

Answers to the Reviewer #2

1. Methods section

Inclusion and exclusion criteria: It is important to include these to clarify the selection process.

Consideration of quality or quality assessment: this is an important omission. The quality of publications and the process of check should be presented and explained.

I.129: Data extraction date range is incomplete – between 11/11/2022...

What does 'heterogeneous studies' mean? Details should be given in this section.

A justification of qualitative approach should come earlier in the section and not just a few sentences at the end of the 'data extraction' paragraph.

Data extraction (p.5) – why is thematic the best approach?

I. 135: does this refer to the identification of themes? Did the author adopt a deductive approach and what were the themes? It would be good to have further elaboration on these in this section.

Answer: We thank the review for supporting the publication of the core ideas of our paper. The suggestion improves the scholastic consistency and it now reads:

"This is a systematically constructed integrative review, allowing the inclusion of qualitative and quantitative studies. This review used the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) recommendations as reporting guidelines (M. J. Page et al., 2021).

To identify all potentially eligible studies, an electronic search was conducted using the following databases: PubMed Central, ScienceDirect, EBSCOhost, and SCOPUS. Citation tracking and reference checking of the included studies were used to identify any further relevant studies. The results of this search were then refined by applying inclusion and exclusion criteria. The search and study selection processes were conducted in November 2022. The references were merged and managed using Mendeley. A combination of medical subject headings (MeSH), subject headings, and keywords was developed to conduct the search. Synonyms or abbreviations that were felt to be appropriate were added to the search terms. The search terms were tailored for each database. The search strategy for PubMed Central was the following: ("ethics"[Subheading] OR "ethics"[All Fields] OR "ethics"[MeSH Terms]) AND ("hallucinogens"[All Fields] OR "hallucinogens"[MeSH Terms] OR "hallucinogens"[All Fields] OR "psychedelics"[All Fields]), and the search strategy used for the other databases was: ("ethics AND (hallucinogens OR psychedelics)"). Available databases on science and human health salvaged for this review were the following: "Academic

Search Complete", "APA PsycArticles", "APA PsycInfo", "eBook University Press Collection (EBSCOhost)", "eBook Collection (EBSCOhost)", "Library, Information Science & Technology Abstracts", "MEDLINE", and "Psychology and Behavioural Sciences Collection".

The papers were consolidated with a review of five journals of ethics (*Nursing Ethics*, *American Journal of Bioethics*, *Journal of Medical Ethics*, *BMC Medical Ethics*, and *Hasting Center Report*) and five journals of psychiatry (*World Psychiatry*, *Lancet Psychiatry*, *Annual Review of Clinical Psychology*, *JAMA Psychiatry*, and *American Journal of Psychiatry*), and yet no new paper was found beyond those on the databases.

The search yielded 55703 studies, and their titles and abstracts were reviewed according to the inclusion and exclusion criteria listed below.

Inclusion criteria:

1. Original peer-reviewed studies, theses/dissertations, reviews, follow-up studies, commentaries, opinion pieces, conference abstracts, study protocols of clinical trials
2. Study designs including quantitative, qualitative, mixed-methods, case reports, case series
3. Studies conducted worldwide
4. Eligible psychedelic compounds: psilocybin, LSD, MDMA, ketamine, and *ayahuasca*
5. Discussion of ethical, legal, and philosophical themes
6. Published in the last five years (2017–2022)
7. English language

Exclusion criteria:

1. Studies in secondary care settings
2. Studies that do not relate their results to ethical, legal, and philosophical issues
3. Duplicated studies
4. Studies that are not free to access.
5. All the studies that do not fulfil the inclusion criteria

At the title and abstract screening, 52373 records were excluded based on the above inclusion and exclusion criteria using Mendeley. A total of 42 papers were included for thematic analysis.

Data extraction, synthesis, and analysis

The studies included were managed using Mendeley. Data extraction was conducted on 11/11/2022. Table 3 presents general information about the studies included, such as bibliographic details, country, design, and purpose.

To make it simpler to comprehend which outcomes were present in each study, a synthesis of findings from chosen publications was done in the next stage by summing earlier findings in another table. The included papers were also subjected to a thematic analysis, which allowed for the identification of themes and subthemes within each of the primary review conclusions. Finding pertinent subjects across the articles was the first part of this procedure. The second step was grouping related topics into bigger groupings in order to organise the final list of subthemes. The themes and subthemes represented in each research study were then summarised in a separate table.

Since this integrative review contains research with a variety of aims, approaches, and results, the findings of all pertinent studies were finally summarised using a qualitative methodology. Because of this, a meta-analysis was not possible.

Quality appraisal

Given the diversity of the studies, the criteria of Hawker's tool (Hawker et al., 2002) were used to evaluate the quality of the research evidence from the chosen publications. There are nine questions in this tool, with answer choices of "good", "fair", "poor", or "very poor". After using the tool, a numerical score was created by grading the responses from 1 (very poor) to 4 (good). As a result, each research project received a score that ranged from 9 to a maximum of 36 points. The following definitions were used to establish the overall quality grades: high quality (A), 30–36 points; medium quality (B), 24–29 points; and low quality (C), 9–23 points. Appendix 1 presents the tool containing the nine questions.

2. Results (p.6)

Grey literature: justification as to why this has been left out. Current research tends to include grey literature so it would be good to know the rationale behind leaving it out of this review.

The description of the selection process doesn't match the PRISMA flow chart. For instance, 16255 articles were excluded, according to the chart, for not being research articles, which makes the reader think that this is an exclusion criteria. However, several non-research publications seem to be included in the final list (opinion, reviews etc.). This needs to be corrected.

Answer: We thank the reviewer for constructively clarifying the negative parts of our paper. The results were rectified and now reads:

“Study selection and characteristics

From the aforementioned search, 55703 articles resulted. A total of 34258 studies were excluded because they were older than 5 years. An additional 1855 articles were excluded for not fitting the theme of this work, and 16255 were excluded for either being off-topic or not having peer review. Another 5 studies were excluded for not being free to access.

A total of 42 articles were considered through the review process (see Flowchart 1) performed by the authors with joint discussion of divergences. The articles’ key characteristics are presented in Table 3. The majority were research articles (15), but there were also reviews (7), perspective articles (8), opinions (8), essays (3), and a brief report (1). A total of 17 countries were represented, with the United States being the most frequent. The studies included were published in the last five years.

Quality appraisal and risk of bias

A quality assessment of the included studies is provided in Appendix 1. All included studies received an A to B grade with a numerical rating of 24–35 (see rating devising on Methods).

Thematic analysis

The themes and subthemes defined after conducting a thematic analysis of each study are presented in the table in Appendix 2. There are three main themes that correspond to the main findings defined during the protocol phase of this review.

Theme 1: Cultural, social, and ecological issues

Theme 2: Subjective effects

2.1. Risks, their mitigation, and informed consent

Theme 3: Political, social, and clinical issues

3.1. Changing legal status and possible consequences

3.2. Lack of diversity in the studies

3.3. Risk of biased research

3.4. Clinical application challenges

3. General

I.79: Not all psychedelics are naturally occurring. LSD is synthetic, for example. And not all of them are part of native American cultures.

I.161 – ‘the use of psychedelics raises’ ALL types of use?

Answer: we thank the reviewer for identifying several flaws of our discussion. We revised to read:

“Firstly, some of these psychedelics are naturally occurring agents that are (or grow in places where they are) ecologically endangered, as well as an important part of Native American and Amazonian cultures.”

“The eventual therapeutic use of psychedelics raises several social issues, including their cultural contextualisation as a colonialist form of appropriation of Indigenous knowledge.”

Overall, we thank the reviewer for constructively clarifying the negative parts of our paper. Our paper was now extensively reviewed addressing both language and clarity – we edited an extensive part of the paper considering the reviewers suggestions and it was also revised by a native English speaker, using the Scribbr Company. Further changes to Methods and Results were also made. We prepared the final revised paper for the reviewer. Thank you so much.