Psychiatry Research 337 (2024) 115960

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Letter to the Editor

Efficacy and safety of psilocybin on treatment-resistant depression: A systematic review and meta-analysis

Dear Editor,

Treatment-resistant depression (TRD) is a type of hard-to-treat depression with inadequate responses to at least two different antidepressant regimens, despite adequate dosage, duration, and adherence (Gaynes et al., 2020). According to the World Health Organization, approximately 5 % of adults suffered from Major Depressive Disorder (MDD) in 2023, among whom 20–35 % of patients developed TRD (European Medicines Agency, 2013). Psilocybin, acting as an agonist on serotonin type 2A receptors (López-Giménez et al., 2018), showed promising effects on promoting neuroplasticity in cortical neurons and improving depressive symptoms. Previous meta-analysis reported significant benefits of psilocybin on anxiety and MDD symptom control (Goldberg et al., 2020); however, overall efficacy and safety evidence of psilocybin on TRD is limited.

We identified eligible publications (PubMed, Embase, Medline, Cochrane, and APA PsycINFO), preprints (bioRvix, medRvix, PeerJ), and unpublished records (ClinicalTrials.gov) updated to 14 July 2023. Inclusion criteria were: 1) adult patients with TRD; 2) psilocybin as the intervention; 3) reported safety (tolerance and adverse events) and/or efficacy outcomes; 4) randomized controlled trials (RCTs) or open-label trials.

The "Meta" and "Metafor" packages were used in R (version 4.3.1) to conduct all the statistical analyses. Random effects models with a statistical significance level of α=0.05 were used. The eligible studies examined the efficacy of psilocybin on TRD, with changes in depressive scores. Standardized mean differences (SMD) were computed to compare the studies that adapted different instruments to measure the primary outcomes. To unify the standard, we recalculated SMD using formulas of Cohen's d or Hedges' g. Higgins' I^2 statistic measured heterogeneity. Univariate meta-regressions, variables including mean age, female proportion, measure times (the duration between psilocybin intake and primary outcome measure), dose of psilocybin, and sample size, were conducted to assess the potential source of heterogeneity. Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) was used for risk of bias assessment. Publication bias was assessed by Egger's test and funnel plot. Three researchers (QF, YJ, JW) independently cross-checked candidate screening, data extraction, and analyses.

Five studies [RCTs: Goodwin et al., 2022 (NCT03775200) and Goodwin et al., 2023 (NCT03775200); open-label trials: Carhart-Harris et al., 2016, Carhart-Harris et al., 2018, and Lyons and Carhart-Harris, 2018] were included in the systematic review from initial screened 823 published literature and 105 preprints and trials. Four studies were used for meta-analyses of efficacy, and three were included for a descriptive analysis of safety. Goodwin et al., 2023 was excluded from the meta-analysis due to duplicated trial information reported in Goodwin et al., 2022. Demographic information, medical conditions, interventions, and outcomes of included studies were documented.

A random effects model with six arms from four studies showed that psilocybin significantly reduced depressive scores compared to baseline conditions (SMD = 4.14, 95 % CI = [1.86, 6.41], I^2 = 97 %, $p < 0.01$) (Fig. 1). Subgroup analysis with 10 plus 25 mg psilocybin also showed a significant reduction (SMD = 1.95, 95 % CI = [1.41, 2.49], I^2 = 14 %, p = 0.31) (Fig. 1). A sensitivity analysis excluding the overlapping of subjects from Carhart-Harris et al., 2016 also showed statistical significance (SMD =4.42, 95 % CI = [1.73, 7.12], I^2 = 98 %, $p < 0.01$). In univariate meta-regressions, the proportion of female patients and sample sizes were related to depressive symptom score changes - SMD ([coefficient = 0.1762, p = 0.0124] and [coefficient = 0.0649, p = 0.0121]), respectively. No high risk of bias was identified. Publication bias was found based on the funnel plot and Egger's test (p = 0.015).

Three studies with 265 patients recruited in total reported adverse events (Table 1). Headache (20.75 %), anxiety (13.58 %), nausea (12.08 %), and confusion (4.91 %), all transient and short-term, were reported in at least two studies. Only one study investigated drug adverse events longitudinally. Suicidal ideation (1.51 %), intentional self-injury (1.13 %), and hospitalization (0.38 %) were reported as serious adverse events from Day 2 to Week 3 since the treatment. Suicidal behavior (1.13 %) was observed from Week 3 to Week 12 after psilocybin use.

This meta-analysis found that psilocybin significantly improved the depressive symptoms of patients with TRD compared to baseline. Moderate-level risk of bias was found in several domains, partially attributed to the open-label study design. Considerable heterogeneity was observed in the overall pooled results and sensitivity analysis driven by female proportion in the participants and sample size. Headache, anxiety, and nausea were common and transient adverse events, while serious adverse events were rare.

The efficacy of psilocybin on TRD could be partly supported by the clear link between psilocybin and its potential to alleviate depressive symptoms. Volunteers who received psilocybin in a controlled and supportive setting rated their experiences as having sustained positive changes in their attitudes and behavior attributed to psilocybin, including a shift in perspective, increased feelings of connectedness, and a greater sense of purpose in life (Griffiths et al., 2006). Significant and substantial improvements in a meta-analysis involving four studies comparing behavioral treatment plus psilocybin to behavioral treatment were observed in anxiety and depression levels of post-treatment and follow-up versus pre-treatment (Hedges' g = [1.16, 1.47]) (Goldberg, 2020), indicating that psilocybin might be an effective treatment option for anxiety and depression. Furthermore, plateaued and bell-shaped curves were observed for patients with primary and secondary depression in another meta-analysis, in which the maximum reduction of depressive symptoms was 24.68 mg/70 kg and 8.92 mg/70 kg,

https://doi.org/10.1016/j.psychres.2024.115960
Received 20 December 2023; Received in revised form 8 May 2024; Accepted 9 May 2024
Available online 22 May 2024

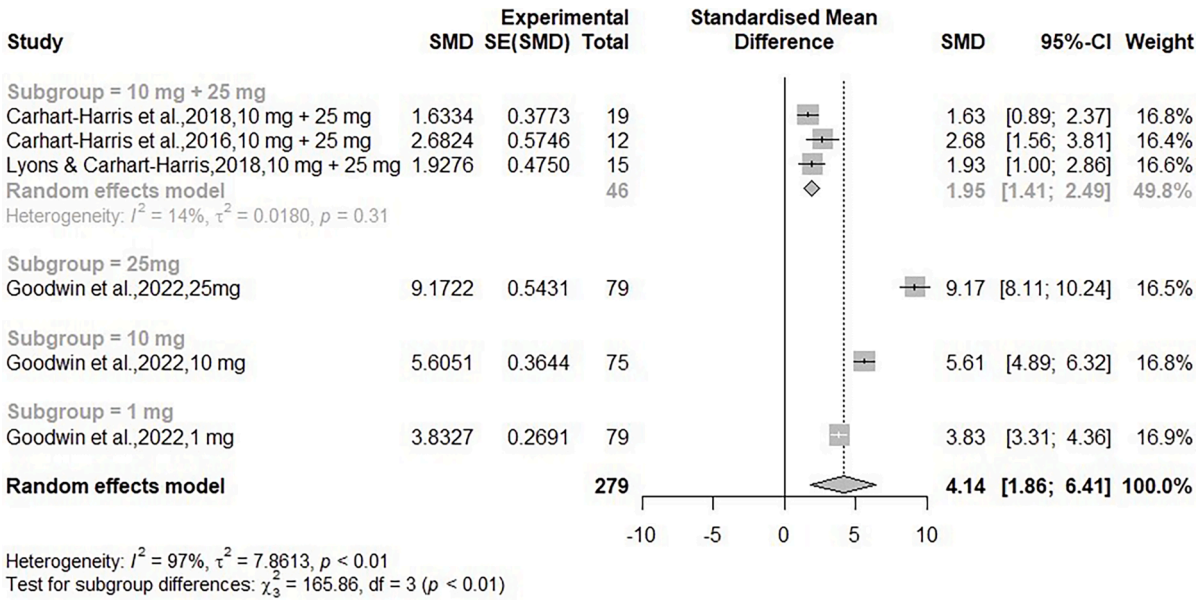

Fig. 1. Meta-analysis of four studies based on subgroup.

Table 1
Summary of Adverse Events.

First Author	Published Year	Subgroup	Subjects (No.)	AE																
				Transient Anxiety		Transient Headache		Transient Nausea		Transient Confusion		Euphoric Mood	Fatigue	Insomnia	Mood Altered	Dizziness	Paresthesia			
Carhart-Harris et al.	2018	10 + 25 mg	20	15		8		5		0		/	/	/	/	/	/			
Carhart-Harris et al.	2016	10 + 25 mg	12	12		4		4		9		/	/	/	/	/	/			
												Day 1								
		25 mg	79	3		19		17		0		5	5	2	4	5	2			
Goodwin et al.	2022	10 mg	75	6		11		5		4		4	2	3	3	1	4			
		1 mg	79	0		13		1		0		3	4	5	0	0	0			
Proportion				13.58 %		20.75 %		12.08 %		4.91 %		4.53 %	4.15 %	3.77 %	2.64 %	2.26 %	2.26 %			
				AE									Serious AE			AE	Serious AE			
First Author	Published Year	Subgroup	Subjects (No.)	Headache	Insomnia	Anxiety	Fatigue	Suicidal Ideation	Depression	Mood Altered		Suicidal Ideation	Intentional Self-injury	Hospitalization		Headache	Suicidal Behavior			
Carhart-Harris et al.	2018	10 + 25 mg	20	/	/	/	/	/	/	/		/	/	/		/	/			
Carhart-Harris et al.	2016	10 + 25 mg	12	/	/	/	/	/	/	/		/	/	/		/	/			
									Day 2 – Week 3							Week 3 – Week 12				
		25 mg	79	9	4	4	6	5	3	4		2	2	0		3	3			
Goodwin et al.	2022	10 mg	75	5	5	6	2	4	3	0		2	1	1		2	0			
		1 mg	79	9	8	3	3	2	4	1		0	0	0		6	0			
Proportion				8.68 %	6.42 %	4.91 %	4.15 %	4.15 %	3.77 %	1.89 %		1.51 %	1.13 %	0.38 %		4.15 %	1.13 %			

AE: adverse events; Serious AE: serious adverse events.

respectively (Perez et al., 2023). They indicated that there might be a dose-response relationship between psilocybin and MDD, and the optimal dose of psilocybin on TRD treatment requires additional evidence due to the variations in specific depression conditions.

A previous systematic review reported that the main adverse events caused by psilocybin were anxiety/fear, headache, and nausea or purging. Although serum hallucinogens caused transient increases in blood pressure, they did not lead to serious cardiovascular adverse events (Andersen et al., 2021), aligning with our findings. Furthermore, the meta-regression found physical discomfort events increased by 2.35 % with each 1 mg/70 kg of psilocybin intake. It also reported significant increases in these side effects, including tachycardia, nausea, vomiting, headache, migraine, and psychiatric adverse events. However, no association was found between doses of psilocybin and the frequency of serious adverse effects (Perez et al., 2023).

The study limitations cast a few future research directions. First, there was still rare evidence from high-quality, large-sample RCTs and long-term follow-up studies that were imperative for the efficacy and safety of psilocybin. Second, SMD could not directly interpret the effect given the introduction of standard deviation. In this study, however, SMD allowed the comparison among different scales. Applying multiple depressive scales in future studies will enable the meta-analyses to compare effect sizes on each scale directly, avoiding the disadvantage of SMD interpretation. Last, the TRD definitions were not unified across included studies, causing great heterogeneity and variance in outcome estimations. Future studies should apply guideline-recommended definitions when designing clinical trials for TRD.

This study provided emerging evidence that psilocybin might be a viable option for TRD in improving depressive symptoms with acceptable safety performance. High-quality RCTs with large sample sizes and a unified definition of TRD are warranted to generate golden evidence with regard to psilocybin's effect on optimizing TRD management.

CRediT authorship contribution statement

Qiwen Fang: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Vivien Kin Yi Chan:** Writing – review & editing, Writing – original draft. **Sandra Sau Man Chan:** Writing – review & editing, Conceptualization. **Yuanshi Jiao:** Data curation. **Jiaqi Wang:** Visualization, Validation. **Xue Li:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

Xue Li received research grants from the Hong Kong Health and Medical Research Fund (HMRF, HMRF Fellowship Scheme, HKSAR), Research Grants Council Early Career Scheme (RGC/ECS, HKSAR), Janssen, and Pfizer; internal funding from the University of Hong Kong; and consultancy fees from Merck Sharp & Dohme and Pfizer; she is also a non-executive director of Advanced Data Analytics for Medical Science (ADAMS) Limited Hong Kong; all are unrelated to this work.

Funding

This research was supported by the UGC Research Impact Fund (Reference number: R7007–22).

Acknowledgement

We thank Ms. Yin Zhang for her help with format revision. We also thank Ms. Lisa Lam for her English proofreading.

For those who are interested, readers are encouraged to contact the author directly to request any additional data or information they may require.

References

Andersen, K.A.A., Carhart-Harris, R., Nutt, D.J., Erritzoe, D., 2021. Therapeutic effects of classic serotonergic psychedelics: A systematic review of modern-era clinical studies. Acta Psychiatr. Scand. 143 (2), 101–118. https://doi.org/10.1111/acps.13249.

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. (Berl) 235 (2), 399–408. https://doi.org/10.1007/s00213-017-4771-x.

Carhart-Harris, R.L., Bolstridge, M., Rucker, J., Day, C.M.J., 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. https://doi.org/10.1016/S2215-0366(16)30065-7.

European Medicines Agency, 2013. Guideline on clinical investigation of medicinal products in the treatment of depression. European Medicines Agency. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-depression-revision-2_en.pdf. (accessed 15 December 2023).

Gaynes, B.N., Lux, L., Gartlehner, G., Asher, G., Forman-Hoffman, V., Green, J., Boland, E., Weber, R.P., Randolph, C., Bann, C., Coker-Schwimmer, E., Viswanathan, M., Lohr, K.N., 2020. Defining treatment-resistant depression. Depress. Anxiety. 37 (2), 134–145. https://doi.org/10.1002/da.22968.

Goldberg, S.B., Pace, B.T., Nicholas, C.R., Raison, C.L., Hutson, P.R., 2020. The experimental effects of psilocybin on symptoms of anxiety and depression: A meta-analysis. Psychiatry Res. 284, 112749 https://doi.org/10.1016/j.psychres.2020.112749.

Goodwin, G.M., Aaronson, S.T., Alvarez, O., Arden, P.C., Baker, A., Bennett, J.C., Bird, C., Blom, R.E., Brennan, C., Brusch, D., Burke, L., Campbell-Coker, K., Carhart-Harris, R., Cattell, J., Daniel, A., DeBattista, C., Dunlop, B.W., Eisen, K., Feifel, D., Malievskaia, E., 2022. Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression. N. Engl. J. Med. 387 (18), 1637–1648. https://doi.org/10.1056/NEJMoa2206443.

Goodwin, G.M., Aaronson, S.T., Alvarez, O., Atli, M., Bennett, J.C., Croal, M., DeBattista, C., Dunlop, B.W., Feifel, D., Hellerstein, D.J., Husain, M.I., Kelly, J.R., Lennard-Jones, M.R., Licht, R.W., Marwood, L., Mistry, S., Páleníček, T., Redjep, O., Repantis, D., Malievskaia, E., 2023. Single-dose psilocybin for a treatment-resistant episode of major depression: Impact on patient-reported depression severity, anxiety, function, and quality of life. J. Affect. Disord. 327, 120–127. https://doi.org/10.1016/j.jad.2023.01.108.

Griffiths, R.R., Richards, W.A., McCann, U., Jesse, R., 2006. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. Psychopharmacology. (Berl) 187 (3), 268–283. https://doi.org/10.1007/s00213-006-0457-5 discussion 284-292.

López-Giménez, J.F., González-Maeso, J., 2018. Hallucinogens and Serotonin 5-HT(2A) Receptor-Mediated Signaling Pathways. Curr. Top. Behav. Neurosci. 36, 45–73. https://doi.org/10.1007/7854_2017_478.

Lyons, T., Carhart-Harris, R.L., 2018. More Realistic Forecasting of Future Life Events After Psilocybin for Treatment-Resistant Depression [Original Research]. Front. Psychol. 9 https://doi.org/10.3389/fpsyg.2018.01721.

Perez, N., Langlest, F., Mallet, L., De Pieri, M., Sentissi, O., Thorens, G., Seragnoli, F., Zullino, D., Kirschner, M., Kaiser, S., Solmi, M., Sabé, M., 2023. Psilocybin-assisted therapy for depression: A systematic review and dose-response meta-analysis of human studies. European Neuropsychopharmacology 76, 61–76. https://doi.org/10.1016/j.euroneuro.2023.07.011.

World Health Organization, 2023. Depressive disorder (depression). World Health Organization. https://www.who.int/news-room/fact-sheets/detail/depression. (accessed 15 December 2023).

Qiwen Fang[a], Vivien Kin Yi Chan[a], Sandra Sau Man Chan[b], Yuanshi Jiao[c], Jiaqi Wang[a], Xue Li[a,c,d,*]

[a] *Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China*

[b] *Department of Psychiatry, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China*

[c] *Department of Medicine, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China*

[d] *Laboratory of Data Discovery for Health ($D^2$4H), Hong Kong SAR, China*

[*] Corresponding author at: Department of Medicine and Department of Pharmacology & Pharmacy, LKS Faculty of Medicine, The University of Hong Kong, PB306, 3/F, Professional Block, Queen Mary Hospital, 102 Pok Fu Lam Road, Hong Kong SAR, China.

E-mail addresses: u3594701@connect.hku.hk (Q. Fang), vchanky@connect.hku.hk (V.K.Y. Chan), schan@cuhk.edu.hk (S.S.M. Chan), jiao19971107@connect.hku.hk (Y. Jiao), jakiwang@hku.hk (J. Wang), sxueli@hku.hk (X. Li).