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Psychedelic therapy vs. open-label antidepressant treatment (#142691)

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1) Have any data been collected for this study already?
It's complicated. We have already collected some data but explain in Question 8 why readers may consider this a valid pre-registration nevertheless.

2) What's the main question being asked or hypothesis being tested in this study?
The aim is to investigate how the lack of effective blinding influences outcomes in psychedelic trials when results are compared to traditional SSRI/SNRIs antidepressants. The correct guess rate (CGR), i.e. what percentage of blinded patients guesses correctly their treatment allocation, is a common metric of blinding quality where 50% indicates effective blinding (Szigeti et al., 2023). Psychedelic studies often report CGR > 90% (Bogenschutz et al., 2022), while for SSRI/SNRIs the CGR is commonly around 65% (Lin et al., 2022; Scott et al., 2022). This blinding quality difference hinders the fair comparison of these two treatment modalities, as psychedelic trials are effectively always open-label.

Given that psychedelic trials are effectively always open-label, results from these trials should be compared to open-label antidepressant trials. Such comparison is fair, because in this case both treatments equally benefit from patients knowing that they receive an active treatment. Therefore, we plan to compare the efficacy of open-label new generation antidepressants (OLAD) vs. psychedelic-assister therapy (PAT). We hypothesize that:

- the estimated mean between-treatment difference at the primary endpoint on the HAMD scale will exceed the 'minimal important difference' (MID) favoring PAT. Previous work has found that a difference of 3-5 points on the HAMD measure corresponds to the MID (Hengartner & Plöderl, 2022), here we will take the lower bound of this estimate to be the MID.
- the estimated mean difference on the HAMD scale at the primary endpoint will not exceed the MID between formally blinded (e.g. when a formal placebo control group was present) and open-label PAT trials.
- the estimated mean difference on the HAMD scale at the primary endpoint will exceed the MID between blinded and open-label SSRI/SNRIs trials, favoring open-label administration. For this comparison, we will use publicly available data on blinded antidepressant trials from (Cipriani et al., 2018).

We predict that the presence of blinding will not make a practical difference for psychedelics as these trials are always effectively open-label. In contrast, we predict that for SSRIs blinding makes a difference as in this case blinding works to some extent.

3) Describe the key dependent variable(s) specifying how they will be measured.
The dependent variable will be HAMD score at the primary endpoint. BDI, MADRS and QIDS scores will also be collected and these will be converted to HAMD scores according to previously established conversion formulas:
-BDI to HAMD: (Furukawa et al., 2019)
-MADRS to HAMD: (Leucht et al., 2018)
-QIDS to HAMD: (Rush et al., 2003)

We will only consider trials that have a primary endpoint between 6 and 12 weeks. If multiple timepoints are available within this timeframe, then we will use the timepoint that was defined as primary in the original publication. If the primary endpoint was not defined in the original study, we will use the timepoint that is closest to 10 weeks.

4) How many and which conditions will participants be assigned to?
Trials are included if they meet all of the inclusion and none of the exclusion criteria listed below.

Inclusion criteria
- open-label treatment with a new generation antidepressant. We use the list provided by (Cipriani et al., 2018) to define what drugs are considered 'new generation antidepressant'
- open-label or blind treatment with psychedelic-assisted therapy using a classic serotonergic psychedelics (Lysergic acid diethylamide / LSD; Psilocybin / magic mushroom; Mescaline / San Pedro / Peyote; DMT / Ayahuasca)
- Patients diagnosed with major depressive disorder (MDD) or persistent depressive disorder (PDD) and a current major depressive episode according to DSM criteria
- Has a timepoint between 6 to 12 weeks of treatment
- Includes at least one of the HAMD / MADRS / BDI / QIDS measures. Various versions of these scales are allowed (e.g., both self-report and clinician-report QIDS; BDI and BDI-II)
- Adult population, i.e. 18 < mean age of patients < 65

Exclusion criteria
- Psychotic and / or inpatient population
- Augmentation / drug combination trials
- Comorbid population, where majority of patients have a concurrent diagnosis of one specific medical or psychiatric condition (or were purposefully recruited due to their having that condition), with the exception of anxiety disorders. We make an exception for anxiety due its frequent co-occurrence with MDD
- Trials that include run-in periods; i.e. any trial where the main treatment was preceded by another treatment. However, data from the first period of such trials are allowed if that period otherwise meets all other criteria (e.g., the open-label treatment portion of a randomized discontinuation trial)

To find relevant papers the PubMed Advanced Search Builder is used with (https://pubmed.ncbi.nlm.nih.gov/advanced/). The specific query can be found on the project's github page (https://github.com/szb37/PsyOLAD-registration.git) for both open-label antidepressant (OLAD_pubmed_search_phrase.md) and psychedelic (PAT_pubmed_search_phrase.md) trials.

Manuscripts describing secondary analysis are excluded, only primary analysis papers are included. If we find secondary analysis where the primary publication was not captured by the search above, the first paper reporting the trial results will be added. Abstract screening, full text screening and data extraction from selected papers will be done independently by two members of the project, conflicts will be resolved by consensus.

5) Specify exactly which analyses you will conduct to examine the main question/hypothesis.
Complete model formulations corresponding to each hypothesis can be found on the project's GitHub site, https://github.com/szb37/PsyOLAD-registration.git, timestamped by GitHub. We provide both Bayesian (PsyOLAD_Bayesian_analysis.Rmd) and frequentist models (PsyOLAD_freq_analysis.r) to analyze the data. The Bayesian analysis should be considered as the primary analysis, while the frequentist models are secondary. The priors defined for the Bayesian models are based on internal discussions, these are subject to change if models do not converge.

Additionally, we will explore possible modulatory effects of several trial related variables. We have no prior hypothesis for the role of these variables; thus, this analysis will be labelled as exploratory.

6) Describe exactly how outliers will be defined and handled, and your precise rule(s) for excluding observations.
We plan the following robustness tests:
- Test each hypothesis using only week 8 data regardless whether it was designated as primary endpoint or not
- Test each hypothesis using only self-rated measures
- Test each hypothesis using only clinician-rated measures
- Prior sensitivity checks

7) How many observations will be collected or what will determine sample size? No need to justify decision, but be precise about exactly how the number will be determined.
No upper/lower sample size is determined, will collect all data as described in the 'Conditions' section.

8) Anything else you would like to pre-register? (e.g., secondary analyses, variables collected for exploratory purposes, unusual analyses planned?)
For the open-label antidepressant trials, we plan to exclude trials that have fewer than 100 participants. This decision is motivated by practical reasons. There are several large sample (n>500) open-label antidepressant trials, and due to inverse variance weighting, these will largely determine the results. Small trials would only have a small influence but would add significant workload that the project could not meet. This minimum sample size requirement is not applied to psychedelic trials, because in this case we expect a much lower number of trials to have ever been conducted.

We expect that most trials will report only the results from the 'intention to treat' sample with the 'last observation carried forward' (LOCF) imputation method. However, when the 'completers' (or 'per protocol') sample is available that will be used in the analysis.

At the time of this registration the abstract screening has already been conducted. This step was made prior to the registration to estimate how many trials will be included in this analysis, thus, whether completing this project is feasible within the timeframe that the study team can commit. Furthermore both S.B. and H.B. extracted data from the same 4 papers already and crosschecked results.