($F(3,60)=15.5$, $P<0.0001$), while global EDE-Q showed a significant effect of time ($F(10,200)=6.6$, $P<0.0001$).

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Panel B. Motivation, psychiatric symptoms, and functional outcomes

Study	Outcome	Instrument	Time point	n	Result	Cohen's d	P value
Douglass et al.	Motivation/readiness	RMQ precontemplation	After dose 2 (first 25 mg)	21	β = −9.71	0.89	0.01
Douglass et al.	Motivation/readiness	RMQ precontemplation	2 months	21	β = −13.3	0.86	0.0001
Douglass et al.	Motivation/readiness	RMQ precontemplation	3 months	21	β = −13.4	0.88	<0.0001
Douglass et al.	Motivation/readiness	RMQ precontemplation	4 months	21	β = −8.36	0.58	0.065
Douglass et al.	Motivation/readiness	RMQ precontemplation	12 months	21	Sustained reduction	0.65	0.0017
Peck et al.	Motivation/readiness	RMQ	1 month	10	Not statistically significant; exact numerical estimates NR	NR	NR
Peck et al.	Trait body-image anxiety	PASTAS	1 month	10	Significant decrease	0.76	0.04
Peck et al.	Trait anxiety	STAI-T	1 month	10	Significant decrease	0.78	0.036
Peck et al.	Eating-related preoccupations/rituals	YBC-EDS	1 month	10	Significant decrease	0.75	0.043
Peck et al.	Functional impairment	CIA	1 month	10	Significant decrease	0.75	0.041
Peck et al.	Depressive symptoms	QIDS	1 month	10	Not statistically significant	NR	NR

Overall RMQ effect in Douglass et al.: F(10,200)=3.99, P<0.0001. Antidepressant withdrawal was not a significant fixed effect (P=0.42, n=20). Raw RMQ means at intermediate time points were not numerically reported.

Panel C. Clinical response based on community-norm proximity

Study	Time point	Outcome definition	Participants meeting criterion	Interpretation
Peck et al.	3 months	Global EDE within 1 SD of community norms	4/10 (40%)	Interpreted by study authors as clinically significant improvement in a subset
Douglass et al.	Final visit (6 weeks)	Global EDE within community-norm range	6/21 (28.6%)	Community-norm proximity
Douglass et al.	3 months	Global EDE within community-norm range	10/21 (47.6%)	Community-norm proximity
Douglass et al.	6 months	Global EDE within community-norm range	8/21 (38.1%)	Two participants were already within this range at baseline

Panel D. BMI

Study	Time point	Result	Statistical interpretation
Douglass et al.	Baseline and serial safety assessments through final visit	Mean baseline BMI 16.4 (SD 1.4) kg/m²; numerical longitudinal BMI changes NR	BMI was monitored as a safety parameter and was not a preregistered efficacy outcome
Peck et al.	3 months	Mean BMI change was not statistically significant; 5/10 participants had increased BMI by 0.4–1.2 kg/m²	No statistically significant mean change; no correlation between BMI status and EDE outcome was reported

Source: The authors

Abbreviations: **CIA** = Clinical Impairment Assessment; **EDE** = Eating Disorder Examination; **EDE-Q** = Eating Disorder Examination Questionnaire; **NR** = not reported; **PASTAS** = Physical Appearance State and Trait Anxiety Scale; **QIDS** = Quick Inventory of Depressive Symptomatology; **RMQ** = Readiness and Motivation Questionnaire; **SD** = standard deviation; **STAI-T** = State-Trait Anxiety Inventory, Trait subscale; **YBC-EDS** = Yale-Brown-Cornell Eating Disorder Scale.

Table 3. Safety and adverse events

Safety outcome	Douglass et al. (n=21)	Peck et al. (n=10)
Overall tolerability		
Participants with ≥1 adverse event	21/21 (100%)	NR as an aggregate summary
Total adverse-event reports	107	NR
Mild adverse-event reports	49 (45.8%)	NR
Moderate adverse-event reports	43 (40.2%)	NR
Severe adverse-event reports	15 (14.0%)	NR
Related adverse-event reports	31 (29.0%)	NR
Possibly related adverse-event reports	61 (57.0%)	NR
Not-related adverse-event reports	15 (~14.0%)	NR
Common adverse events		
Headache	18/21 (85.7%); 41 reports	8/10 (80%)
Nausea	12/21 (57.1%); 27 reports	3/10 (30%)
Fatigue	NR	7/10 (70%)
Dizziness	1/21 (4.8%); 6 reports	2/10 (20%)
Migraine	1/21 (4.8%); 4 reports	2/10 (20%)
Anxiety	2/21 (9.5%); 3 reports	1/10 (10%)
Feeling abnormal	NR	2/10 (20%)
Illusion	NR	2/10 (20%)
Serious and psychiatric safety		
Serious adverse events	2 events in 1 participant (4.8%)	0
Suicide attempts	2 attempts in 1 participant; moderate severity; judged unlikely related to psilocybin	None reported
Suicidal ideation/increased suicidal ideation	1/21 (4.8%); 1 reported event	No clinically significant C-SSRS increase (0/10); 1 participant with pre-existing MDD and SI reported

		increased SI at 3 months, judged unrelated to study participation
Suicidality assessment	Routine health-change questioning/unprompted report; no named structured instrument reported	Columbia-Suicide Severity Rating Scale (C-SSRS), assessed at each time point
Psychiatric hospitalization	NR	NA
Cardiovascular and metabolic safety		
Hypoglycemia	NR; not formally assessed	2/10 (20%); asymptomatic; resolved within 24 h; no intervention required
Clinically significant ECG changes	NR	0/10 (0%)
Clinically significant vital-sign changes	NR	0/10 (0%)
Other clinically significant laboratory abnormalities	NR	None reported beyond hypoglycemia
Treatment discontinuation and rescue medication		
Anxiolytic rescue medication	0/21; lorazepam not required	0/10; no anxiolytic rescue required
Treatment discontinuation during active treatment	1/21 (4.8%); withdrew after dose 2 because of time and emotional obligations of study participation	0/10
Treatment-period dropout	1/21 (4.8%)	0/10 (0%)

Source: The authors
Abbreviations: AE = adverse event; **C-SSRS** = Columbia-Suicide Severity Rating Scale; **ECG** = electrocardiogram; **MDD** = major depressive disorder; **NA** = not applicable; **NR** = not reported; SI = suicidal ideation.

Table 4. Durability, response, and follow-up outcomes

Study	Outcome	Immediate/ early	1 month	3 months	6 months	12 months	Durability assessment	Key caveat
Douglass et al.	Global EDE Interview	6-week final visit: 2.2 (0.9), d=1.08, P=0.0001	NR as a separate prespecified EDE assessment	2.0 (1.3), d=1.09, P<0.0001	2.1 (1.3), d=0.98, P<0.0001	Not assessed	Significant reduction sustained through 6 months	Authors reported substantial inter-individual variability, with some participants maintaining gains and others showing less maintenance or return toward baseline
Douglass et al.	Global EDE-Q	Reduction present at final visit; overall time effect F(10,200)=6.6, P<0.0001	Exact mean/change NR	Maximal numerical reduction of approximately 1.1 points	Reduction maintained	Approximately 1.1-point maximal reduction; sustained within overall longitudinal effect	Improvement sustained through available 12-month follow-up	Exact numerical means at individual time points were not consistently reported
Douglass et al.	RMQ precontemplation	After dose 2: β=−9.71, d=0.89, P=0.01	Exact mean NR	β=−13.4, d=0.88, P<0.0001; β=−13.3 at 2 months, d=0.86, P=0.0001	Exact mean NR; 4-month β=−8.36, d=0.58, P=0.065	d=0.65, P=0.0017	Significant reduction persisted to 12 months, although attenuated relative to the 2–3-month peak	Raw RMQ means were not numerically reported at intermediate time points

Douglass et al.	EDE community-norm proximity	6/21 (28.6%) at final visit	NR	10/21 (47.6%)	8/21 (38.1%)	Not assessed	Community-norm proximity observed through 6 months	This is not equivalent to formal diagnostic remission; 2 participants were already within the community-norm range at baseline
Peck et al.	Global EDE responder analysis	NR	Exact global mean NR; trend toward reduction	4/10 (40%) within 1 SD of community norms (mean 0.93, SD 0.80)	Not assessed	Not assessed	Response evaluated through 3 months only	Community-norm proximity was interpreted as clinically significant by study authors but is not formal diagnostic remission; individual responses were highly variable
Peck et al.	EDE shape concern	—	2.43 (1.84); P=0.036, d=0.78	2.43 (1.95); P=0.081, d=0.62	Not assessed	Not assessed	Not maintained to 3 months	Significant at 1 month but no longer statistically significant at 3 months
Peck et al.	EDE weight concern	—	2.76 (1.81); P=0.036, d=0.78	2.30 (2.00); P=0.036, d=0.78	Not assessed	Not assessed	Maintained through 3 months	Significant at both reported post-treatment assessments
Peck et al.	EDE dietary restraint	—	P=0.107, d=0.57	P=0.169, d=0.47	Not assessed	Not assessed	No statistically significant improvement demonstrated	Exact changes from baseline were available in Table 3 but statistical significance was not demonstrated

Peck et al.	EDE eating concern	—	P=0.075, d=0.64	P=0.051, d=0.71	Not assessed	Not assessed	No statistically significant improvement demonstrated	Improvement approached statistical significance at 3 months
Peck et al.	Body-image anxiety (PASTAS)	—	Significant decrease; P=0.04, d=0.76	NR	Not assessed	Not assessed	Durability beyond 1 month not reported	Only 1-month numerical effect reported in the extraction
Peck et al.	Trait anxiety (STAI-T)	—	Significant decrease; P=0.036, d=0.78	NR	Not assessed	Not assessed	Durability beyond 1 month not reported	—
Peck et al.	Eating-related preoccupations/rituals (YBC-EDS)	—	Significant decrease; P=0.043, d=0.75	NR	Not assessed	Not assessed	Durability beyond 1 month not reported	—
Peck et al.	Eating-disorder functional impairment (CIA)	—	Significant decrease; P=0.041, d=0.75	NR	Not assessed	Not assessed	Durability beyond 1 month not reported	—

Source: The authors

Abbreviations: CIA = Clinical Impairment Assessment; **EDE** = Eating Disorder Examination; **EDE-Q** = Eating Disorder Examination Questionnaire; **NR** = not reported; **PASTAS** = Physical Appearance State and Trait Anxiety Scale; **RMQ** = Readiness and Motivation Questionnaire; **SD** = standard deviation; **STAI-T** = State-Trait Anxiety Inventory, Trait subscale; **YBC-EDS** = Yale-Brown-Cornell Eating Disorder Scale.

Table 5. Characteristics of included trials and participants

Characteristic	Douglass et al. (PSI-AN-01)	Peck et al. (PSI-AN-02)
Study characteristics		
Publication	2026, British Journal of Psychiatry	2023, Nature Medicine; reprinted 2024 in Focus
Country	United Kingdom	United States
Setting	NIHR Imperial Clinical Research Facility, Imperial College London	UC San Diego ACTRI; Eating Disorder Treatment & Research Center
Study design	Single-arm, single-blind, within-participant, fixed-order pilot study	Single-arm, open-label, phase 1 feasibility study
Trial registration	ISRCTN10441504; NCT04505189; EudraCT 2019-004054-28	NCT04661514
Enrollment period	April 2021–April 2023	April–December 2021
Sample size	21 enrolled	10 enrolled
Follow-up	12 months	3 months
Participant characteristics		
Age, years	23–52; mean 32.0 (SD 7.1)	Mean 28.3 (SD 3.7); range NR
Female sex	21/21 (100%)	10/10 (100%)
Diagnostic criteria	DSM-5 anorexia nervosa	DSM-5 anorexia nervosa or partial-remission anorexia nervosa
AN status/subtype	Current AN; subtype distribution NR	Current AN: 5/10 (50%); AN-R 4/10 (40%), AN-BP 1/10 (10%); partial-remission AN-R 5/10 (50%)
Illness duration, years	4–22; mean 10.8 (SD 5.0)	Mean 8.9 (SD 5.9)
Treatment resistance/chronicity	Non-remission despite prior treatment required for eligibility; population described as treatment-resistant	Explicit treatment-resistance criterion NR
Baseline BMI, kg/m²	Mean 16.4 (SD 1.4)	Mean 19.7 (SD 3.7)
Psychiatric comorbidity	11/21 (52.4%) with ≥1 MINI-assessed psychiatric comorbidity; GAD 7/21 (33.3%); MDD 5/21 (23.8%)	Self-reported MDD 7/10 (70%), GAD 7/10 (70%), OCD 3/10 (30%)
Intervention characteristics		
Psilocybin formulation	COMP360, synthetic pharmaceutical-grade psilocybin	Synthetic psilocybin; COMP360 identified in the adverse-event table

Dose	1 mg → 25 mg → 25 mg	Single 25 mg
Number of doses	3	1
Dose sequence/interval	Fixed ascending order; 2-week intervals	NA
Intervention duration	Approximately 6 weeks	Single dosing session
Psychological treatment context		
Preparation	Session on the day before each dosing session	Therapist-led pre-dosing preparation
Dosing-day support	Therapist support during each dosing session	Therapist support throughout dosing
Integration	Integration session the day after each dose, with remote preparation/integration sessions	Integration therapy on days 1, 7, and 28
Psychotherapy framework	Emotion-focused family therapy, compassion-focused therapy, and systemic therapy	Psychological support; specific framework NR
Background treatment	Continued NHS eating-disorder service and/or private therapy	Concurrent background treatment not consistently characterized; among four EDE responders, three were not receiving concurrent mental-health services and one remained in longstanding outpatient therapy
Attrition and retention		
Completers	20/21	10/10
Retention	95.2%	100% of treated participants
Withdrawal/dropout	1/21 (4.8%), after dose 2; withdrawal attributed to time and emotional obligations of the study	0/10 among treated participants

Source: The authors

Abbreviations: **AN** = anorexia nervosa; **AN-BP** = anorexia nervosa, binge-purge subtype; **AN-R** = anorexia nervosa, restricting subtype; **ACTRI** = Altman Clinical and Translational Research Institute; **BMI** = body mass index; **DSM-5** = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; **GAD** = generalized anxiety disorder; **MDD** = major depressive disorder; **MINI** = Mini-International Neuropsychiatric Interview; **NA** = not applicable; **NR** = not reported; **SD** = standard deviation.

Table S1. Database Search Strategies

Database	Search Strategy	Limits / Notes
PubMed (MEDLINE)	("Anorexia Nervosa"[Mesh] OR "anorexia nervosa"[Title/Abstract] OR "anorexia nervosa, restricting type"[Title/Abstract] OR "restricting type anorexia nervosa"[Title/Abstract] OR "restricting-type anorexia nervosa"[Title/Abstract] OR "anorexia nervosa, binge-eating/purging type"[Title/Abstract] OR "binge-eating/purging type anorexia nervosa"[Title/Abstract] OR "binge-eating/purging-type anorexia nervosa"[Title/Abstract] OR "restricting-type anorexia"[Title/Abstract]) AND ("Psilocybin"[Mesh] OR psilocybin[Title/Abstract] OR psilocybine[Title/Abstract] OR "psilocybin-assisted therapy"[Title/Abstract] OR "psilocybin-assisted psychotherapy"[Title/Abstract] OR "psilocybin therapy"[Title/Abstract] OR "psilocybin treatment"[Title/Abstract] OR COMP360[Title/Abstract] OR "COMP 360"[Title/Abstract] OR "synthetic psilocybin"[Title/Abstract] OR "pharmaceutical-grade psilocybin"[Title/Abstract] OR "pharmaceutical grade psilocybin"[Title/Abstract] OR "psilocybin-containing mushroom*"[Title/Abstract] OR "psilocybin containing mushroom*"[Title/Abstract] OR "psilocybe mushroom*"[Title/Abstract] OR psilocybe[Title/Abstract] OR "magic mushroom*"[Title/Abstract])	Fields: [Title/Abstract] and [MeSH Terms] No publication-type or language restriction applied at query level
Scopus (Elsevier)	TITLE-ABS-KEY ("anorexia nervosa" OR "anorexia nervosa, restricting type" OR "restricting type anorexia nervosa" OR "restricting-type anorexia nervosa" OR "anorexia nervosa, binge-eating/purging type" OR "binge-eating/purging type anorexia nervosa" OR "binge-eating/purging-type anorexia nervosa" OR "restricting-type anorexia") AND TITLE-ABS-KEY (psilocybin OR psilocybine OR "psilocybin-assisted therapy" OR "psilocybin-assisted psychotherapy" OR "psilocybin therapy" OR "psilocybin treatment" OR COMP360 OR "COMP 360" OR "synthetic psilocybin" OR "pharmaceutical-grade psilocybin" OR "pharmaceutical grade psilocybin" OR "psilocybin-containing mushroom*" OR "psilocybin containing mushroom*" OR "psilocybe mushroom*" OR psilocybe OR "magic mushroom*")	Field: TITLE-ABS-KEY No document-type or language restriction applied at query level

Database	Search Strategy	Limits / Notes
Web of Science (Core Collection)	TS=("anorexia nervosa" OR "anorexia nervosa, restricting type" OR "restricting type anorexia nervosa" OR "restricting-type anorexia nervosa" OR "anorexia nervosa, binge-eating/purging type" OR "binge-eating/purging type anorexia nervosa" OR "binge-eating/purging-type anorexia nervosa" OR "restricting-type anorexia") AND TS=(psilocybin OR psilocybine OR "psilocybin-assisted therapy" OR "psilocybin-assisted psychotherapy" OR "psilocybin therapy" OR "psilocybin treatment" OR COMP360 OR "COMP 360" OR "synthetic psilocybin" OR "pharmaceutical-grade psilocybin" OR "pharmaceutical grade psilocybin" OR "psilocybin-containing mushroom*" OR "psilocybin containing mushroom*" OR "psilocybe mushroom*" OR psilocybe OR "magic mushroom*")	Free-text search across Topic fields (title, abstract, keywords) No publication-type or language restriction applied at query level
Cochrane Library (CENTRAL)	("anorexia nervosa" OR "restricting type anorexia nervosa" OR "restricting-type anorexia nervosa" OR "binge-eating/purging type anorexia nervosa" OR "binge-eating/purging-type anorexia nervosa") AND (psilocybin OR psilocybine OR "psilocybin-assisted therapy" OR "psilocybin-assisted psychotherapy" OR "psilocybin therapy" OR "psilocybin treatment" OR COMP360 OR "COMP 360" OR "synthetic psilocybin" OR "pharmaceutical-grade psilocybin" OR psilocybe OR "magic mushroom*")	Condensed term set (reduced synonym list per Cochrane search conventions) No publication-type or language restriction applied at query level

Source: The authors

Table S2. Full Participant Characteristics

Participant characteristic	Douglass et al. **(PSI-AN-01; n=21)**	Peck et al. **(PSI-AN-02; n=10)**
A. Enrollment and analytical population		
Expressions of interest	450	158
Sent information sheet / completed prescreening	161 sent full participant information sheet	64 completed prescreening telephone call
Telephone screening	100 attended telephone screening	40 met initial eligibility criteria at prescreening; 24 excluded (19 nonlocal, 3 nonresponsive, 1 medication contraindication)
In-person screening	26 attended in-person screening	16 screened in person at ACTRI
Enrolled	21	10; 3 additional participants screen-failed after in-person screening (1 discontinued, 2 waitlisted)
Treated	21; all received ≥1 dose	10
Completers	20; 1 withdrew after dose 2	10; no treatment-period dropout reported
Included in efficacy analysis	21; intention-to-treat analysis with LOCF for withdrawn participant	10
Included in safety analysis	21	10
Withdrawn	1	0 among treated participants
Reason for withdrawal	Time and emotional obligations of study participation; withdrawal occurred after dose 2	NA
Retention	95.2% (20/21)	100% (10/10) among treated participants
Treatment-period attrition	4.8% (1/21)	0% among treated participants
Follow-up attrition / missing data	Missing monthly data points at 4 months (n=1), 5 months (n=3), 6 months (n=1), and 12 months (n=1); LOCF used	NR; no treatment-period missingness reported in the extracted data
B. Demographic characteristics		
Age range, years	23–52	NR
Mean age, years (SD)	32.0 (7.1)	28.3 (3.7)
Median age	NR	NR
Sex	Female, 21/21 (100%)	Female, 10/10 (100%)
Gender reported separately from sex	NR	NR

Ethnicity/race	White British, 16/21 (76.2%); other/NR for remainder	White/Caucasian, 9/10 (90%); Hispanic, 1/10 (10%)
Country	United Kingdom	United States
Religious orientation	No religious orientation, 14/21 (66.7%)	NR
Employment	Employed, 17/21 (81.0%)	NR
Education	Postgraduate degree or higher, 11/21; source reports 55.4%[1]	NR
Other socioeconomic characteristics	NR	NR
C. Anorexia nervosa diagnostic characteristics		
Diagnostic criteria	DSM-5 anorexia nervosa; illness likely present for >3 years as an eligibility criterion	DSM-5 anorexia nervosa or partial-remission anorexia nervosa
Diagnostic interview / instrument	NR for AN diagnosis; multi-stage clinical screening described	NR
AN subtype	NR as a numerical breakdown at enrollment	Current AN-R, 4/10 (40%); current AN-BP, 1/10 (10%); partial-remission AN-R, 5/10 (50%)
Current AN	NR as a discrete numerical subgroup	5/10 (50%)
Partial-remission AN	NR as a discrete numerical subgroup; eligibility required non-remission despite prior treatment	5/10 (50%); all AN-R
Full remission	NA; remission was excluded by eligibility criteria	NA; participants were classified as current AN or partial remission
Duration of illness, years	4–22; mean 10.8 (SD 5.0)	Mean 8.9 (SD 5.9)
Age at illness onset	NR	NR
Chronicity / treatment-resistance status	Eligibility required failure to achieve remission despite prior treatment; participants were described by authors as treatment-resistant	NR as an explicit eligibility criterion
Specialist eating-disorder treatment / prior treatment	Registration with a UK specialist eating-disorder care service was required	Referral/recruitment through the UCSD eating-disorder clinic and community sources; further prior-treatment detail NR

D. Anthropometric and clinical severity characteristics		
Baseline BMI, kg/m²	14.3–20.5; mean 16.4 (SD 1.4)[3]	Mean 19.7 (SD 3.7)
Alternative source-reported BMI	16.7 kg/m² cited in Discussion during cross-study comparison[3]	NA
Baseline body weight	NR	NR
Expected body weight	NR	NR
Nutritional status	NR beyond BMI and eligibility screening	NR beyond BMI
Medical severity	NR beyond BMI and screening eligibility	NR beyond BMI
Medical/psychiatric eligibility restrictions	Excluded unstable medical or psychiatric conditions, history of psychotic disorder, substance dependence within 6 months, and MRI/EEG contraindications	Detailed exclusion criteria not fully reported in the extracted text
E. Psychiatric comorbidity		
Major depressive disorder	5/21 (23.8%)	7/10 (70%)
Generalized anxiety disorder	7/21 (33.3%)	7/10 (70%)
Obsessive-compulsive disorder	NR	3/10 (30%)
Other psychiatric comorbidity	11/21 had ≥1 MINI-assessed psychiatric comorbidity; specific additional diagnoses NR	NR beyond MDD, GAD, and OCD
Psychotic disorders	History of psychotic disorder was an exclusion criterion; prevalence among enrolled participants NR	NR
Substance-use disorders	Substance dependence within 6 months was an exclusion criterion; prevalence among enrolled participants NR	NR
Comorbidity ascertainment	MINI, clinician-administered	Self-reported
F. Prior psychedelic exposure		
Prior psilocybin use	18/21 (85.7%) had never used psilocybin; 3/21 (14.3%) had used it once	NR
Prior non-psilocybin psychedelic exposure	NR	NR

Psilocybin-naïve status	18/21 (85.7%)	NR
G. Medication characteristics		
Baseline antidepressant/serotonergic medication use	NR as an overall baseline prevalence	7/10 (70%) prescribed serotonergic medications requiring titration
Other psychotropic medication use	NR	NR
Participants undergoing medication withdrawal/titration	10/21 (47.6%) withdrew from contraindicated medication	Exact number withdrawn NR; participant-initiated antidepressant titration off before baseline if necessary
Timing of medication withdrawal	Before dosing; overseen by study psychiatrists	Before baseline visit
Reason for medication withdrawal	Contraindication with psilocybin administration	Titration off serotonergic/antidepressant medication when necessary
Washout duration	NR	NR
Participants remaining on medication	1 participant remained on 2.5 mg citalopram	NR
Medication-related protocol deviation	1 participant remained on 2.5 mg citalopram; addressed in sensitivity analysis	NR
H. Treatment history and concurrent treatment		
Specialist eating-disorder treatment	Continued specialist NHS eating-disorder care throughout the study	NR beyond UCSD eating-disorder clinic referral/recruitment
Previous psychotherapy	NR as a separately quantified variable	NR
Previous nutritional treatment	NR	NR
Concurrent treatment as usual	NHS eating-disorder service and/or private therapy continued throughout	Ongoing TAU not explicitly characterized; among four EDE responders, three were not receiving concurrent mental-health services and one remained in longstanding outpatient therapy
Concurrent eating-disorder treatment	Continued alongside study intervention	NR
Study-delivered treatment	Psilocybin plus structured talk therapy including EFFT, compassion-focused therapy, and systemic-therapy-informed approaches	Psilocybin plus psychological support and integration therapy

I. Other participant characteristics		
Support person	Family member/friend identified for external support; not present during dosing	NR as a formal participant characteristic
Living situation	NR	NR
Travel/logistical characteristics	NR	Some non-local participants travelled for screening and the day-28 visit
Additional clinically relevant baseline characteristics	NR beyond variables reported above	NR beyond variables reported above

Source: The authors

Abbreviations: ACTRI = Altman Clinical and Translational Research Institute; **AN** = anorexia nervosa; **AN-BP** = anorexia nervosa, binge-purge subtype; **AN-R** = anorexia nervosa, restricting subtype; **BMI** = body mass index; **DSM-5** = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; **EDE** = Eating Disorder Examination; **EFFT** = emotion-focused family therapy; **GAD** = generalized anxiety disorder; **ITT** = intention-to-treat; **LOCF** = last observation carried forward; **MDD** = major depressive disorder; **MINI** = Mini-International Neuropsychiatric Interview; **NA** = not applicable; **NHS** = National Health Service; **NR** = not reported; **OCD** = obsessive-compulsive disorder; **pAN** = partial-remission anorexia nervosa; **SD** = standard deviation; **UCSD** = University of California San Diego; **UK** = United Kingdom; **US** = United States.

Table S3. Detailed Intervention and Psychological-Support Characteristics

Intervention characteristic	Douglass et al.**Douglass et al. (PSI-AN-01)**	**Knatz** Peck et al.**Peck et al. (PSI-AN-02)**
A. Psilocybin formulation		
Formulation	COMP360; synthetic pharmaceutical-grade psilocybin	Synthetic psilocybin; COMP360 identified in the adverse-event table
Synthetic vs natural	Synthetic	Synthetic
Product/brand name	COMP360	COMP360 identified in the adverse-event table; article text otherwise generally uses "synthetic psilocybin"[5]
Manufacturer/company	COMPASS Pathfinder Ltd	NR
Route of administration	Oral	NR in extracted text
B. Dose and dosing regimen		
Dose(s) administered	1 mg → 25 mg → 25 mg	Single 25 mg
Number of doses	3	1
Dose sequence	Fixed ascending order	Single dose; no sequence
Dose escalation	Yes	NA
Fixed versus individualized dosing	Fixed schedule	Fixed single dose
Dosing interval	2 weeks between doses	NA
Cumulative administered dose	Not separately reported; dose sequence = 1 mg + 25 mg + 25 mg	Single 25 mg dose
Session duration	NR	NR
Active intervention period	Approximately 6 weeks	Single dosing session
C. Preparation		
Preparation sessions	One before each dosing session; 3 total	Exact number NR; therapist-led pre-dosing preparation visit(s)
Timing	Day before each dosing session	Before dosing; baseline visit on day −1
Duration	NR	NR
Therapist involvement	Trial therapist involvement	Therapist-led
Preparation content	NR beyond preparation sessions	NR beyond therapist-led preparation
Expectation-setting / support-person preparation	NR	NR

Dietary/nutritional preparation	NR	NR
Medication-related preparation	Medication withdrawal procedures conducted before dosing where required	Participant-initiated antidepressant/serotonergic medication titration off before baseline if necessary
D. Dosing-session environment		
Therapist presence	Therapist support during each dosing session	Therapist support throughout dosing
Number of therapists	NR	NR
Setting	NIHR Imperial Clinical Research Facility, Imperial College London	UC San Diego ACTRI; Eating Disorder Treatment & Research Center
Monitoring procedures	General study safety monitoring; detailed dosing-session monitoring NR	General study safety monitoring; ECG, vital-sign, laboratory, and C-SSRS assessment reported
Fasting/breakfast requirement	NR	Standardized breakfast provided before dosing
Food availability	NR	Food availability reported during dosing; standardized breakfast provided before dosing
Rescue medication	Lorazepam available; not required	No anxiolytic rescue required
Procedures for acute psychological distress	NR beyond therapist support and rescue medication availability	NR beyond therapist support
E. Psychological support during dosing		
Therapist role	Support during dosing as part of study-delivered talk therapy	Support throughout dosing
Directive vs non-directive approach	NR	NR
Psychotherapy framework	Emotion-focused family therapy, compassion-focused therapy, and systemic-therapy-informed approaches	Specific psychotherapy framework NR
Session structure	Preparation → dosing → integration across three dosing sessions	Preparation → single dosing session → post-dosing integration
Approximate therapeutic contact	Approximately 50 total therapeutic-contact hours across the 6-week protocol	NR
Standardization	Delivered by trial therapists; further standardization details NR	NR

Therapist training/model	Delivery included EFFT, compassion-focused, and systemic-therapy-informed approaches; specific training details NR	NR
F. Integration		
Timing	Day after each dose; additional remote preparation/integration between visits	Day 1, day 7, and day 28 after dosing
Number of integration sessions	3 formal post-dose integration sessions; additional remote sessions reported	3 scheduled integration sessions; optional virtual day-84 visit
Remote/virtual sessions	Remote integration/preparation sessions between in-person visits	Optional virtual day-84 visit
Therapist involvement	Trial therapists	Trial therapists
Integration content	NR beyond integration sessions	NR beyond integration therapy
G. Background treatment / treatment as usual		
Treatment as usual	NHS eating-disorder service and/or private therapy continued throughout	Ongoing TAU not explicitly characterized
Specialist eating-disorder services	Continued specialist NHS care	UCSD eating-disorder clinic involved in recruitment/referral
Private therapy	Included where applicable as TAU	NR
Nutritional rehabilitation during study	No nutritional intervention included in study protocol	NR
Concurrent psychotherapy	Part of TAU and study-delivered psychological treatment	Psychological support and integration delivered as part of study
Medication changes during study	Antidepressant withdrawal in 10/21 (47.6%); TAU otherwise continued	Antidepressant/serotonergic medication titration before baseline where necessary; extent NR
H. Medication management		
Medication restrictions	Contraindicated medications required withdrawal before dosing	Serotonergic medications required titration where necessary
Washout duration	NR	NR
Titration	NR beyond withdrawal process	7/10 participants were prescribed serotonergic medications requiring titration

Medication withdrawal	10/21 (47.6%)	Exact number NR
Exception to withdrawal	1 participant remained on 2.5 mg citalopram	NR
Protocol deviation	1 participant remained on 2.5 mg citalopram; sensitivity analysis performed	NR
Timing relative to dosing	Before dosing	Before baseline visit
I. Support person / external support		
Support person	Family member/friend identified for each participant	NR
Presence during dosing	Not present	NR
Purpose	External support outside dosing sessions; detailed role NR	NR
Remote support	NR	NR
J. Total treatment exposure		
Dosing sessions	3	1
Preparation sessions	3	Exact number NR
Integration sessions	3 formal sessions, with additional remote sessions	3 scheduled sessions; optional day-84 virtual visit
Approximate therapeutic-contact hours	Approximately 50 hours	NR
Active treatment duration	Approximately 6 weeks	Single dosing session
Follow-up duration	Monthly follow-up to 6 months; remote follow-up to 12 months	Day 1, day 7, day 28, and day 84/3 months
K. Blinding and expectancy-related characteristics		
Participant blinding	Single-blind; participants knew psilocybin would be administered and that the maximum dose was 25 mg, but were not told the order/strength of the remaining doses	Open-label; participants knew they were receiving 25 mg psilocybin
Information provided about dosing	Maximum dose disclosed; remaining dose order/strength not disclosed	Single administered dose disclosed
Maximum dose disclosed	Yes, 25 mg	Yes, 25 mg
Dose order disclosed	No	NA
Therapist/clinician blinding	Not blinded	Not blinded

Outcome-assessor blinding	EDE interviewer was not blinded to dosing regimen	NR
Expectancy manipulation	No formal expectancy manipulation reported	No formal expectancy manipulation reported
Fixed-order effects	Present; 1 mg → 25 mg → 25 mg	NA
L. Trial logistics		
Treatment location	NIHR Imperial Clinical Research Facility, Imperial College London	UC San Diego ACTRI; Eating Disorder Treatment & Research Center
Recruitment setting	Two NHS specialist eating-disorder services plus online self-referral	ClinicalTrials.gov, community outreach, UCSD eating-disorder clinic and community referrals
Treatment-site count	NR	NR
Screening requirements	Information sheet → telephone screening → in-person screening → GP/eating-disorder-team confirmation	Prescreening telephone assessment → in-person screening at ACTRI
Support-person requirement	Yes	NR
Participant travel requirements	NR	Some non-local participants travelled for screening and day-28 visit
Treatment delivery personnel	Study psychiatrists and trial therapists	Trial therapists and study clinicians for medical/safety monitoring

Source: The authors
Abbreviations: Altman Clinical and Translational Research Institute; **BISS** = Body Image States Scale; **C-SSRS** = Columbia-Suicide Severity Rating Scale; **EDE** = Eating Disorder Examination; **EDE-QS** = Eating Disorder Examination Questionnaire, short form; **EDI-3** = Eating Disorder Inventory-3; **EFFT** = emotion-focused family therapy; **ICRF** = Imperial Clinical Research Facility; **NA** = not applicable; **NHS** = National Health Service; **NIHR** = National Institute for Health and Care Research; **NR** = not reported; **QIDS** = Quick Inventory of Depressive Symptomatology; **RMQ** = Readiness and Motivation Questionnaire; **STAI** = State-Trait Anxiety Inventory; **TAU** = treatment as usual; **VAS** = visual analogue scale; **YBC-EDS** = Yale-Brown-Cornell Eating Disorder Scale.

Table S4. Full Adverse-Event Dataset

Study	Adverse event	Participants, n (%)	Event reports, n (%)	Severity	Relationship to psilocybin	Serious?	Timing	Action/resolution
Douglass et al.	Any adverse event	21/21 (100%)	107 total reports	Mild: 49 (45.8%); moderate: 43 (40.2%); severe: 15 (14.0%)	Related: 31 (29.0%); possibly related: 61 (57.0%); not related: 15 (~14.0%)[a]	SAEs reported separately	Across dosing and follow-up	Lorazepam rescue not required
Douglass et al.	Headache	18/21 (85.7%)	41 (37.3% of all reports)	NR	NR	No	NR	NR
Douglass et al.	Nausea	12/21 (57.1%)	27 (25.2%)	NR	NR	No	NR	NR
Douglass et al.	Dizziness	1/21 (4.8%)	6 (5.6%)	NR	NR	No	NR	NR
Douglass et al.	Migraine	1/21 (4.8%)	4 (3.7%)	NR	NR	No	NR	NR
Douglass et al.	Light-headedness	1/21 (4.8%)	4 (3.7%)	NR	NR	No	NR	NR
Douglass et al.	Anxiety	2/21 (9.5%)	3 (2.8%)	NR	NR	No	NR	NR
Douglass et al.	Indigestion	1/21 (4.8%)	2 (1.9%)	NR	NR	No	NR	NR
Douglass et al.	Pain in left hip	1/21 (4.8%)	1 (0.9%)	NR	NR	No	NR	NR
Douglass et al.	Female bacterial infection	1/21 (4.8%)	1 (0.9%)	NR	NR	No	NR	NR

Douglass et al.	Diarrhoea	1/21 (4.8%)	1 (0.9%)	NR	NR	No	NR	NR
Douglass et al.	Head-banging/self-harm	1/21 (4.8%)	1 (0.9%)	NR	NR	No	NR	NR
Douglass et al.	Suicidal ideation (routine AE)	1/21 (4.8%)	1 (0.9%)	NR	NR	No; distinct from later suicide-attempt SAEs	NR	NR
Douglass et al.	Hip pain (fall down stairs)	1/21 (4.8%)	1 (0.9%)	NR	NR	No	NR	NR
Douglass et al.	Confusion/anxiety	1/21 (4.8%)	1 (0.9%)	NR	NR	No	NR	NR
Douglass et al.	Chest muscle pain (fall down stairs)	1/21 (4.8%)	1 (0.9%)	NR	NR	No	NR	NR
Douglass et al.	Dissociative seizure	1/21 (4.8%)	1 (0.9%)	NR	NR	No	NR	NR
Douglass et al.	Stomach ache	1/21 (4.8%)	1 (0.9%)	NR	NR	No	NR	NR
Douglass et al.	Wisdom tooth pain	1/21 (4.8%)	1 (0.9%)	NR	NR	No	NR	NR
Douglass et al.	Pain around ears (from headphones)	1/21 (4.8%)	1 (0.9%)	NR	NR	No	NR	NR
Douglass et al.	Pins and needles (hands)	1/21 (4.8%)	1 (0.9%)	NR	NR	No	NR	NR
Douglass et al.	Sore throat	1/21 (4.8%)	1 (0.9%)	NR	NR	No	NR	NR
Douglass et al.	Sore stomach	1/21 (4.8%)	1 (0.9%)	NR	NR	No	NR	NR

Douglass et al.	Cold/cough	1/21 (4.8%)	1 (0.9%)	NR	NR	No	NR	NR
Douglass et al.	Heaviness in head	1/21 (4.8%)	1 (0.9%)	NR	NR	No	NR	NR
Douglass et al.	Pain in arm	1/21 (4.8%)	1 (0.9%)	NR	NR	No	NR	NR
Douglass et al.	Suicide attempts (2 events in 1 participant)	1/21 (4.8%)	2 events	Moderate	Unlikely related	Yes — SAE	Approximately 7 and 9 months after the final 6-week study visit	Hospitalization NR
Peck et al.	Headache	8/10 (80%)	NR	NR	NR	No	NR	NR
Peck et al.	Fatigue	7/10 (70%)	NR	NR	NR	No	NR	NR
Peck et al.	Nausea	3/10 (30%)	NR	NR	NR	No	NR	NR
Peck et al.	Feeling abnormal	2/10 (20%)	NR	NR	NR	No	NR	NR
Peck et al.	Migraine	2/10 (20%)	NR	NR	NR	No	NR	NR
Peck et al.	Dizziness	2/10 (20%)	NR	NR	NR	No	NR	NR
Peck et al.	Illusion	2/10 (20%)	NR	NR	NR	No	NR	NR
Peck et al.	Pain	1/10 (10%)	NR	NR	NR	No	NR	NR
Peck et al.	Anxiety	1/10 (10%)	NR	NR	NR	No	NR	NR
Peck et al.	Orthostatic heart-rate response increased	1/10 (10%)	NR	NR	NR	No	NR	NR
Peck et al.	Upper abdominal pain	1/10 (10%)	NR	NR	NR	No	NR	NR
Peck et al.	Hypoglycemia	2/10 (20%)	NR	Asymptomatic	Investigator interpretation did not establish direct causality	No	During post-dosing safety assessment; both had eaten a standardized	Resolved within 24 h; no intervention

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							breakfast before dosing	
Peck et al.	Clinically significant ECG changes	0/10 (0%)	NA	NA	NA	No	Assessed according to study safety schedule	No clinically significant abnormality requiring action
Peck et al.	Clinically significant vital-sign changes	0/10 (0%)	NA	NA	NA	No	NR	No clinically significant abnormality requiring action
Peck et al.	Clinically significant C-SSRS increase	0/10 (0%)	NA	NA	NA	No	Assessed at each time point	None requiring action
Peck et al.	Increased suicidal ideation at 3 months	1/10 (10%)	1	NR	Judged not related to study participation	No	3-month follow-up	Participant had pre-existing MDD and SI; further action NR
Peck et al.	Serious adverse events	0/10 (0%)	0	NA	NA	No	Throughout follow-up	No SAEs reported
Peck et al.	Rescue/anxiolytic medication	0/10 (0%)	0	NA	NA	No	During dosing	Not required

Source: The authors

Abbreviations: **AE** = adverse event; **C-SSRS** = Columbia-Suicide Severity Rating Scale; **ECG** = electrocardiogram; **MDD** = major depressive disorder; **NA** = not applicable; **NR** = not reported; **SAE** = serious adverse event; **SI** = suicidal ideation.

Table S5. Complete Outcome-by-Timepoint Extraction

Study	Outcome domain	Outcome /instrument	Time point	n	Baseline value	Follow-up value	Change/ effect estimate	Effect size	P value	Statistical method	Interpretation /notes
Douglass et al.	Eating-disorder psychopathology	Global EDE Interview	Baseline	21	3.2 (1.0)	—	Reference	—	—	Repeated-measures model	Primary efficacy outcome
Douglass et al.	Eating-disorder psychopathology	Global EDE Interview	6-week final visit	21	3.2 (1.0)	2.2 (0.9)	Δ=−1.0	d=1.08	0.0001	Repeated-measures model	Significant reduction; LOCF used for 1 withdrawn participant
Douglass et al.	Eating-disorder psychopathology	Global EDE Interview	3 months	21	3.2 (1.0)	2.0 (1.3)	Δ=−1.2	d=1.09	<0.0001	Repeated-measures model	Significant reduction
Douglass et al.	Eating-disorder psychopathology	Global EDE Interview	6 months	21	3.2 (1.0)	2.1 (1.3)	Δ=−1.1	d=0.98	<0.0001	Repeated-measures model	Significant reduction; last EDE assessment/primary durability endpoint
Douglass et al.	Eating-disorder psychopathology	Global EDE Interview	12 months	—	—	—	Not assessed	—	—	—	EDE was not administered at 12 months per protocol
Douglass et al.	Eating-disorder psychopathology	EDE dietary restraint	Longitudinal assessment through 6 months	21	NR	NR	Overall time effect	NR	<0.0001	Repeated-measures model, F(3,60)= 15.0	Significant overall time effect; sustained through 6 months

https://doi.org/10.25118/2763-9037.2026.v16.1677

Douglass et al.	Eating-disorder psychopathology	EDE eating concern	Longitudinal assessment through 6 months	21	NR	NR	Overall time effect	NR	<0.0001	Repeated-measures model, F(3,60)= 15.7	Significant overall time effect; sustained through 6 months
Douglass et al.	Eating-disorder psychopathology	EDE shape concern	Longitudinal assessment through 6 months	21	NR	NR	Overall time effect	NR	0.0001	Repeated-measures model, F(3,60)= 7.9	Significant overall time effect; sustained through 6 months
Douglass et al.	Eating-disorder psychopathology	EDE weight concern	Longitudinal assessment through 6 months	21	NR	NR	Overall time effect	NR	0.02	Repeated-measures model, F(3,60)= 3.4	Significant overall effect, but significance not maintained at 6 months
Douglass et al.	Eating-disorder psychopathology	EDE subscales, per-time-point β/d/P	All reported time points	21	NR	NR	NR	NR	NR	—	Detailed values were reported in Supplementary Table S8, which was not included in the uploaded extraction
Douglass et al.	Eating-disorder psychopathology	Global EDE-Q	Final visit through 12 months	21 (20 for medication-	NR	NR	Maximal numerical reduction ≈1.1 points at	NR	<0.0001 overall	Repeated-measures model, F(10,200) =6.6	Significant longitudinal improvement sustained through 12 months;

				withdrawal covariate model)			3 and 12 months				antidepressant-withdrawal fixed effect P=0.28
Douglass et al.	Motivation/readiness	RMQ precontemplation	After dose 2	20	NR	NR	β=−9.71	d=0.89	0.01	Repeated-measures model	Significant reduction
Douglass et al.	Motivation/readiness	RMQ precontemplation	2 months	20	NR	NR	β=−13.3	d=0.86	0.0001	Repeated-measures model	Near-maximal reduction
Douglass et al.	Motivation/readiness	RMQ precontemplation	3 months	20	NR	NR	β=−13.4	d=0.88	<0.0001	Repeated-measures model	Near-maximal reduction
Douglass et al.	Motivation/readiness	RMQ precontemplation	4 months	20	NR	NR	β=−8.36	d=0.58	0.065	Repeated-measures model	Trend-level, not statistically significant
Douglass et al.	Motivation/readiness	RMQ precontemplation	12 months	20	NR	NR	NR	d=0.65	0.0017	Repeated-measures model	Significant sustained reduction; attenuated relative to peak
Peck et al.	Motivation/readiness	RMQ	1 month	10	NR	NR	NR	NR	NR	NR	Not statistically significant; exact numerical results

											unavailable in extraction
Peck et al.	Anxiety	STAI-T	1 month	10	NR	NR	NR	d=0.78	0.036	Paired t-test	Significant decrease
Peck et al.	Depression	QIDS	1 month	10	NR	NR	NR	NR	NR	NR	Not statistically significant; exact values unavailable in extraction
Peck et al.	Body image	PASTAS	1 month	10	NR	NR	NR	d=0.76	0.04	Paired t-test	Significant decrease
Peck et al.	Eating-related preoccupations/ rituals	YBC-EDS	1 month	10	NR	NR	NR	d=0.75	0.043	Paired t-test	Significant decrease
Peck et al.	Functional impairment	CIA	1 month	10	NR	NR	NR	d=0.75	0.041	Paired t-test	Significant decrease
Peck et al.	Eating-disorder psychopathology	EDE dietary restraint	Baseline	10	2.18 (1.76)	—	Reference	—	—	Paired t-test	Reference
Peck et al.	Eating-disorder psychopathology	EDE dietary restraint	1 month	10	2.18 (1.76)	1.38 (1.56)	Δ=−0.80; 95% CI −1.81 to 0.21	d=0.57	0.107	Paired t-test	Not significant
Peck et al.	Eating-disorder psychopathology	EDE dietary restraint	3 months	10	2.18 (1.76)	1.46 (1.84)	Δ=−0.72; 95% CI −1.81 to 0.37	d=0.47	0.169	Paired t-test	Not significant
Peck et al.	Eating-disorder psychopathology	EDE eating concern	Baseline	10	2.10 (1.75)	—	Reference	—	—	Paired t-test	Reference
Peck et al.	Eating-disorder psychopathology	EDE eating concern	1 month	10	2.10 (1.75)	1.24 (1.50)	95% CI −1.83 to 0.11	d=0.64	0.075	Paired t-test	Not significant

Peck et al.	Eating-disorder psychopathology	EDE eating concern	3 months	10	2.10 (1.75)	1.00 (1.32)	95% CI −2.20 to 0.00	d=0.71	0.051	Paired t-test	Not significant; approached significance
Peck et al.	Eating-disorder psychopathology	EDE shape concern	Baseline	10	3.68 (1.30)	—	Reference	—	—	Paired t-test	Reference
Peck et al.	Eating-disorder psychopathology	EDE shape concern	1 month	10	3.68 (1.30)	2.43 (1.84)	95% CI −2.40 to −0.10	d=0.78	0.036	Paired t-test	Significant decrease
Peck et al.	Eating-disorder psychopathology	EDE shape concern	3 months	10	3.68 (1.30)	2.43 (1.95)	95% CI −2.69 to 0.19	d=0.62	0.081	Paired t-test	Not maintained; significance lost at 3 months
Peck et al.	Eating-disorder psychopathology	EDE weight concern	Baseline	10	3.64 (1.65)	—	Reference	—	—	Paired t-test	Reference
Peck et al.	Eating-disorder psychopathology	EDE weight concern	1 month	10	3.64 (1.65)	2.76 (1.81)	95% CI −1.69 to −0.07	d=0.78	0.036	Paired t-test	Significant decrease
Peck et al.	Eating-disorder psychopathology	EDE weight concern	3 months	10	3.64 (1.65)	2.30 (2.00)	95% CI −2.57 to −0.11	d=0.78	0.036[a]	Paired t-test	Significant decrease maintained through 3 months
Peck et al.	Eating-disorder psychopathology	Global EDE, responder analysis	3 months	10	NR	NR	4/10 (40%) within 1 SD of community norms; norm mean	NR	NR	Descriptive	Investigator-interpreted as clinically significant improvement in a subset; not formal diagnostic remission; 3/4

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							0.93 (SD 0.80)				responders had current AN
Douglass et al.	Response/remission-related outcome	Global EDE, community-norm proximity	Final visit	21	2/21 already within community-norm range at baseline	6/21 (28.6%) within range	NR	NR	NR	Descriptive	Not formal diagnostic remission
Douglass et al.	Response/remission-related outcome	Global EDE, community-norm proximity	3 months	21	2/21 already within range at baseline	10/21 (47.6%) within range	NR	NR	NR	Descriptive	Not formal diagnostic remission
Douglass et al.	Response/remission-related outcome	Global EDE, community-norm proximity	6 months	21	2/21 already within range at baseline	8/21 (38.1%) within range	NR	NR	NR	Descriptive	Not formal diagnostic remission
Douglass et al.	BMI/weight	BMI	Baseline	21	Mean 16.4 kg/m² (SD 1.4); range 14.3–20.5	—	—	—	—	Safety monitoring	BMI was not a preregistered efficacy outcome
Douglass et al.	BMI/weight	BMI	Dose 2, dose 3, final visit	21	Baseline as above	NR	NR	NR	NR	Safety monitoring	Numerical follow-up BMI values unavailable in extraction
Peck et al.	BMI/weight	BMI	Baseline	10	Mean 19.7	—	—	—	—	—	Secondary clinical outcome

					kg/m² (SD 3.7)						
Peck et al.	BMI/weight	BMI	3 months	10	19.7 kg/m² (SD 3.7)	NR as aggregate follow-up value	Mean change not statistically significant; 5/10 had BMI increase of 0.4–1.2 kg/m²	NR	NR	NR	No correlation between BMI outcome and EDE response reported
Peck et al.	Quality of life	Overall quality of life	3 months	10	—	—	70% agreement	—	—	Qualitative self-report	Study-specific qualitative outcome
Peck et al.	Quality of life/subjective	Decreased importance of physical appearance	3 months	10	—	—	60% agreement	—	—	Qualitative self-report	Study-specific qualitative outcome
Peck et al.	Quality of life/subjective	More optimistic about life endeavors	3 months	10	—	—	90% agreement	—	—	Qualitative self-report	Study-specific qualitative outcome
Peck et al.	Quality of life/subjective	Shift in personal identity/sense of self	3 months	10	—	—	70% agreement	—	—	Qualitative self-report	Study-specific qualitative outcome
Peck et al.	Quality of life/subjective	Greater sense of spirituality	3 months	10	—	—	60% agreement	—	—	Qualitative self-report	Study-specific qualitative outcome

Peck et al.	Acceptability/meaningfulness	Experience among top-five most meaningful life experiences	3 months	10	—	—	80% agreement	—	—	Qualitative self-report	Study-specific acceptability outcome
Peck et al.	Acceptability	Felt one dosing session was not enough	3 months	10	—	—	90% disagreed that one session was enough	—	—	Qualitative self-report	Indicates preference for additional dosing; not an efficacy outcome
Douglass et al.	Safety-related clinical outcome	Suicidality	Full study period	21	—	—	1/21 routine SI AE; 2 suicide-attempt SAEs in 1 participant	—	—	AE/SAE monitoring	Detailed safety data presented separately in Supplementary Table S3
Peck et al.	Safety-related clinical outcome	C-SSRS suicidality	All reported time points	10	—	—	0/10 clinically significant increase; 1/10 increased SI at 3 months	—	—	C-SSRS	Individual increase in SI judged unrelated to study participation
Peck et al.	Safety-related clinical outcome	ECG, vital signs,	Safety follow-up	10	—	—	Clinically significant ECG	—	—	Safety assessments	Hypoglycemia asymptomatic

		hypoglycemia					changes 0/10; vital-sign changes 0/10; hypoglycemia 2/10				and resolved within 24 h

Source: The authors

Abbreviations: AN = anorexia nervosa; **BMI** = body mass index; **CIA** = Clinical Impairment Assessment; **C-SSRS** = Columbia-Suicide Severity Rating Scale; **EDE** = Eating Disorder Examination; **EDE-Q** = Eating Disorder Examination Questionnaire; **LOCF** = last observation carried forward; **NA** = not applicable; **NR** = not reported; **PASTAS** = Physical Appearance State and Trait Anxiety Scale; **QIDS** = Quick Inventory of Depressive Symptomatology; **RMQ** = Readiness and Motivation Questionnaire; **SD** = standard deviation; **SI** = suicidal ideation; **STAI-T** = State-Trait Anxiety Inventory, Trait; **YBC-EDS** = Yale-Brown-Cornell Eating Disorder Scale.

Table S6. Study Funding and Conflicts of Interest

Study	Funding source	Drug/product support	Institutional/setting support reported	Author-reported conflicts of interest	Role of sponsor/ company	Data/code availability
Douglass et al. (PSI-AN-01)	NR in the uploaded extraction	COMP360 identified as the study drug; explicit drug-supply/donation statement NR	NIHR Imperial Clinical Research Facility, Imperial College London; recruitment through two NHS specialist eating-disorder services. Whether these institutions provided direct study funding is NR	NR in the uploaded extraction	NR	NR
Peck et al. (PSI-AN-02)	NR in the uploaded extraction	Intervention identified as synthetic psilocybin; "COMP360 25 mg" appears in the adverse-event table; explicit drug-supply/manufacturer statement NR	UC San Diego ACTRI and Eating Disorder Treatment & Research Center	NR in the uploaded extraction	NR	NR

Source: The authors
Abbreviations: **ACTRI** = Altman Clinical and Translational Research Institute; **COMP360** = study psilocybin formulation identified in the source; **NIHR** = National Institute for Health and Care Research; **NHS** = National Health Service; **NR** = not reported.