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# Psychedelics and related compounds in cluster headache and migraine: a systematic review and meta-analysis

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## Abstract

This protocol describes a systematic review and meta-analysis assessing the efficacy and safety of classic serotonergic psychedelics and related serotonergic ergoline or lysergamide compounds in cluster headache and migraine.

The review will include clinical studies evaluating psilocybin, psilocin, LSD, LSA, DMT/ayahuasca, mescaline, BOL-148 / 2-bromo-LSD / bromolysergide, lisuride, methysergide and methylergonovine.

The expected result is a structured synthesis of the available evidence on changes in headache burden, safety and tolerability, quality of life, and functional impact. If sufficient comparable data are available, random-effects meta-analyses will be conducted separately according to headache disorder and compound used.

## Guidelines

This systematic review and meta-analysis will be conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.

As the review is expected to include both interventional and observational studies, reporting will also take into account the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) recommendations when applicable.

## Materials

The following materials will be required to conduct this systematic review and meta-analysis:
- access to bibliographic databases: PubMed/MEDLINE; Embase; Scopus; ClinicalTrials.gov;
- Rayyan or equivalent systematic review screening software;
- a standardized study selection form for title/abstract screening and full-text eligibility assessment;
- a standardized data extraction form including:
- Joanna Briggs Institute (JBI) Critical Appraisal Tools adapted to the design of each included study;
software for statistical analyses:
- R statistical software;
- R packages for meta-analysis, such as meta, metafor or equivalent;

## Background and rationale

1 Cluster headache and migraine are disabling primary headache disorders associated with substantial individual, social and professional burden. Although several acute and preventive treatments are available, a proportion of patients remain insufficiently relieved, experience frequent relapses, or discontinue treatments because of adverse effects. This has led to renewed interest in alternative therapeutic approaches, including classic serotonergic psychedelics and related compounds.
Classic psychedelics, such as psilocybin, LSD, DMT/ayahuasca and mescaline, mainly act through serotonergic pathways, particularly 5-HT2A receptor agonism. In headache disorders, the clinical literature appears to be especially concentrated around cluster headache and migraine, with historical and recent reports suggesting potential effects on attack frequency, cycle interruption, remission and treatment burden.
Closely related serotonergic ergoline and lysergamide compounds may also be relevant because of their structural, pharmacological or historical relationship with serotonergic psychedelic research in headache disorders. These include LSD, LSA, BOL-148 / 2-bromo-LSD / bromolysergide, lisuride, methysergide and methylergonovine.
However, the available evidence remains heterogeneous, with different study designs, populations, dosing regimens, outcomes and follow-up durations. A systematic review is therefore needed to summarize the efficacy and safety of classic serotonergic psychedelics and related serotonergic ergoline or lysergamide compounds in cluster headache and migraine, and to determine whether quantitative synthesis is feasible.

## Objective

2 The primary objective of this systematic review and meta-analysis is to evaluate the efficacy and safety of classic serotonergic psychedelics and related compounds in adults with cluster headache or migraine.

## Population

3 We will include studies involving individuals diagnosed with:

- episodic cluster headache;
- chronic cluster headache;
- episodic migraine;
- chronic migraine.

Studies including mixed headache populations will be eligible if data for cluster headache or migraine can be extracted separately.

## Intervention

4 We will include serotonergic psychedelics and related serotonergic ergoline or lysergamide compounds with reported clinical outcomes in cluster headache or migraine, including:

- tryptamine psychedelics, such as psilocybin, psilocin, DMT and ayahuasca;
- phenethylamine psychedelics, such as mescaline;
- ergoline and lysergamide compounds, including LSD, LSA, BOL-148 / 2-bromo-LSD / bromolysergide, lisuride, methysergide and methylergonovine.

These compounds will be considered eligible because of their structural, pharmacological or historical relationship with serotonergic psychedelic research in headache disorders.

We will exclude ketamine, MDMA, cannabis, dextromethorphan, memantine, GHB, kratom, palmitoylethanolamide and kudzu, as they are not classic serotonergic psychedelics or related serotonergic ergoline/lysergamide compounds.

## Outcomes

5 **Primary outcome**

The primary outcome, used to assess treatment efficacy, will be the change in headache burden from baseline to follow-up after psychedelic or related lysergamide exposure.

Headache burden will be defined according to the outcome measures reported in each study and may include:

- change in headache attack frequency;
- change in the number of headache days;
- change in headache duration;

When several efficacy outcomes are reported within the same study, the outcome most relevant to the headache disorder will be prioritized for quantitative synthesis. For cluster headache, change in attack frequency will be prioritized. For migraine, change in the number of migraine days or headache days will be prioritized when available.

Follow-up time points will be extracted as reported by each study. When multiple follow-up assessments are available, the time point closest to the primary endpoint defined by the original study authors will be used for the main analysis.

6 **Secondary outcomes**

Secondary outcomesTo further evaluate efficacy, safety, tolerability and broader clinical impact, the following secondary outcomes will be extracted when reported:

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- headache intensity;
- interruption or remission of a cluster headache bout, when applicable;
- responder status, according to the definition used in each study;
- use of acute headache medication;
- duration of clinical response or remission;
- time to recurrence or relapse;
- quality of life;
- functional impact;
- adverse events;
- treatment discontinuation.

When sufficient data are available, exploratory analyses will assess differences in efficacy and safety according to:

- headache disorder, particularly cluster headache versus migraine;
- compound used, including psilocybin, LSD, LSA, DMT/ayahuasca, mescaline

## Study selection

7 **Inclusion criteria**

Eligible study designs will include:

- randomized controlled trials;
- non-randomized interventional studies, including open-label and uncontrolled studies;
- prospective and retrospective cohort studies;
- case-control studies;
- case series;
- case reports or small case series reporting more than five participants;
- observational survey studies reporting clinical outcomes in cluster headache or migraine.

8 **Exclusion criteria**

We will exclude:

- preclinical studies;
- animal studies;
- reviews, editorials, commentaries and letters without original patient-level or study-level data;

- studies focused only on non-psychedelic or non-lysergamide compounds.

We will exclude ketamine, MDMA, cannabis, dextromethorphan, memantine, kratom, GHB, palmitoylethanolamide and kudzu, as they are not classic serotonergic psychedelics or closely related lysergamides.

We will also exclude ergot-derived compounds such as methysergide, methylergonovine and Lysenyl.

## Information sources

9 The following databases and registries will be searched from inception to the search date:

- PubMed/MEDLINE;
- Embase;
- Scopus;
- ClinicalTrials.gov.

The reference lists of included studies and relevant reviews will also be screened manually to identify additional eligible publications.

The protocol will be developed according to PRISMA guidelines

## Search strategy

10 The search strategy will combine terms related to psychedelics and related lysergamides with terms related to cluster headache and migraine.

## Study selection

11 All records will be imported into reference management software and duplicates will be removed. Two reviewers will independently screen titles and abstracts, then full texts, according to the eligibility criteria. Disagreements will be resolved by discussion or by a third reviewer.
The study selection process will be reported using a PRISMA flow diagram.

## Data extraction

12 Two reviewers will independently extract data using a standardized extraction form.
Extracted data will include:

- author;
- year of publication;

- country;
- study design;
- type of headache;
- sample size;
- intervention substance;
- dose;
- number of administrations;
- treatment setting;
- comparator;
- follow-up duration;
- primary and secondary outcomes;
- efficacy results;
- safety results;
- adverse events;
- discontinuations;

## Assessment of risk of bias

13 The methodological quality of the included studies will be assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Tools, selected according to the study design of each included study.

Two reviewers will independently perform the risk of bias assessment. Discrepancies will be resolved through discussion, and when necessary, a third reviewer will act as an arbitrator.

Based on the pattern of responses across the JBI appraisal domains, studies will be categorized as having a low, moderate, or high risk of bias. Particular attention will be given to participant selection, diagnostic validity, intervention description, outcome measurement, completeness of follow-up, and the reporting of adverse events.

Risk of bias assessments will not be used as exclusion criteria, in order to preserve the comprehensiveness of the evidence base, but will be considered in the interpretation of the results and, when appropriate, in sensitivity analyses.

## Analyse and data synthesis

14 Narrative synthesis will be performed for all included studies.

Where at least two studies are sufficiently homogeneous in terms of population, intervention, comparator and outcome, meta-analysis will be considered.

Separate syntheses will be performed for: cluster headache; migraine; each molecules

If quantitative synthesis is feasible, random-effects models will be used because clinical and methodological heterogeneity are expected. Effect measures will include: risk ratios or odds ratios for dichotomous outcomes; mean differences or standardized mean differences for continuous outcomes; rate ratios for attack frequency when appropriate.

Heterogeneity will be assessed using the $I^2$ statistic and by visual inspection of forest plots. If substantial heterogeneity is present, possible sources will be explored through subgroup analyses or narrative discussion.

15 **Planned subgroup analyses**

If data permit, subgroup analyses will be conducted according to:

- headache disorder: cluster headache versus migraine;
- substance: psilocybin, LSD, LSA, DMT/ayahuasca, mescaline, BOL-148 / 2-bromo-LSD / bromolysergide, lisuride, methysergide and methylergonovine;
- substance class: classic tryptamine psychedelics, phenethylamine psychedelics, ergoline and lysergamide compounds
- hallucinogenic versus non-hallucinogenic or weakly hallucinogenic compounds, when this distinction is clinically and pharmacologically relevant.

16 **Sensitivity analyses**

A sensitivity analysis will be planned in the presence of substantial heterogeneity, defined as $I^2 > 75\%$, when heterogeneity cannot be explained by clinical or methodological differences, or when influential studies are suspected.

When feasible, a leave-one-out sensitivity analysis will be performed to assess the influence of individual studies on the pooled estimates.

If the number of included studies is too limited or if there is marked imbalance in sample sizes, sensitivity analyses will not be performed and this limitation will be reported narratively.

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