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Review article

The experimental effects of psilocybin on symptoms of anxiety and depression: A meta-analysis

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ABSTRACT

The current meta-analysis examined the effects of psilocybin in combination with behavioral interventions on anxiety and depression in samples with elevated symptoms. Across four studies (one uncontrolled; three randomized, placebo-controlled; $N = 117$), within-group pre-post and pre-follow-up effects on anxiety and depression were large (Hedges' $gs = 1.16$ to 1.47) and statistically significant. Across three placebo-controlled studies, pre-post placebo-controlled effects were also large ($gs = 0.82$ to 0.83) and statistically significant. No serious adverse events were reported. Limitations include the small number of studies and risk for bias within studies. Results tentatively support future research on psilocybin for the treatment of anxiety and depression.

1. Introduction

There has been remarkable progress developing pharmacological and behavioral treatments for anxiety and depressive disorders in the past century (Baldwin et al., 2005; Butler et al., 2006; Cipriani et al., 2018). While many benefit from existing therapies, others remain symptomatic, do not comply with treatment, or experience withdrawal or adverse side effects (Davies and Read, 2019; Gartlehner et al., 2016; Rossom et al., 2016; Simon et al., 2001; Westen and Morrison, 2001). Thus, there is a need for new treatment approaches.

Researchers have recently resumed investigating psychedelic compounds as a novel treatment approach. One such substance is psilocybin (4-phosphoroyloxy-N,N-dimethyltryptamine), a plant alkaloid and 5-HT_{2A} receptor agonist. Research on the potential therapeutic benefits of psilocybin have focused on treating anxiety (Griffiths et al., 2016; Grob et al., 2011), depression (Carhart-Harris et al., 2016, 2018; Ross et al., 2016), and substance use (Bogenschutz et al., 2015; Johnson et al., 2017). Although thorough narrative reviews of this literature exist (dos Santos et al., 2018; Reiche et al., 2018), no meta-analysis has been conducted. A quantitative synthesis can support planning future trials and allows formal assessment of publication bias and heterogeneity. The current study meta-analyzed clinical trials testing psilocybin for anxiety and depression.

2. Methods

2.1. Eligibility criteria

Studies involved administration of psilocybin. Clinically elevated anxiety and/or depression symptoms were required (i.e., diagnosis and/or clinical interview). Studies reported effects on anxiety and/or depression and provided data for computing effect sizes.

2.2. Information sources

PRISMA guidelines were followed (Moher et al., 2009). The study was registered through PROSPERO (CRD42018111732). We searched PubMed, PsycInfo, Scopus, Web of Science, Cochrane, recent systematic reviews, and clinicaltrials.gov.

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2.3. Search

Search terms were: (psiloc* AND depress*) OR (psiloc* AND anx*) OR (psiloc* AND mood) OR (psiloc* AND psychological distress). No restrictions were placed on publication status, language, or date. Clinicaltrials.gov was searched using the term "psilocybin." The search was conducted October 6th, 2018.

2.4. Study selection

Two authors independently coded titles and abstracts.

2.5. Data collection process

Standardized spreadsheets were created. Coders were experienced, doctoral-level researchers trained in meta-analysis.

2.6. Data items

Data for computing effect sizes were coded along with study design, adverse events, assessment timing, dose, behavioral interventions, control condition, age, gender, race/ethnicity, retention, use of intent-to-treat (ITT), and location.

2.7. Risk of bias within studies

Risk of bias within studies was evaluated based on Cochrane recommendations (Higgins and Green, 2011). We assessed selection bias (random sequence generation, allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), and reporting bias (selective reporting).

2.8. Summary measures

A pre-post within-group Cohen's (1988) *d* was computed using data from the psilocybin groups alone. Pre-post data were drawn from both single group studies and controlled studies. Effect sizes were converted to Hedges' *g* to account for small sample bias (Borenstein et al., 2009).

A between-groups effect size was computed for studies that included a control condition, reflecting the difference in pre-post effects for the psilocybin and control conditions (i.e., Becker's [1988] Δ). Post-treatment data were used from the latest assessment prior to the control condition receiving the active intervention.

A pre- to follow-up effect size was also computed. As the controlled trials involved cross-over designs in which both groups received the active treatment, pre- to follow-up effect sizes included both psilocybin and control conditions. Data from last available follow-up was used.

2.9. Synthesis of results

When multiple measures of anxiety and/or depression were included, effects were aggregated within study using the 'MAd' package (Del Re and Hoyt, 2010) in R (R Core Team, 2018). We employed random effects models in the 'metafor' package (Viechtbauer, 2010) using standard methods that weighted by effect sizes' inverse variance (Borenstein et al., 2009). Heterogeneity was indexed using I^2 and interpreted based on Higgins et al. (2003).

2.10. Risk of bias across studies

We computed a fail-safe N (FSN; Rosenthal, 1979; Viechtbauer, 2010) to evaluate publication bias. Funnel plots and trim-and-fill analyses assessed asymmetry. Due to the small sample, these were considered exploratory.

3. Results

3.1. Study selection

A total of 864 citations were retrieved (Supplemental Fig. 1). No studies with eligible unpublished data were identified through Clinicaltrials.gov. The final sample include five studies representing four unique trials.

3.2. Study characteristics

Across the four trials, one used a single group design and three used randomized, placebo-controlled, cross-over designs. Psilocybin dose and placebo condition varied (see Supplemental Table 1 for study characteristics).

All studies included behavioral interventions pre-intervention visits, support during the administration of psilocybin or placebo, and post-intervention support. Transient adverse reactions were similar across studies and resolved within hours of administration of psilocybin. No serious or persistent adverse events were reported.

Sample sizes were small (M = 29.25, SD = 19.14). Post-treatment assessment occurred on average at 3.75 weeks (SD = 2.75) and all follow-up occurred at six months. Samples were on average 58.25% female and 86.33% White. Three trials occurred in the United States and one in the United Kingdom. Retention was on average 94.00% at post-treatment and 79.50% at follow-up.

3.3. Risk of bias within studies

Risk of bias varied across studies and domains (Supplemental Table 2). All studies had high risk for detection bias due to limited blinding of participants and personnel. The nature of psilocybin appeared to make blinding not possible. Blinding of outcome was assessed as high risk for bias in three studies due to self-report measures and unclear in one study. Attrition bias was high in three of four studies due to a lack of ITT analyses. Selective reporting risk for bias was low across all studies.

3.4. Results of individual studies

Study-level effect sizes are reported in Supplemental Table 3 and Supplemental Fig. 2. Outcome measures are listed in Supplemental Table 4.

3.5. Synthesis of results

Meta-analytic results are reported in Table 1. Across four studies (n = 69), within-group, pre-post effect sizes indicated large reductions of anxiety (g = 1.38, 95% *CI* [0.78, 1.99]) and depression (g = 1.47, [0.72, 2.21]) within the psilocybin conditions. Heterogeneity was high (I^2 = 74.51% to 82.41%).

Across three studies (n = 97), placebo-controlled, pre-post effect sizes indicated large reductions of anxiety (g = 0.82, [0.40, 1.23]) and depression (g = 0.83, [0.39, 1.26]). Heterogeneity was low (I^2 = 0.00%), although with wide confidence intervals.

Across four studies (n = 117), within-group, pre- to follow-up effect sizes indicated large reductions of anxiety (g = 1.16, [0.57, 1.75]) and depression (g = 1.17, [0.80, 1.53]) at six-month follow-up. Heterogeneity was high (I^2 = 57.15% to 82.33%).

3.6. Risk of bias across studies

For within-group pre-post and pre- to follow-up effect sizes, a large number of unpublished studies with null results would be necessary to nullify the observed effects (FSNs = 117 to 141). FSNs were below the recommended cut-off for placebo-controlled pre-post effects

Table 1
Meta-analytic intervention effects on anxiety and depressive symptoms.

Time point	Comparison	Domain	*N*	*k*	ES [95% CI]	I^2 [95% CI]	Fail-safe *N*
Post	Pre-post	Anxiety	69	4	1.38 [0.78, 1.99]	74.51 [15.82, 98.37]	117
Post	Pre-post	Depression	69	4	1.47 [0.72, 2.21]	82.41 [43.88, 98.79]	125
Post	Controlled	Anxiety	97	3	0.82 [0.40, 1.23]	0.00 [0.00, 81.85]	14
Post	Controlled	Depression	97	3	0.83 [0.39, 1.26]	0.00 [0.00, 91.42]	12
FU	Pre-FU	Anxiety	117	4	1.16 [0.57, 1.75]	82.33 [42.56, 98.79]	130
FU	Pre-FU	Depression	117	4	1.17 [0.80, 1.53]	57.15 [0.00, 96.82]	141

Note: ES = effect size in Hedges' *g* units; I^2 = degree of heterogeneity among study effect sizes; Fail-safe N computed per (Rosenthal, 1979); FU = follow-up; Pre-post = pre-post within-group effect size (i.e., psilocybin group only); Controlled = randomized, double-blind, placebo-controlled pre-post between-group effect size; Pre-FU = pre- to follow-up within-group effect size (as all groups received psilocybin by follow-up).

(FSNs = 12 to 14; Rosenberg, 2005). Funnel plots and trim-and-fill analyses did not show evidence that effect size estimates were inflated.

4. Discussion

The current meta-analysis evaluated effects of psilocybin coupled with supportive behavioral interventions on anxiety and depression. Although a small number of studies were included, available data were promising. Within-group effects at post-treatment and six-month follow-up showed large reductions in anxiety and depression symptoms with no evidence of publication bias. Qualitative assessment of risk of bias was more concerning, with high risk in several domains. High between-study heterogeneity suggests there may be systematic variation across the studies. Future meta-analyses should examine study features (e.g., psilocybin dose) as moderators of treatment effects.

Effects of psilocybin on anxiety and depression were also evident in three randomized, double-blind, placebo-controlled studies. Effect sizes (*g*s = 0.82 to 0.83 for psilocybin vs. placebo) are similar to psychological interventions versus no treatment (d = 0.80; Wampold and Imel, 2015) and cognitive behavioral therapy versus no treatment (d = 0.82; Butler et al., 2006). Given both psilocybin and placebo groups received equivalent behavioral interventions, the additive benefit of psilocybin may be substantial. However, this effect was not robust to publication bias, highlighting the need for further placebo-controlled studies. As supportive behavioral interventions were included in all studies, results cannot be interpreted to indicate general benefits associated with the use of psilocybin in the absence of support.

Additional large-scale studies examining the effects of psilocybin on treatment-resistant depression may be warranted, as only one of the four studies focused on this population. It may be valuable to evaluate various behavioral interventions to support or extend benefits of psilocybin treatments.

The current meta-analysis has several limitations. Only four studies (N = 117) were available, limiting the reliability of the observed effects. Small sample studies can introduce biases (Button et al., 2013). Heterogeneity in effect sizes and design features were generally high. High risk of bias was present for most studies (performance bias and detection bias due to lack of blinding, attrition bias). Selection bias also limits generalizability of the available evidence as all participants were willing to receive a Schedule I substance. Three of the four studies included individuals with terminal cancer diagnoses, which may not represent anxiety and depression generally. Limited racial/ethnic diversity reduces generalizability.

Nonetheless, the current meta-analysis suggests psilocybin in combination with behavioral support may provide a safe and effective treatment option for reducing symptoms of anxiety and depression. This is an area for additional careful, scientific study.

Declaration of competing interest

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Christopher R. Nicholas received salary offsets from Usona Institute. In the prior 12 months, Charles L. Raison has served as a consultant for Usona Institute, Alkermes and Shire. All other authors declare that there is no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2020.112749.

References

Baldwin, D.S., Anderson, I.M., Nutt, D.J., Bandelow, B., Bond, A., Davidson, J.R., den Boer, J.A., Fineberg, N.A., Knapp, M., Scott, J., Wittchen, H.U., 2005. Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology. J. Psychopharmacol. 19 (6), 567–596.

Becker, B., 1988. Synthesizing standardized mean-change measures. Br. J. Math. Stat. Psychol. 41, 257–278.

Bogenschutz, M.P., Forcehimes, A.A., Pommy, J.A., Wilcox, C.E., Barbosa, P.C.R., Strassman, R.J., 2015. Psilocybin-assisted treatment for alcohol dependence: a proof-of- concept study. J. Psychopharmacol. 29 (3), 289–299. https://doi.org/10.1177/0269881114565144.

Borenstein, M., Hedges, L.V., Higgins, J.P.T., Rothstein, H.R., 2009. Introduction to Meta-Analysis. Wiley, New York.

Butler, A.C., Chapman, J.E., Forman, E.M., Beck, A.T., 2006. The empirical status of cognitive-behavioral therapy: a review of meta-analyses. Clin. Psychol. Rev. 26 (1), 17–31. https://doi.org/10.1016/j.cpr.2005.07.003.

Button, K.S., Ioannidis, J.P., Mokrysz, C., Nosek, B.A., Flint, J., Robinson, E.S., Munafò, M.R., 2013. Power failure: why small sample size undermines the reliability of neuroscience. Nat. Rev. Neurosci. 14 (5), 365–376. https://doi.org/10.1038/nrn3475.

Carhart-Harris, R.L., Bolstridge, M., Day, C.M.J., Rucker, J., Watts, R., Erritzoe, D.E., Kaelen, M., Giribaldi, B., Bloomfield, M., Pilling, S., Rickard, J.A., Forbes, B., Feilding, A., Taylor, D., Curran, H.V., Nutt, D.J., 2018. Psilocybin with psychological support for treatment-resistant depression: six-month follow-up. Psychopharmacology 235 (2), 399–408.

Carhart-Harris, R.L., Bolstridge, M., Rucker, J., Day, C.M., Erritzoe, D., Kaelen, M., Bloomfield, M., Rickard, J.A., Forbes, B., Feilding, A., Taylor, D., Pilling, S., Curran, V.H., Nutt, D.J., 2016. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. Lancet Psychiatry 3 (7), 619–627 doi: 10.1016/ S2215-0366(16)30065-7.

Cipriani, A., Furukawa, T.A., Salanti, G., Chaimani, A., Atkinson, L.Z., Ogawa, Y., Leucht, S., Ruhe, H.G., Turner, E.H., Higgins, J.P.T., Egger, M., Takeshima, N., Hayasaka, Y., Imai, H., Shinohara, K., Tajika, A., Ioannidis, J.P.A., Geddes, J.R., 2018. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet 391 (10128), 1357–1366.

Cohen, J., 1988. Statistical Power Analysis for the Behavioral Sciences, second ed. Erlbaum, Hillsdale, NJ.

Davies, J., Read, J., 2019. A systematic review into the incidence, severity and duration of antidepressant withdrawal effects: are guidelines evidence-based. Addict. Behav. 97, 111–121. https://doi.org/10.1016/j.addbeh.2018.08.027.

Del Re, A.C., Hoyt, W.T., 2010. MAd: meta-analysis with mean differences. R package version 0.8, http://CRAN.R-project.org/package=MAd.

Dos Santos, R.G., Bouso, J.C., Alcázar-Córcoles, M., Hallak, J.E., 2018. Efficacy, tolerability, and safety of serotonergic psychedelics for the management of mood, anxiety, and substance-use disorders: a systematic review of systematic reviews. Expert Rev. Clin. Pharmacol. 11 (9), 889–902. https://doi.org/10.1080/17512433.2018.1511424.

Gartlehner, G., Gaynes, B.N., Amick, H.R., Asher, G.N., Morgan, L.C., Coker-Schwimmer, E., Forneris, C., Boland, E., Lux, L.J., Gaylord, S., Bann, C., Pierl, C.B., Lohr, K.N., 2016. Comparative benefits and harms of antidepressant, psychological, complementary, and exercise treatments for major depression: an evidence report for a clinical practice guideline from the American College of Physicians. Ann. Intern. Med. 164 (5), 331–341. https://doi.org/10.7326/M15-1813.

Griffiths, R.R., Johnson, M.W., Carducci, M.A., Umbricht, A., Richards, W.A., Richards, B.D., Cosimano, M.P., Klinedinst, M.A., 2016. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: a randomized double-blind trial. J. Psychopharmacol. 30 (12), 1181–1197. https://doi.org/10.1177/0269881116675513.

Grob, C.S., Danforth, A.L., Chopra, G.S., Hagerty, M., McKay, C.R., Halberstadt, A.L., Greer, G.R., 2011. Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. Arch. Gen. Psychiatry 68 (1), 71–78. https://doi.org/10.1001/archgenpsychiatry.2010.116.

Higgins, J.P.T., Green, S., 2011. Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0. The Cochrane Collaboration updated March 2011Available from. www.handbook.cochrane.org.

Higgins, J.P., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in meta-analyses. BMJ 327 (7414), 557–560.

Johnson, M.W., Garcia-Romeu, A., Griffiths, R.R., 2017. Long-term follow-up of psilocybin-facilitated smoking cessation. Am. J. Drug Alcohol Abuse 43 (1), 55–60. https://doi.org/10.3109/00952990.2016.1170135.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., the PRISMA Group, 2009. Preferred reporting items for systematic reviews and meta-analyses: the Prisma statement. Ann. Intern. Med. 151 (4), 264–269.

R. Core Team, 2018. R: a language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria URL. https://www.R-project.org/.

Reiche, S., Hermle, L., Gutwinski, S., Jungaberle, H., Gasser, P., Majić, T., 2018. Serotonergic hallucinogens in the treatment of anxiety and depression in patients suffering from a life-threatening disease: a systematic review. Prog. Neuropsychopharmacol. Biol. Psychiatry 81, 1–10. https://doi.org/10.1016/j.pnpbp.2017.09.012.

Rosenthal, R., 1979. The “file drawer problem” and tolerance for null results. Psychol. Bull. 86 (3), 638–641.

Ross, S., Bossis, A., Guss, J., Agin-Liebes, G., Malone, T., Cohen, B., Mennenga, S.E., Belser, A., Kalliontzi, K., Babb, J., Su, Z., Corby, P., Schmidt, B.L., 2016. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. J. Psychopharmacol. 30 (12), 1165–1180. https://doi.org/10.1177/0269881116675512.

Rosenberg, M.S., 2005. The file-drawer problem revisited: a general weighted method for calculating fail-safe numbers in meta-analysis. Evolution 59 (2), 464–468.

Rossom, R.C., Shortreed, S., Coleman, K.J., Beck, A., Waitzfelder, B.E., Stewart, C., Ahmedani, B.K., Zeber, J.E., Simon, G.E., 2016. Antidepressant adherence across diverse populations and healthcare settings. Depress. Anxiety 33 (8), 765–774. https://doi.org/10.1002/da.22532.

Simon, G.E., Von Korff, M., Rutter, C.M., Peterson, D.A., 2001. Treatment process and outcomes for managed care patients receiving new antidepressant prescriptions from psychiatrists and primary care physicians. Arch. Gen. Psychiatry 58 (4), 395–401.

Viechtbauer, W., 2010. Conducting meta-analyses in R with the metafor package. J. Stat. Softw. 36 (3), 1–49.

Wampold, B., Imel, Z.E., 2015. The Great Psychotherapy debate: the evidence for What Makes Psychotherapy Work, second ed. Routledge, New York.

Westen, D., Morrison, K., 2001. A multidimensional meta-analysis of treatments for depression, panic, and generalized anxiety disorder: an empirical examination of the status of empirically supported therapies. J. Consult. Clin. Psychol. 69 (6), 875–899.