INPLASY

Nitrous Oxide for Depression: A Systematic Review and Meta-analysis of Clinical Response and Remission

INPLASY202620075
doi: 10.37766/inplasy2026.2.0075
Received: 25 February 2026
Published: 25 February 2026

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ADMINISTRATIVE INFORMATION

Support - This study received no external funding. The research was self-funded by the authors.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202620075

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 26 February 2026 and was last updated on 26 February 2026.

INTRODUCTION

Review question / Objective Review question: What is the efficacy of inhaled nitrous oxide compared with placebo, sham inhalation, or active control interventions in achieving clinical response and remission among adults with depressive disorders?

Objective: To systematically review and quantitatively synthesize evidence from randomized controlled trials evaluating the effects of inhaled nitrous oxide on clinical response and remission outcomes in adults diagnosed with depressive disorders, compared with placebo, sham inhalation, or active control interventions.

Rationale Depressive disorders represent a major global health burden, with a substantial proportion of patients failing to achieve adequate response or remission with conventional antidepressant treatments. Nitrous oxide, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist with a long-standing clinical safety record in anesthesia, has emerged as a potential rapid-acting antidepressant. Several randomized controlled trials have reported rapid reductions in depressive symptoms following inhaled nitrous oxide; however, the existing evidence has not been comprehensively synthesized with a focus on clinically meaningful dichotomous outcomes. Previous systematic reviews have primarily examined continuous changes in depression scale scores and included a limited number of trials, without pooling clinical response and remission rates. Given the increasing number of recent randomized controlled trials and the clinical relevance of response and remission outcomes for treatment decision-making, a systematic review and meta-analysis is warranted to quantitatively evaluate the efficacy of inhaled nitrous oxide in achieving clinical response and remission among adults with depressive disorders.

Condition being studied Depressive disorders in adults, including major depressive disorder (MDD), treatment-resistant depression (TRD), and bipolar depression, as diagnosed using standardized diagnostic criteria (e.g., DSM or ICD) or validated clinical assessment tools. The review focuses on depressive episodes characterized by insufficient response or remission with standard treatments, where clinical response and remission are defined according to established thresholds on validated depression rating scales.

METHODS

Search strategy A systematic literature search will be conducted in the following electronic databases: PubMed (MEDLINE), Scopus, ScienceDirect, and Google Scholar. The search will include studies published between January 1, 2016, and December 31, 2025, to capture the most contemporary evidence on nitrous oxide as an antidepressant intervention.

The search strategy will combine controlled vocabulary terms (e.g., Medical Subject Headings [MeSH] in PubMed) and free-text keywords related to nitrous oxide and depressive disorders. Key search terms will include: "nitrous oxide," "N2O," "laughing gas," "depression," "depressive disorder," "major depressive disorder," "treatment-resistant depression," "bipolar depression," "clinical response," "remission," and "randomized controlled trial." Boolean operators (AND, OR) will be used to combine search terms appropriately, and the search syntax will be adapted to the indexing requirements of each database.

In addition to electronic database searching, backward citation tracking will be performed by screening the reference lists of all included studies and relevant systematic reviews. Forward citation tracking will also be conducted using Google Scholar to identify additional eligible trials. Only full-text articles published in peer-reviewed journals will be considered. No restrictions on geographical location will be applied.

Participant or population Adults (aged ≥18 years) diagnosed with a depressive disorder, including major depressive disorder (MDD), treatment-resistant depression (TRD), or bipolar depression. Diagnosis must be established using standardized diagnostic criteria (e.g., DSM or ICD) or validated clinical assessment instruments. Studies enrolling mixed psychiatric populations will be included only if data for participants with depressive disorders can be clearly extracted. Studies exclusively involving pediatric or adolescent populations (<18 years) will be excluded.

Intervention Inhaled nitrous oxide administered at any concentration (e.g., 25% or 50%), for any duration and frequency, either as a single session or as repeated treatment sessions. Nitrous oxide may be administered as monotherapy or as an adjunct to ongoing standard antidepressant treatment, provided that the intervention is clearly defined and the comparator group does not receive nitrous oxide.

Comparator Comparator interventions will include placebo (e.g., 100% oxygen, medical air, or air–oxygen mixtures), sham inhalation, standard care, or active control interventions such as sedative agents (e.g., midazolam), provided that nitrous oxide is not administered in the comparator group.

Study designs to be included Randomized controlled trials (RCTs), including both parallel-group and crossover designs, that evaluate the effects of inhaled nitrous oxide compared with placebo, sham inhalation, standard care, or active control interventions in adults with depressive disorders.

Eligibility criteria Inclusion criteria:
Studies will be included if they meet all of the following criteria:
(1) full-text articles published in peer-reviewed journals;
(2) randomized controlled trial (RCT) design, including parallel-group or crossover trials;
(3) adult participants (aged ≥18 years) diagnosed with depressive disorders, including major depressive disorder (MDD), treatment-resistant depression (TRD), or bipolar depression, based on standardized diagnostic criteria (e.g., DSM or ICD) or validated clinical assessment tools;
(4) intervention consisting of inhaled nitrous oxide administered at any concentration, duration, or frequency;
(5) inclusion of a comparator group receiving placebo, sham inhalation, standard care, or an active control intervention; and
(6) reporting sufficient quantitative data on clinical response and/or remission outcomes to allow meta-analytic pooling.

Exclusion criteria:
Studies will be excluded if they:
(1) enroll exclusively pediatric or adolescent populations (<18 years);
(2) lack an appropriate comparator or control group;

(3) do not report clinical response or remission outcomes or provide insufficient data for quantitative synthesis;
(4) are non-original research articles, including narrative reviews, systematic reviews, meta-analyses, editorials, commentaries, letters, conference abstracts, or case reports; or
(5) present overlapping populations without sufficient information to extract unique data.

Information sources The following electronic databases will be systematically searched: PubMed (MEDLINE), Scopus, ScienceDirect, and Google Scholar. The search will cover studies published from January 1, 2016, to December 31, 2025.
In addition to database searching, backward citation tracking will be conducted by screening the reference lists of all included studies and relevant systematic reviews. Forward citation tracking will also be performed using Google Scholar to identify additional eligible studies.
Only full-text articles published in peer-reviewed journals will be considered.

Main outcome(s) The primary outcomes of this review will be clinical response rate and clinical remission rate following inhaled nitrous oxide treatment. Clinical response will be defined as a ≥50% reduction from baseline in validated depression rating scale scores, while clinical remission will be defined as achieving a score below established thresholds on validated scales (e.g., Hamilton Depression Rating Scale [HAM-D] ≤7 or Montgomery–Åsberg Depression Rating Scale [MADRS] ≤10), as specified in the individual trials.

Additional outcome(s) Secondary outcomes will include the incidence of adverse events associated with inhaled nitrous oxide, as reported in the included trials, as well as changes in depressive symptom severity measured by validated depression rating scales (e.g., HAM-D, HDRS, MADRS) at reported follow-up time points. When available, information on treatment tolerability and withdrawal due to adverse effects will also be descriptively summarized.

Data management All records identified through database searches will be imported into reference management software for de-duplication. Following removal of duplicates, titles and abstracts will be screened independently by two reviewers. Full-text articles of potentially eligible studies will then be retrieved and assessed for inclusion.

Data extraction will be performed independently by two reviewers using a standardized, pre-piloted data extraction form. Extracted data will be cross-checked for accuracy and completeness. Any discrepancies between reviewers will be resolved through discussion and consensus, with consultation of a third reviewer if necessary.

Extracted data will be securely stored in password-protected electronic files accessible only to the review team. The final dataset used for analysis will be archived and retained for transparency and reproducibility.

Quality assessment / Risk of bias analysis The methodological quality of included randomized controlled trials will be independently assessed by two reviewers using the revised Cochrane Risk of Bias tool for randomized trials (RoB 2.0). Each study will be evaluated across five domains: (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcome; and (5) bias in selection of the reported result.

For each domain, studies will be judged as having "low risk of bias," "some concerns," or "high risk of bias," and an overall risk of bias judgment will be derived according to the RoB 2.0 algorithm. Disagreements between reviewers will be resolved through discussion and consensus; if consensus cannot be reached, a third reviewer will be consulted. Results of the risk of bias assessment will be presented in both tabular and graphical formats.

Strategy of data synthesis Quantitative data synthesis will be performed when at least two studies report comparable outcomes. For the primary outcomes of clinical response and remission, pooled risk ratios (RRs) with corresponding 95% confidence intervals (CIs) will be calculated using a random-effects meta-analysis model to account for potential between-study variability.

Statistical heterogeneity will be assessed using Cochran's Q test and quantified with the I^2 statistic, with values of 25%, 50%, and 75% indicating low, moderate, and high heterogeneity, respectively. When appropriate, forest plots will be generated to visually display pooled estimates and individual study effects.

If quantitative synthesis is not feasible due to insufficient data or substantial clinical heterogeneity, results will be summarized

narratively. All analyses will be conducted using Stata statistical software.

Subgroup analysis No subgroup analyses are planned for this review due to the limited number of available studies and the small overall sample size.

Sensitivity analysis No sensitivity analyses are planned for this review due to the limited number of included studies.

Language restriction Only studies published in the English language will be included.

Country(ies) involved This systematic review and meta-analysis is being carried out in Thailand. All authors are affiliated with academic institutions in Thailand.

Other relevant information No additional information is provided.

Keywords Nitrous oxide; Depression; Treatment-resistant depression; Clinical response; Remission; Systematic review; Meta-analysis; Randomized controlled trial.

Dissemination plans The findings of this systematic review and meta-analysis will be submitted for publication in a peer-reviewed international journal. Results may also be presented at national or international academic conferences and disseminated through academic and institutional platforms to inform clinicians, researchers, and policymakers.

Contributions of each author

Author 1 - Ariyachart Kalawa - conceived the study idea, designed the review protocol, conducted the literature search, performed study selection and data extraction, carried out the statistical analyses, and drafted the manuscript.
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Author 2 - Passakorn Ongarj - contributed to study selection, data extraction, and risk of bias assessment, and critically reviewed the manuscript for important intellectual content.
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