



Short communication

Assessing the risk of symptom worsening in psilocybin-assisted therapy for depression: A systematic review and individual participant data meta-analysis

Otto Simonsson^{a,b,*}, Per Carlbring^c, Robin Carhart-Harris^{d,e}, Alan K. Davis^{f,g,h}, David J. Nutt^e, Roland R. Griffiths^{h,i,j}, David Erritzoe^e, Simon B. Goldberg^k

^a Department of Neurobiology, Care Sciences and Society, Karolinska Institute, Norra Stationsgatan 69, Stockholm 113 64, Sweden

^b Department of Sociology, University of Oxford, Oxford, United Kingdom

^c Department of Psychology, Stockholm University, Stockholm, Sweden

^d Neuroscape Psychedelics Division, Department of Neurology, University of California San Francisco, San Francisco, CA, United States

^e Centre for Psychedelic Research, Imperial College London, London, United Kingdom

^f Center for Psychedelic Drug Research and Education, College of Social Work, The Ohio State University, Columbus, OH, United States

^g Department of Psychiatry, The Ohio State University, Columbus, OH, United States

^h Center for Psychedelic and Consciousness Research, Department of Psychiatry and Behavioral Sciences, Johns Hopkins School of Medicine, Baltimore, MD, United States

ⁱ Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD 21205, United States

^j Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD 21205, United States

^k Department of Counseling Psychology, University of Wisconsin, Madison, WI, United States

ARTICLE INFO

Keywords:

Psilocybin

Depression

Meta-analysis

ABSTRACT

We conducted a meta-analysis using individual participant data from three, two-dose psilocybin trials for depression ($N = 102$) with the aim of assessing the risk of symptom worsening. Clinically significant symptom worsening occurred for a minority of participants in the psilocybin and escitalopram conditions (~10%) and for a majority of participants in the waitlist condition (63.6%). Using data from the two trials with control arms, the psilocybin arm showed a lower likelihood of symptom worsening versus waitlist, and no difference in the likelihood of symptom worsening versus escitalopram. The limitation of a relatively small sample size should be addressed in future studies.

1. Introduction

The leading factor contributing to disability worldwide is depression, a mood disorder that is estimated to affect more than 350 million people (Cuijpers et al., 2020a). Standard treatments for depression are effective for some patients, but many do not respond to treatment at all, and some experience worsening of depressive symptoms (Kolovos et al., 2017). Such treatments can also take weeks or even months to produce clinically relevant reductions in depressive symptoms, highlighting the need for novel treatments for depressive disorders (Cuijpers et al., 2020b).

One intervention that shows promise is psilocybin-assisted therapy (Nutt and Carhart-Harris, 2021). The administration of psilocybin in conjunction with therapy has been shown to reduce depressive symptoms in several clinical trials (Leger and Unterwald, 2022), but no study to date has evaluated clinically relevant worsening of depressive

symptoms in psilocybin clinical trials for depression. There is also limited information on whether baseline demographic characteristics are associated with symptom worsening or treatment response to psilocybin-assisted therapy (Aday et al., 2021).

In this study, we identified all published psilocybin clinical trials on depression. We requested the primary depression outcome data from study authors and conducted an individual participant data meta-analysis 1) assessing prevalence of clinically relevant worsening of depressive symptoms and 2) examining baseline demographic characteristics associated with symptom worsening or treatment response. We hypothesized that rates of clinically relevant worsening of depressive symptoms would be lower in psilocybin conditions than rates in control conditions for studies that included control groups, but we had no *a priori* hypotheses about baseline demographic characteristics associated with symptom worsening or treatment response.

* Corresponding author.

E-mail address: otto.simonsson@ki.se (O. Simonsson).

<https://doi.org/10.1016/j.psychres.2023.115349>

Received 13 April 2023; Received in revised form 9 July 2023; Accepted 16 July 2023

Available online 23 July 2023

0165-1781/© 2023 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY-NC license (<http://creativecommons.org/licenses/by-nc/4.0/>).

2. Methods

This independent participant data meta-analysis is reported following the PRISMA guidelines (Stewart et al., 2015). The study protocols were registered at the Open Science Framework: <https://osf.io/ctfzs> and <https://osf.io/jwbkf>. Deviations from our preregistration are reported in Supplemental Materials. The study was determined to be exempt from review by the Internal Review Board (IRB) at UW-Madison.

2.1. Search strategy and study selection

We searched PubMed, PsycINFO, Embase and the Cochrane Library with the following search term: *psilo**. The search was conducted on 28th March 2022. The databases were searched since their inception. No restrictions were placed on language or publication status. Studies that had this term appear in the abstract, title, and/or keywords were reviewed. Bibliographies of recent meta-analyses examining psilocybin and psychedelic trials were also searched for potentially relevant studies (Li et al., 2022; Kisely et al., 2022; Leger and Unterwald, 2022; Yu et al., 2022; Zeifman et al., 2022). Eligible studies had to have used psilocybin as the primary intervention and have reported outcome data on standardized measures of depression. Controlled and uncontrolled studies on both clinical and non-clinical populations were eligible (see Supplemental Materials for information about data extraction).

2.2. Statistical analyses

To characterize symptom change, we calculated standardized mean difference (SMD) scores for the depression measures (GRID-Hamilton Depression Rating Scale; Williams et al., 2008; Quick Inventory of Depression Symptoms Self-Report – 16; Rush et al., 2003), in keeping with meta-analytic methods (Borenstein et al., 2009). Specifically, we calculated pre-post change scores (post minus pre) and divided this value by the baseline standard deviation of each measure. To define symptom worsening, we used a value of $SMD \geq 0.24$ (Cuijpers et al., 2014). We then conducted a series of one-step meta-analyses with a random effects component (i.e., random intercept multilevel models; Burke et al., 2017) examining predictors of symptom worsening and treatment response. In keeping with Burke et al. (2017), we modeled the nesting of effects within study ID. We examined five demographic variables which were available across all three studies as predictors.

Models examining response to psilocybin included the psilocybin arm from all three trials. Models examining treatment response as a continuous variable (SMD) used multilevel linear regression while models examining treatment response as a dichotomous variable (i.e., symptom worsening) used multilevel logistic regression. Analyses were conducted in R (R Core Team, 2022; see Supplemental Materials for R code).

3. Results

Three studies were included in the independent participant data meta-analysis (Carhart-Harris et al., 2016, 2021; Davis et al., 2021; see Fig. 1),¹ which were all of the eligible studies with two dosing sessions focused on populations with depressive disorders (see Supplemental Materials and Supplemental Tables 1–3 for details of studies included). Collectively, these studies included 102 participants who completed the measures at both baseline and at six-week follow-up, of whom 62 received psilocybin-assisted therapy, 29 received escitalopram, and 11 received waitlist. Five baseline demographic characteristics across the three studies were included: age, gender (coded as male versus female), race/ethnicity (coded as White versus non-White), education (coded as

¹ The full sample from Carhart-Harris and colleagues (2016) is reported in Carhart-Harris and colleagues (2018).

undergraduate degree or higher versus other), and employment status (coded as unemployed versus other).

Participants in the psilocybin and escitalopram conditions showed large reductions in depressive symptoms at post-test in both conditions (SMDs = -2.38 and -1.56 , SD = 1.69 and 1.36, respectively) while participants in the waitlist control showed a worsening of symptoms on average (SMD = 0.26, SD = 1.06). A minority of participants in the psilocybin and escitalopram conditions showed clinically significant symptom worsening (9.7% and 10.3%, respectively), while the majority of participants in the waitlist control condition showed clinically significant symptom worsening (63.6%; see Supplemental Table 4). When restricted to the two studies that included a control condition, assignment to the psilocybin arm was associated with a lower likelihood of symptom worsening relative to waitlist (OR = 13.30, 95% CI [3.02, 70.74], $p = .001$) and no difference in the likelihood of symptom worsening relative to escitalopram (OR = 0.88, 95% CI [0.17, 3.89], $p = .865$).²

None of the five demographic variables examined were associated with response to the psilocybin arm (Supplemental Table 5). One empty cell was detected when examining demographic variables in association with symptom worsening. Specifically, no non-White participants reported worsening symptoms following psilocybin. To examine these this demographic predictor, we implemented Firth's (1993) bias-reduced penalized likelihood logistic regression implemented in the 'logistf' package in R (Heinze et al., 2022). None of the five demographics variables examined were associated with likelihood of symptom worsening in response to psilocybin (Supplemental Table 6).³

4. Discussion

This study was an individual participant data meta-analysis assessing the prevalence of clinically relevant worsening of depressive symptoms and examining baseline demographic characteristics associated with symptom worsening or treatment response. Results showed clinically significant symptom worsening in a minority (~10%) of participants in the psilocybin and escitalopram conditions. This is in line with rates for psychotherapy, where ~7% of the patients show symptom worsening (Mechler and Holmqvist, 2016). By contrast, a majority (63.6%) of the waitlist condition showed symptom worsening. That is a surprisingly high proportion when compared with a meta-analysis of waitlist controls in psychotherapy that found only 17.4% of patients showed symptom worsening (Rozental et al., 2017). However, had the psychotherapy meta-analysis used the same conservative cut-off of 0.24 instead of 0.84 SMD units, the proportion may have been comparable. This relatively high rate of worsening in the waitlist condition may reflect a kind of "nocebo" effect, where participants not receiving a desired treatment are actively disappointed, resulting in symptom worsening. Worsening associated with waitlist conditions specifically has been observed in psychotherapy trials previously (Furukawa et al., 2014).

In the two clinical trials with control conditions, assignment to the psilocybin arm was associated with a lower likelihood of symptom worsening relative to waitlist and no difference in the likelihood of symptom worsening relative to escitalopram. Thus, it appears that receipt of psilocybin confers risk of symptom worsening similar to an FDA-approved antidepressant medication and is substantially protective against risk of symptom worsening relative to treatment with delayed

² Significance tests did not change when including the five demographic variables as covariates (OR = 35.83, 95% CI [5.33, 407.26], $p < .001$ for psilocybin vs. waitlist; OR = 1.20, 95% CI [0.19, 7.16], $p = .833$ for psilocybin vs. escitalopram).

³ Whether the study focused on participants with treatment-resistant depression was not associated with frequency of symptom worsening (5.3% for treatment-resistant depression vs. 18.1% for other studies, OR = 0.42, 95% CI [0.02, 3.30], $p = .446$).

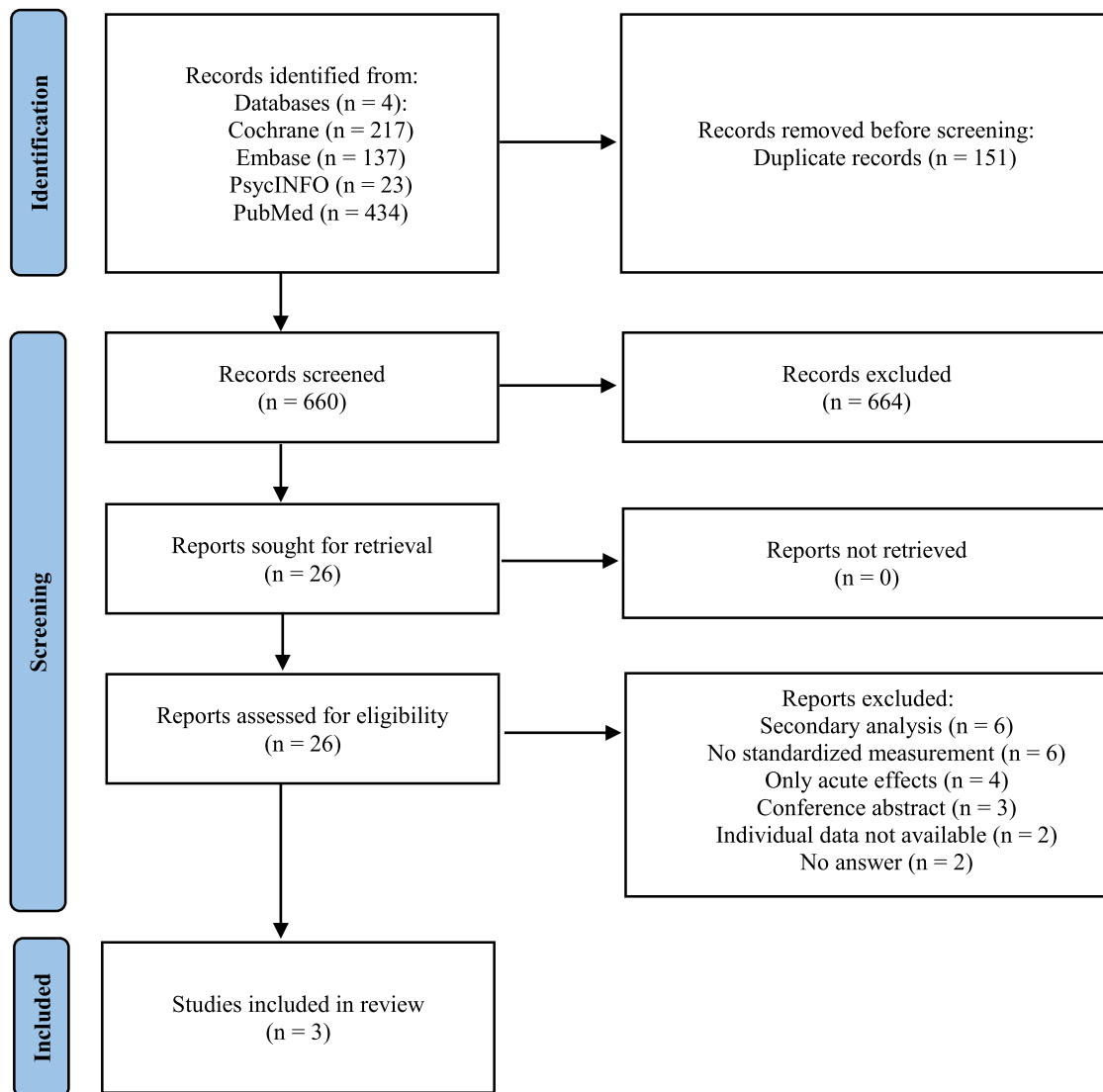


Fig. 1. Flow Diagram.

start (i.e., waitlist; Cuijpers and Cristea, 2016). None of the five baseline demographic characteristics examined were associated with response to psilocybin or likelihood of symptom worsening in response to psilocybin.

There are several limitations to consider when interpreting the results of this study. First, the combined sample size of the included studies was relatively small, which limited statistical power to detect potentially smaller magnitude associations. The sample size of the waitlist control condition ($n = 11$) was especially small and may therefore have impacted the reliability of comparisons. Second, there are many ways to operationalize worsening of clinical status (e.g., increase in suicidality), but this study focused solely on worsening of depressive symptoms. Third, the included studies were heterogeneous in terms of research design. Fourth, participant-level predictors were limited to five baseline demographic characteristics. It would be useful in future studies to examine additional potential predictors of treatment response (e.g., psychological, genetic). Fifth, the diversity (e.g., race and ethnicity) in the samples was limited and should be addressed in future studies to increase the generalizability of findings (Michaels et al., 2018). Sixth, only six-week follow-up was examined in this study. It was therefore not possible for this analysis to provide guidance on the time course of symptom worsening or any sustained effects beyond these assessments.

Although the findings in this study should be considered preliminary,

these results suggest that clinically relevant symptom worsening in depressed patients is not more common with psilocybin-assisted therapy than with standard pharmacological treatment (i.e., escitalopram). If such findings are replicated in future studies, it would further strengthen the overall safety profile of psilocybin, which appears favorable based on the evidence to date (Roscoe and Lozy, 2022).

Author contributions

OS, PC, and SBG conceptualized and preregistered the study. OS and PC conducted the screening. SBG supervised the study and conducted the analyses. RCH, AKD, DJN, RRG, DE provided data and made critical revisions.

Funding

OS was supported by Ekhaga Foundation and Olle Engkvist Foundation. SBG was supported by the National Center for Complementary & Integrative Health of the National Institutes of Health under Award Number K23AT010879. AKD is supported by the Center for Psychedelic Drug Research and Education. RRG and AKD are supported by the Johns Hopkins Center for Psychedelic and Consciousness Research with funding from Tim Ferriss, Matt Mullenweg, Craig Nerenberg, Blake

Mycoskie, the Steven and Alexandra Cohen Foundation.

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: OS was a co-founder of Eudelics AB. RCH is a scientific advisor to Synthesis Institute, Osmind, Journey Colab, Maya Health, Mydecine, Beckley Psytech and Mindstate. AKD is a board member of Source Research Foundation and Lead Training at Fluence. DJN is a scientific advisor to COMPASS Pathways who have an interest in psilocybin therapy for depression. He is also chair of PAREA (Psychedelic access and research European alliance) and a member of the UK Drug Science charity's Medical Psychedelic Working Group. DE is a scientific advisor to Clerkenwell Health, Aya Biosciences, Field Trip Health, Mindstate, Pangea Botanica, and Smallpharma LTD. RRG is on the Board of Directors of the Heffter Research Institute. All other authors declare that there is no conflict of interest.

Acknowledgments

The authors would like to thank Joseph M Peill for his help in transferring the independent participant data from the trials at Imperial College London. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.psychres.2023.115349](https://doi.org/10.1016/j.psychres.2023.115349).

References

- Aday, J.S., Davis, A.K., Mitzkovitz, C.M., Bloesch, E.K., Davoli, C.C., 2021. Predicting reactions to psychedelic drugs: a systematic review of states and traits related to acute drug effects. *ACS Pharmacol. Transl. Sci.* 4 (2), 424–435.
- Borenstein, M., Cooper, H., Hedges, L., Valentine, J., 2009. Effect sizes for continuous data. *Handb. Res. Synth. Meta-Anal.* 2, 221–235.
- Burke, D.L., Ensor, J., Riley, R.D., 2017. Meta-analysis using individual participant data: one-stage and two-stage approaches, and why they may differ. *Stat. Med.* 36 (5), 855–875.
- Carhart-Harris, R.L., Bolstridge, M., Rucker, J., Day, C.M., Erritzoe, D., Kaelen, M., Nutt, D.J., 2016. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. *Lancet Psychiatry* 3 (7), 619–627.
- Carhart-Harris, R.L., Bolstridge, M., Day, C.M., Rucker, J., Watts, R., Erritzoe, D.E., Nutt, D.J., 2018. Psilocybin with psychological support for treatment-resistant depression: six-month follow-up. *Psychopharmacology (Berl.)* 235, 399–408.
- Carhart-Harris, R., Giribaldi, B., Watts, R., Baker-Jones, M., Murphy-Beiner, A., Murphy, R., Nutt, D.J., 2021. Trial of psilocybin versus escitalopram for depression. *N. Engl. J. Med.* 384 (15), 1402–1411.
- Core Team, R., 2022. R: A language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. URL: <https://www.R-project.org/>.
- Cuijpers, P., Cristea, I.A., 2016. How to prove that your therapy is effective, even when it is not: a guideline. *Epidemiol. Psychiatr. Sci.* 25 (5), 428–435.
- Cuijpers, P., Noma, H., Karyotaki, E., Vinkers, C.H., Cipriani, A., Furukawa, T.A., 2020b. A network meta-analysis of the effects of psychotherapies, pharmacotherapies and their combination in the treatment of adult depression. *World Psychiatry* 19 (1), 92–107.
- Cuijpers, P., Stringaris, A., Wolpert, M., 2020a. Treatment outcomes for depression: challenges and opportunities. *Lancet Psychiatry* 7 (11), 925–927.
- Cuijpers, P., Turner, E.H., Koole, S.L., Van Dijke, A., Smit, F., 2014. What is the threshold for a clinically relevant effect? The case of major depressive disorders. *Depress. Anxiety* 31 (5), 374–378.
- Davis, A.K., Barrett, F.S., May, D.G., Cosimano, M.P., Sepeda, N.D., Johnson, M.W., Griffiths, R.R., 2021. Effects of psilocybin-assisted therapy on major depressive disorder: a randomized clinical trial. *JAMA Psychiatry* 78 (5), 481–489.
- Firth, D., 1993. Bias reduction of maximum likelihood estimates. *Biometrika* 80, 27–38.
- Furukawa, T.A., Noma, H., Caldwell, D.M., Honyashiki, M., Shinohara, K., Imai, H., Churchill, R., 2014. Waiting list may be a nocebo condition in psychotherapy trials: a contribution from network meta-analysis. *Acta Psychiatr. Scand.* 130 (3), 181–192.
- Heinze, G., Ploner, M., Jiricka, L. (2022). *logistf: firth's bias-reduced logistic regression. R package Version 1.24.1*. <<https://CRAN.R-project.org/package=logistf>>.
- Kisely, S., Connor, M., Somogyi, A.A., Siskind, D., 2022. A systematic literature review and meta-analysis of the effect of psilocybin and methylenedioxymethamphetamine on mental, behavioural or developmental disorders. *Austr. N. Z. J. Psychiatry*, 00048674221083868.
- Kolovos, S., van Tulder, M.W., Cuijpers, P., Prigent, A., Chevreur, K., Riper, H., Bosmans, J.E., 2017. The effect of treatment as usual on major depressive disorder: a meta-analysis. *J. Affect. Disord.* 210, 72–81.
- Leger, R.F., Unterwald, E.M., 2022. Assessing the effects of methodological differences on outcomes in the use of psychedelics in the treatment of anxiety and depressive disorders: a systematic review and meta-analysis. *J. Psychopharmacol.* 36 (1), 20–30.
- Li, N.X., Hu, Y.R., Chen, W.N., Zhang, B., 2022. Dose effect of psilocybin on primary and secondary depression: a preliminary systematic review and meta-analysis. *J. Affect. Disord.* 296, 26–34.
- Mechler, J., Holmqvist, R., 2016. Deteriorated and unchanged patients in psychological treatment in Swedish primary care and psychiatry. *Nord. J. Psychiatry* 70 (1), 16–23.
- Michaels, T.I., Purdon, J., Collins, A., Williams, M.T., 2018. Inclusion of people of color in psychedelic-assisted psychotherapy: a review of the literature. *BMC Psychiatry* 18 (1), 1–14.
- Nutt, D., Carhart-Harris, R., 2021. The current status of psychedelics in psychiatry. *JAMA Psychiatry* 78 (2), 121–122.
- Roscoe, J., Lozy, O., 2022. Can psilocybin be safely administered under medical supervision? A systematic review of adverse event reporting in clinical trials. *Drug Sci., Policy aLaw*, 8, 20503245221085222.
- Rush, A.J., Trivedi, M.H., Ibrahim, H.M., Carmody, T.J., Arnow, B., Klein, D.N., Keller, M.B., 2003. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol. Psychiatry*, 54 (5), 573–583.
- Rozental, A., Magnusson, K., Boettcher, J., Andersson, G., Carlbring, P., 2017. For better or worse: an individual patient data meta-analysis of deterioration among participants receiving Internet-based cognitive behavior therapy. *J. Consult. Clin. Psychol.* 85 (2), 160.
- Stewart, L.A., Clarke, M., Rovers, M., Riley, R.D., Simmonds, M., Stewart, G., Tierney, J. F., 2015. Preferred reporting items for a systematic review and meta-analysis of individual participant data: the PRISMA-IPD statement. *JAMA* 313 (16), 1657–1665.
- Yu, C.L., Liang, C.S., Yang, F.C., Tu, Y.K., Hsu, C.W., Carvalho, A.F., Su, K.P., 2022. Trajectory of antidepressant effects after single- or two-dose administration of psilocybin: a systematic review and multivariate meta-analysis. *J. Clin. Med.* 11 (4), 938.
- Williams, J.B., Kobak, K.A., Bech, P., Engelhardt, N., Evans, K., Lipsitz, J., Kalali, A., 2008. The GRID-HAMD: standardization of the Hamilton depression rating scale. *Int. Clin. Psychopharmacol.* 23 (3), 120–129.
- Zeifman, R.J., Yu, D., Singhal, N., Wang, G., Nayak, S.M., Weissman, C.R., 2022. Decreases in suicidality following psychedelic therapy: a meta-analysis of individual patient data across clinical trials. *J. Clin. Psychiatry* 83 (2), 39235.