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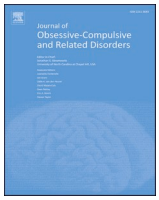

Psychedelics, OCD and Related Disorders: Setting methodological strategies for future studies

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ABSTRACT

Background: There is interest in the potential of psychedelics as treatments for Obsessive-Compulsive and Related Disorders (OCRDs), though research in this field is still at an early stage. In this review, we examine the methodological issues present in existing research investigating the use of psychedelics in OCRDs, as a basis for improved trial design.

Methods: We searched PubMed and PsycInfo for published studies and Clinicaltrial.gov for unpublished studies investigating the use of psychedelic in individuals with OCRDs. We reviewed the identified studies and described the main methodological issues undermining study outcomes. We analyzed the published selected papers using standard tools (Cochrane Risk of Bias for Non-Randomized Studies, ROBINS-I).

Results: We found just two published and seven unpublished studies. Risk of bias analysis revealed a critical risk of bias, primarily related to experimental design (e.g., absence of adequate control condition), expectation bias among study participants and problems ensuring adequate blinding. The analysis of unpublished studies, although limited, identified parallel concerns, while also highlighting the implementation of promising strategies for advancing the field.

Discussion: There is a shortage of unbiased evidence. Although the shortcomings in the design of the few existing studies raise important concerns, early potential efficacy justify further, well-designed research. Potential strategies, some of which already implemented in ongoing studies, to address current issues and improve the validity of future studies include the use of blinded raters and of a credible control (such as virtual reality), the choice of a lower drug dose and the inclusion of only drug-naive subjects.

1. Background

Increasing enthusiasm for the repurposing of drugs with other established indications for the clinical treatment of OCD and related disorders, including drugs with potential for abuse such as ketamine, psilocybin and cannabis, is raising important challenges for the psychopharmacology community. A systematic review published by Graziosi and colleagues (Graziosi) analyzed the contemporary use of psychedelics, mostly involving psilocybin, in obsessive-compulsive disorder (OCD) and related disorders (OCRDs). The authors reported that psilocybin was well-tolerated, and that some individuals experienced a reduction in symptoms over time. They drew the conclusion in relation to the use of psychedelics in OCD that "further investigation is warranted".

However, the conclusions drawn by Graziosi et al. was based on the outcomes of just two small sized clinical trials (one open label trial of psilocybin in patients with OCD (Moreno et al., 2006) and one open label trial of psilocybin in patients with Body Dysmorphic Disorder

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(BDD) (Schneier)). Both lacked a placebo control and employed samples that were too small to derive reliable results from (respectively n = 9 and n = 12). The authors also considered eight case reports, two non-systematic reviews and eleven preclinical studies. Arguably, therefore, the amount of outcome data in OCD currently available for analysis is insufficient to allow meaningful conclusions to be drawn about efficacy.

The authors also drew attention to a growing number of new, as yet incomplete and unpublished, studies of psilocybin in OCD available on clinical trials registries (e.g. clinicaltrials.gov). However, the methodological issues raised by these studies were not fully discussed (Graziosi). These include potential for critical biases in study design that could undermine interpretation of the results. To date, similar concerns have been raised but almost exclusively in relation to the use of psychedelics in anxiety, depression and alcohol use disorder (Hovmand; Soliman et al., 2024; De Giorgi & Ede, 2024). OCRDs are distinct, usually chronic disorders, which respond to pharmacological treatment differently from depression and anxiety. In the case of OCD, there is usually a slow and incremental treatment response and a tendency to relatively swift relapse once treatment has stopped, of specific relevance for psychedelic trial design.

Against this background, we, as a group of clinicians with clinical experience of investigating and treating OCRDs, decided to perform this narrative brief review. Our aim was to extend the work of Graziosi et al. by reviewing the existing methodologies used to investigate the clinical effects of psychedelics in individuals with OCRDs, as a basis for improved trial design for this specific group of disorders.

2. Methods

We searched PubMed and PsycInfo for published studies using the search terms: ("OCD" OR "Obsessive Compulsive Disorder" OR "BDD" OR "Body Dysmorphic Disorder" OR "Hoarding Disorder" OR "Skin Picking Disorder" OR "Trichotillomania" OR "Excoriation") AND ("Psychedelic*" OR "Psilocybin" OR "DMT" OR "Dimethyltryptamine" OR "Lysergic Acid Diethylamide" OR "LSD" OR "Mescaline"). For unpublished studies, we searched ClinicalTrials.gov using similar search terms as listed above, adapted for the contingencies of the website.

Included studies had to meet the following criteria: 1) An appropriate case definition of OCRDs (diagnosis made through structured clinical interviews and/or standardized international criteria); 2) The use of classic psychedelics (drugs targeting the 5-HT2A receptor, e.g., Psilocybin, DMT, LSD, Mescaline) to treat OCRDs. We included clinical trials (both randomized and non-randomized, controlled and uncontrolled, open-label and blinded), and excluded single case reports, uncontrolled case series, non-systematic reviews, editorials, book chapters, preclinical trials involving non-human animals, and studies not written in English.

Two groups of researchers, one based in Trieste, Italy, and one based in Welwyn Garden City, UK, independently reviewed all the included studies and narratively described the main methodological issues undermining study outcomes. Alongside the narrative review, we additionally applied a standardized instrument (Cochrane Risk of Bias for Non-Randomized Studies (ROBINS-I)) to evaluate sources of bias in the two published trials. We could not adequately apply the Cochrane tool to the unpublished reports or prepublished protocol papers, as there were domains that could not be completed (e.g., "Risk of Bias in the Selection of the Reported Results" and "Bias due to Missing Data").

Disagreements about the main methodological concerns or the score of the Cochrane instruments were discussed and resolved during three dedicated online meetings between the two research groups.

3. Results

We found two published and fully reported studies and seven ongoing yet unreported studies (Table 1). A single pre-published study protocol was found both in our search of ClinicalTrials.gov (NCT03356483) and as a published paper (Ching).

Published studies: one reported study (Moreno et al., 2006) investigated the effect in OCD of four different doses of psilocybin (equivalent in a 70 kg person to 1,75 mg, 7 mg, 14 mg, 21 mg), one dose per test session, in a modified dose escalation protocol, and the other (Schneier) investigated the effect of a single 25 mg dose of psilocybin in BDD. Both studies lacked a control treatment for the active drug and did not use blinded raters as a potential resource to mitigate expectation bias.

The ROBINS-I assessment indicated a critical risk of bias in favour of the experimental treatment for both completed studies. Both studies showed multiple confounding factors and received a critical risk of bias rating in the domains "Bias due to confounding", representing in the main ascertainment bias in favour of participants with a past history of psychedelics use and "Bias in measurement of outcomes.", representing inadequacy of blinding procedure. The full ROBINS-I analysis for both studies is available in the Supplementary Material.

Unpublished studies: of the seven unpublished studies, four are randomized controlled clinical trials (Ching; NCT03300947; NCT05370911; NCT05546658) each with different degrees and methods of blinding; two (NCT04882839; NCT06299319) are unblinded, uncontrolled (open-label) studies and one (NCT06258031) follows a within-subject design, in which participants knew they are taking a single dose of psilocybin twice but are blinded to the dosage (1 and 10 mg). An active control and blinding of participants and on-site investigators, although the proposed strategies are unlikely to be effective as blinding strategies, are implemented in three studies: Lorazepam 1 mg in NCT03300947, Niacin 250 mg in Ching et al., 2023, Psilocybin 1 mg in NCT06258031. Two studies use a waiting list as a comparator (NCT05546658). Blinded raters are employed in four studies (Ching; NCT03300947; NCT05370911; NCT06258031), though in two of these studies, the duration of blinding is limited to only a few days or weeks (Ching; NCT06258031).

The detailed characteristics of all studies are summarized in Table 1.

4. Discussion

Based on a rigorous literature search, the amount of outcome data for the use of psychedelics in OCD currently available for analysis is limited.

Working in this clinical field, our impression has been that enthusiasm and high expectations among the public for a beneficial effect have led to unprecedented demand to participate in trials of psychedelics, and the pressures on researchers to include inappropriate participants can be high.

Of note, both the completed clinical trials (Moreno et al., 2006; Schneier et al., 2023) were uncontrolled and both were found to have been subject to "bias due to confounding" because they selected participants with a history of exposure to psychedelics, who may be expected to have had a positive experience of psychedelics. This bias may be interpreted as a positive 'expectation' bias, defined as a cognitive bias where individuals tend to expect positive outcomes or results, often disregarding potential negative outcomes (C Curkovic and Kosec, 2019). Furthermore, the study by Moreno et al. not only positively selected participants who had taken psychedelics before, but also required them to have tolerated them as an inclusion criterion, potentially strengthening this form of bias. Considering that the use of illegal drugs is atypical among treatment-seeking patients with OCD (Fineberg), though the use of alcohol is not unusual, inclusion of those with a prior history of psychedelic use introduces additional uncertainty about the typicality of the participants and thus generalizability of the findings to the majority of patients with OCD. Expectation bias is recognized to correlate with the placebo-effect (C Curkovic and Kosec, 2019) and is therefore an important confound of particularly relevance in uncontrolled trials. Furthermore, it is acknowledged that expectancy might play a role in driving the therapeutic effect of psychedelics (Szigeti & Heifets, 2024). As improvement driven by the placebo effect in OCD is traditionally

Table 1
Psychedelics in OCRDs - Descriptive characteristics of published studies and ongoing unpublished trials included in the review

Published trials: First author and Publication	Trial register number	Diagnosis	Study Design and Drug Dosage	Placebo/ Control	Duration of outcome assessment	Blinding of participants and investigators	Blinding of raters
Moreno 2006	–	OCD	Multiple dose cross-over trial. Subjects received up to 4 different doses, 1 dose per test session, in a modified dose escalation protocol. Doses were 25 (very low dose [VLD]), 100 (low dose [LD]), 200 (medium dose [MD]), and 300 (high dose [HD]) μg/kg of body weight. LD, MD, and HD were assigned in that order, and VLD was inserted randomly at any time after the first dose (LD). Testing days were separated by at least 1 week.	No	Outcomes following each dose were measured only up to 24 h	No Patients knew they were on escalating doses of psilocybin but did not know when the VLD was administered	No No mention of the raters blinding in the report, however the timing of the VLD was described by the authors as being double blind
Schneier 2023	–	BDD	Single arm, 25 mg of psilocybin, fixed single dose	No	Outcomes following each dose were measured for a maximum of 12 weeks after drug administration	No	No

Unpublished trials: Institution	Trial register number	Diagnosis	Study Design	Placebo/ control	Duration of outcome assessment	Blinding of participants and investigators	Blinding of raters
University of Arizona	NCT03300947	OCD	Multiple dose cross-over trial. Phase 1 involves participants randomized to either 4 weekly sessions of low dose (100 μg/kg) psilocybin, High dose (300 μg/kg) psilocybin, or Lorazepam (1 mg). Phase 2 involves cross-over to another 4 weeks of the above treatment. All subjects are exposed to psilocybin at some point during the study	Yes (Lorazepam 1 mg)	Follow up assessment up to six months after the last dose	Phase 1 described as double blind, but Lorazepam is very unlikely to be effective at masking. Phase 2 is single blind (participants) with the same caveat	Yes (at least up to the one week assessment after the last dose. Not specified if raters are blinded up to the six months follow up)
Yale University	NCT03356483 Ching et al. (2023)	OCD	Randomized controlled parallel arm study with open label follow up. Participants will be randomized to receive single fixed dose of psilocybin (0.25 mg/kg) or Niacin 250 mg. Participants who were randomized to Niacin will be offered open-label psilocybin	Yes (Niacin 250 mg)	Follow up assessment up to one week after dosing (blind) and 12 weeks (unblind)	Yes, but only until 48 h after drug administration. Niacin is very unlikely to be effective at masking	Yes, but up to the first-week endpoint only
Yale University	NCT05370911	OCD	Randomized control trial. Participants will be randomized to either two weekly doses of psilocybin at variable doses from 25 to 30 mg or waitlist. After 7 weeks those allocated to waiting list are offered the same psilocybin regimen under open label conditions	Yes (waiting list) up to week 7	Follow up assessment up to four days post second dose for the main outcome measure (Y-BOCS)	No	Yes, until week 7 only (i.e., 4 weeks post-second dosing
John Hopkins University	NCT05546658	OCD	Randomized Cross-Over. Participants randomized to either two sessions of psilocybin (20–30 mg) separated by two weeks or waitlist control. Those randomized to waiting list offered open label psilocybin at same doses.	Yes (waiting list)	Follow up assessment up to one week post second dose for the main outcome measure (Y-BOCS)	No	No
Beersheva Mental Health Center	NCT04882839	OCD	Single arm. Participants offered three weekly doses of open label psilocybin (10mg/70 kg, then 30mg/70 kg twice) within a 15 weeks psychotherapy protocols.	No	Follow up assessment up to six months after study termination	No (open label)	No
Centre for Addiction and	NCT06299319	OCD	Single arm. Participants will receive two 25 mg dose of	No	Follow up assessment up to	No (open label)	No

(continued on next page)

Table 1 (*continued*)

Unpublished trials: Institution	Trial register number	Diagnosis	Study Design	Placebo/ control	Duration of outcome assessment	Blinding of participants and investigators	Blinding of raters
Mental Health, Canada			psilocybin separated by two weeks.		one week post second dose		
Imperial College, London	NCT06258031	OCD	Single arm, within subject design. Participants will take 1 mg, then 10 mg of psilocybin in a fixed order separated by 4 weeks	Yes (Psilocybin 1 mg)	Follow up assessment up to four weeks post second dose	Participants know they will take psilocybin but are blinded to the dosage	Yes

weaker than in other conditions such as anxiety and depressive disorders (Bschor; Fineberg et al., 2006), this may have implications for trial design and outcome interpretation: patients with OCRDs, compared to those with other disorders such as depression, may be less susceptible to the non-specific effects of the drug. As a result, the role of expectation may have a reduced influence in determining both the placebo effect and the effect of psilocybin, so that the treatment gains of the latter may be more fully attributable to the specific pharmacological effects of the drug. However, it is important to recognize that specific expectations related to psychedelics may still arise due to the unique nature of these treatments, even in individuals with OCRDs. Therefore, trials with robust methodological designs are necessary to account for these potential influences. In future trials on OCRDs, it will be crucial to measure expectation to better understand whether its impact on the efficacy of psychedelics is less pronounced than in other disorders.

Regarding the pre-published clinical trial methodologies, there is some encouraging evidence of attempts to reduce expectation bias. Thus, while two prospective trials (NCT06258031; NCT03300947) do not include previous use of psychedelics among the exclusion criteria, four (NCT05370911; Ching et al., 2023, NCT04882839; NCT06299319) exclude patients who have used psychedelics in the past year, and one (NCT05546658) applies the stricter criterion “have limited lifetime use of hallucinogens (the following criteria are preferred: no use in the past 5 years; total hallucinogen use less than 10 times)". Hovmand et al. (Hovmand) even suggest serial assessment as a tool to estimate the risk of expectation bias in trial participants and propose standardized instruments such as the Credibility/Expectancy Questionnaire (Younger et al., 2012) or other alternative instruments (see Szigeti & Heifets, 2024). So far, we were unable to see evidence of such scales being used based on our search on Clinicaltrial.gov, however, our analysis is limited by the fact that the study designs may change, and further modifications could occur after the peer review process.

Participants with prior experiences of psychedelics are also more likely to recognize their effects (or the effects of the placebo/active control when used), complicating the already controversial process of blinding. Maintaining blinded conditions for an adequate duration to fully assess outcomes is considered an important quality standard (Hovmand; Naudet et al., 2013). In the case of psychedelic trials, this is difficult if not impossible to achieve, owing to the strong psychoactive effects of psychedelic drugs, especially when used at moderate to high doses (Hovmand; Soliman et al., 2024; De Giorgi & Ede, 2024). Soliman et al., in their review of the use of psychedelics in psychiatric disorders (Soliman), argued for the development of more suitable methodologies for strengthening the blinding process. Such strategies include the use of blinded raters. Researchers should attempt to ensure the same raters do not assess the efficacy outcomes and the side effects, as the latter act as a potent source of unblinding. We positively note that each of the four pre-registered methodologies described as having some degree of blinding that are yet to be published states that blinded raters will be used (NCT05370911; Ching et al., 2023; NCT03300947; NCT06258031), but in two of these studies the duration of blinding of the outcome assessment is limited to a few days or weeks (NCT05370911; Ching et al., 2023) and in only one description (NCT06258031) of these studies it is clearly stated that the blinded outcome assessors would not evaluate adverse effects.

Another option is to choose a lower dose of the experimental agent. In the study by Moreno et al. (Moreno et al., 2006) a sub-hallucinogenic dose of 100 μg/kg of psilocybin (equivalent of 7 mg for a 70 kg person) was effective and well-tolerated, suggesting a low dose of psilocybin may be suitable for testing in OCD with reduced risk of unblinding.

The use of an active pharmacological placebo or of an active non-pharmacological comparator may also be considered to mimic the altered state of consciousness produced by psychedelics. Niacin and Lorazepam have been used in two of the unpublished randomized clinical trials (Ching; NCT03300947), but their psychoactive effects are not fully convincing, and they produce their own effects and side effects, confounding interpretation of the study. The other two unpublished randomized studies (NCT05370911; NCT05546658) use waiting list as a control, which may produce a nocebo effect (Patterson et al., 2016) and bias the treatment in favour of the experimental drug, especially if participants are offered the opportunity to receive the experimental treatment should they fail to respond to placebo.

Another approach, used by Moreno et al. and in one unpublished study (NCT06258031), could be the use of a very low psychedelic dose of around 1 mg psilocybin, which is expected to be ineffective, as a possible placebo. An advantage of this approach is that participants allocated to this very low dose can still be informed they are taking psilocybin. However, in the absence of a placebo comparison for this very low dose, we cannot be certain of its veracity as a true placebo.

Other, novel approaches include the use of virtual reality (Kaup) or holotropic breathing (Fincham) as control for the effects induced by psychedelics. These approaches, as far as we are aware, have not been applied in the context of a psychedelic treatment trial. Recent studies suggest that virtual reality could be a valuable tool for mimicking the psychedelic perceptual experience (Suzuki et al., 2017). Simulating phenomenological aspects of psychedelically induced states of mind such as visual distortion and the ability to evoke awe in users (Aday), virtual reality could be used as a control (e.g., all participants could use a wearable Virtual Reality (VR) device, with VR implemented only in the control group).

Another tool potentially capable of mimicking psychedelic phenomenology is holotropic breathwork, an intense breathing method in which participants are instructed to breathe rapidly and deeply for about three hours, accompanied by rhythmic music. First developed by psychiatrist Stanislav Grof (GrofGrof), it can induce an altered state of consciousness similar to that of psychedelics (Fincham). Alternatively, the use of a relapse prevention design, where treatment in responders is discontinued in a double-blind fashion and which relies on relative rates of symptomatic worsening, which has proved a useful methodology in other OCD research (Koran et al., 2004), and which may be less subject than the typical acute-phase trial to non-specific positive outcomes, could be another approach to consider.

In conclusion, methodologically rigorous randomized controlled trials are needed to test the efficacy of psychedelics in OCD and related disorders, and we agree with the cautions expressed by De Giorgi and Ede (De Giorgi & Ede, 2024), when they say that the existing findings (for depression) "support a prudent approach in both scholarly and public settings, because more and better evidence is needed before any clinical recommendation can be made about therapeutic use of psilocybin".

Nevertheless, despite the critical shortage of unbiased evidence and the issues with the design of the few published and unpublished studies, which raise some concerns, these trials still show early and promising potential efficacy and fully justify further, well-designed research to corroborate the findings. Moreover, some ongoing clinical trials are already applying important methodological innovations to counterbalance possible flaws (such as the use of blinded raters, the enrollment of drug-naive patients, and the option of using doses of the agent less likely to cause psychoactive effects that could compromise blinding) that are fully expected to strengthen confidence in the findings. This is of particular relevance for obsessive-compulsive and related disorders, as current evidence-based treatments show rates of non- or partial response rates of up to 50 % (Stein et al., 2019; Howes et al., 2022), and novel treatments are urgently needed. It is important to emphasize that the effectiveness and subsequent approval of these novel treatments must be supported by high-level methodological research, in order for them to be implemented in clinical practice and ultimately be beneficial for patients. Nevertheless, it is well recognized that a large part of research in psychiatry involves unblinded data, e.g., published trials of ECT, neurosurgery, deep brain stimulation in OCD do not always meet the highest standards of blinding. Clinical guidelines can usually take account of these shortcomings by applying 'levels of evidence' algorithms to moderate the strength of the clinical recommendation linked to the specific intervention. In addition, for those promising modalities of treatment where class 1A evidence of effectiveness is not available owing to issues with blinded ratings, further evidence of clinical effectiveness can be derived through naturalistic studies in clinical populations. Therefore, it is crucial to discuss issues with trials' design and research biases and set high methodological standards now so that future investigations adequately address current methodological concerns and the efficacy of these promising treatments can be properly verified. This is of particular importance in the field of psychedelics, where some potentially effective treatments have not been approved because of flaws in methodology (Kupferschmidt Kai, 2024). Given that these novel treatments primarily target disorders which are resistant to current therapeutic options and have been described as having the potential to introduce a new paradigm of care in mental health (Yehuda & Lehrner, 2023), we do not consider these shortcomings to fatally compromise the research. However, they should be addressed clearly and transparently by researchers. In Table 2, we suggest strategies that researchers might consider to improve the reliability and validity of studies of psychedelics in OCD.

Table 2
Strategies to improve the reliability and validity of studies of Psychedelics in OCRDs

- Enroll drug-naive subjects
- Assess patients' expectancies before, during and after the trial
- Choose doses of agent less liable to cause psychoactive effects that could compromise blinding
- Choose a credible control; avoid waiting list, consider novel approaches e.g. virtual reality or holotropic breathing
- Avoid offering psychedelics to non-responders randomized to the control
- Ensure adequate duration of blinded treatment
- Use independent blinded raters and blinded analysis
- Ensure the same raters do not assess the efficacy of outcomes and the adverse effects as this is likely to unblind them
- Avoid self-reported outcome measures where possible, as these are less likely to be blinded
- Avoid interim analysis, especially in the case of small studies, which might unblind the study
- Consider assessing blinding efficacy (for both patients and researchers)

CRediT authorship contribution statement

Rodolfo Leuzzi: Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Giovanni Tardivo:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Luca Pellegrini:** Writing – review & editing, Supervision, Conceptualization. **Umberto Albert:** Writing – review & editing, Supervision. **Naomi A. Fineberg:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Conceptualization.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Giovanni Tardivo declare that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Rodolfo Leuzzi declare that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Umberto Albert declare that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocrd.2025.100951.

Data availability

Data will be made available on request.

References

Aday, J. S., Davoli, C. C., & Bloesch, E. K. (2020). Psychedelics and virtual reality: Parallels and applications. *Therapeutic Advances in Psychopharmacology, 10*, Article 2045125320948356. https://doi.org/10.1177/2045125320948356

Bschor, T., Nagel, L., Unger, J., Schwarzer, G., & Baethge, C. (2024). Differential outcomes of placebo treatment across 9 psychiatric disorders: A systematic review and meta-analysis. *JAMA Psychiatry, 81*(8), 757–768. https://doi.org/10.1001/jamapsychiatry.2024.0994

C Curkovic, M., & Kosec, A. (2019). Significance of participants' expectations in managing the placebo effect in antidepressant research. *Frontiers in Psychiatry, 10*. https://doi.org/10.3389/fpsyt.2019.00713

Ching, T. H. W., Grazioplene, R., Bohner, C., Kichuk, S. A., DePalmer, G., D'Amico, E., Eilbott, J., Jankovsky, A., Burke, M., Hokanson, J., Martins, B., Witherow, C., Patel, P., Amoroso, L., Schaer, H., Pittenger, C., & Kelmendi, B. (2023). Safety, tolerability, and clinical and neural effects of single-dose psilocybin in obsessive–compulsive disorder: Protocol for a randomized, double-blind, placebo-controlled, non-crossover trial. *Frontiers in Psychiatry, 14*, Article 1178529. https://doi.org/10.3389/fpsyt.2023.1178529

De Giorgi, R., & Ede, R. (2024). Psilocybin for depression. *BMJ*. , Article q798. https://doi.org/10.1136/bmj.q798

Fincham, G. W., Kartar, A., Uthaug, M. V., Anderson, B., Hall, L., Nagai, Y., Critchley, H., & Colasanti, A. (2023). High ventilation breathwork practices: An overview of their effects, mechanisms, and considerations for clinical applications. *Neuroscience & Biobehavioral Reviews, 155*, Article 105453. https://doi.org/10.1016/j.neubiorev.2023.105453

Fineberg, N. A., Hawley, C. J., & Gale, T. M. (2006). Are placebo-controlled trials still important for obsessive compulsive disorder? *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 30*(3), 413–422. https://doi.org/10.1016/j.pnpbp.2005.11.012

Fineberg, N. A., Hengartner, M. P., Bergbaum, C., Gale, T., Rössler, W., & Angst, J. (2013). Lifetime comorbidity of obsessive-compulsive disorder and sub-threshold obsessive-compulsive symptomatology in the community: Impact, prevalence, socio-demographic and clinical characteristics. *International Journal of Psychiatry in Clinical Practice, 17*(3), 188–196. https://doi.org/10.3109/13651501.2013.777745

Graziosi, M., Rohde, J. S., Tiwari, P., Siev, J., & Yaden, D. B. (2024). Psychedelics, OCD and related disorders: A systematic review. *Journal of Obsessive-Compulsive and Related Disorders, 41*, Article 100873. https://doi.org/10.1016/j.jocrd.2024.100873

Grof, S., & Grof, C. (2010). *Holotropic breathwork: A new approach to self-exploration and therapy*. SUNY Press. https://doi.org/10.1515/9781438433950

Hovmand, O. R., Poulsen, E. D., Arnfred, S., & Storebø, O. J. (2023). Risk of bias in randomized clinical trials on psychedelic medicine: A systematic review. *Journal of Psychopharmacology, 37*(7), 649–659. https://doi.org/10.1177/02698811231180276

Howes, O. D., Thase, M. E., & Pillinger, T. (2022). Treatment resistance in psychiatry: State of the art and new directions. *Molecular Psychiatry, 27*(1), 58–72. https://doi.org/10.1038/s41380-021-01200-3

Kaup, K. K., Vasser, M., Tulver, K., Munk, M., Pikamäe, J., & Aru, J. (2023). Psychedelic replications in virtual reality and their potential as a therapeutic instrument: An open-label feasibility study. *Frontiers in Psychiatry, 14*, Article 1088896. https://doi.org/10.3389/fpsyt.2023.1088896

Koran, L. M., Gamel, N. N., Choung, H. W., Smith, E. H., & Aboujaoude, E. N. (2004). Mirtazapine for obsessive-compulsive disorder: An open trial followed by double-blind discontinuation. *The Journal of Clinical Psychiatry, 66*(4), 515–520. https://doi.org/10.1016/S0084-3970(08)70234-2

Kupferschmidt Kai. (2024). What's next for psychedelics after MDMA rejection? *What's next for Psychedelics after MDMA Rejection?, 385*(6710), 702–703. https://doi.org/10.1126/science.zhveq6h

Moreno, F. A., Wiegand, C. B., Taitano, E. K., & Delgado, P. L. (2006). Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. *The Journal of Clinical Psychiatry, 67*(11), 1735–1740. https://doi.org/10.4088/JCP.v67n1110

Naudet, F., Millet, B., Reymann, J. M., & Falissard, B. (2013). Improving study design for antidepressant effectiveness assessment. *International Journal of Methods in Psychiatric Research, 22*(3), 217–231. https://doi.org/10.1002/mpr.1391

NCT03300947. (2017). Psilocybin for treatment of obsessive compulsive disorder. Retrieved from: https://clinicaltrials.gov/study/NCT03300947.

NCT03356483. (2024). Psilocybin treatment in obsessive-compulsive disorder: A preliminary efficacy study and exploratory investigation of neural correlates. Retrieved from: https://clinicaltrials.gov/study/NCT03356483.

NCT04882839. (2022). Evaluating the feasibility. *Safety and Efficacy of Psychotherapy Assisted Psilocybin for Treatment of Severe OCD*. Retrieved from: https://clinicaltrials.gov/study/NCT04882839.

NCT05370911. (2022). Effects of repeated dosing of psilocybin on obsessive-compulsive disorder: A randomized. *Waitlist-Controlled Study*. Retrieved from https://clinicaltrials.gov/study/NCT05370911.

NCT05546658. (2024). Effects of psilocybin in obsessive compulsive disorder. Retrieved from https://clinicaltrials.gov/study/NCT05546658.

NCT06258031; PsilOCD. (2024). Evaluating the effects of the 5-HT2A agonist psilocybin on the neurocognitive and clinical correlates of compulsivity (A pharmacological-challenge feasibility study). Retrieved from https://clinicaltrials.gov/study/NCT06258031.

NCT06299319. (2024). Feasibility, clinical effects, and safety of psilocybin-assisted psychotherapy for treatment-resistant obsessive-compulsive disorder (PAP-OCD). Retrieved from https://clinicaltrials.gov/study/NCT06299319.

Patterson, B., Boyle, M. H., Kivlenieks, M., & Van Ameringen, M. (2016). The use of waitlists as control conditions in anxiety disorders research. *Journal of Psychiatric Research, 83*, 112–120. https://doi.org/10.1016/j.jpsychires.2016.08.015

Schneier, F. R., Feusner, J., Wheaton, M. G., Gomez, G. J., Cornejo, G., Naraindas, A. M., & Hellerstein, D. J. (2023). Pilot study of single-dose psilocybin for serotonin reuptake inhibitor-resistant body dysmorphic disorder. *Journal of Psychiatric Research, 161*, 364–370. https://doi.org/10.1016/j.jpsychires.2023.03.031

Soliman, P. S., Curley, D. E., Capone, C., Eaton, E., & Haass-Koffler, C. L. (2024). In the new era of psychedelic assisted therapy: A systematic review of study methodology in randomized controlled trials. *Psychopharmacology, 241*(6), 1101–1110. https://doi.org/10.1007/s00213-024-06598-6

Stein, D. J., Costa, D. L. C., Lochner, C., Miguel, E. C., Reddy, Y. C. J., Shavitt, R. G., van den Heuvel, O. A., & Simpson, H. B. (2019). Obsessive–compulsive disorder. *Nature Reviews Disease Primers, 5*(1), 1–21. https://doi.org/10.1038/s41572-019-0102-3

Suzuki, K., Roseboom, W., Schwartzman, D. J., & Seth, A. K. (2017). A deep-dream virtual reality platform for studying altered perceptual phenomenology. *Scientific Reports, 7*(1), Article 15982. https://doi.org/10.1038/s41598-017-16316-2

Szigeti, B., & Heifets, B. D. (2024). Expectancy effects in psychedelic trials. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 9*(5), 512–521. https://doi.org/10.1016/j.bpsc.2024.02.004

Yehuda, R., & Lehrner, A. (2023). Psychedelic therapy—a new paradigm of care for mental health. *JAMA, 330*(9), 813. https://doi.org/10.1001/jama.2023.12900

Younger, J., Gandhi, V., Hubbard, E., & Mackey, S. (2012). Development of the stanford expectations of treatment scale (SETS): A tool for measuring patient outcome expectancy in clinical trials. *Clinical Trials, 9*(6), 767–776. https://doi.org/10.1177/1740774512465064