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Pharmacological Alternatives to Neuraxial Analgesia for Labor Pain: A Protocol for Bayesian Network Meta-Analysis

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Data analysis.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 11 August 2026 and was last updated on 11 August 2026.

INTRODUCTION

Review question / Objective Objective: to quantitatively assess and consistently rank the relative efficacy and safety of non-regional pharmacological methods of labour pain relief (remifentanil, fentanyl, meperidine, and nitrous oxide) in parturients with contraindications to regional analgesia.
Clinical Question: Which pharmacological method of labour pain relief provides the greatest efficacy and the best safety profile for the mother and the fetus/newborn in parturients with contraindications to regional analgesia?
PICOS:
• Population: Parturients receiving systemic opioids or inhaled analgesia for labour pain relief. No restrictions regarding ASA physical status, parity, age, gestational age, or fetal presentation.
• Intervention: Non-regional pharmacological methods of labour pain relief: remifentanil, fentanyl, meperidine (pethidine), and nitrous oxide (N_2O).
• Comparison: Any of the above-mentioned agents (direct or indirect comparisons within the network).
• Outcomes: primary – pain intensity (VAS 0–10 cm); maternal satisfaction; Apgar score at 5 minutes (<7); secondary–nausea; desaturation (SpO_2 <95%); spontaneous vaginal delivery; instrumental delivery; umbilical artery pH; pruritus; naloxone use; Neurologic and Adaptive Capacity Score (NACS), duration of labour, breastfeeding initiation.
• Study Design: Randomised controlled trials (RCTs) and randomised cross-over studies.

Rationale Epidural analgesia is the gold standard for labour pain relief but is contraindicated or unavailable for a number of women. The main alternatives are systemic opioids (remifentanil, fentanyl, meperidine) and inhaled nitrous oxide. However, their comparative efficacy and safety remain uncertain. Traditional pairwise meta-analyses cannot compare all four interventions simultaneously. A recent network meta-analysis (Wydall et al., 2023) focused on epidural techniques and used intravenous opioids only as a control, without directly comparing them against each other. To date, no network

meta-analysis has directly compared remifentanil, fentanyl, meperidine, and nitrous oxide for labour pain relief in women with contraindications to neuraxial analgesia. The present review aims to fill this gap by providing a quantitative synthesis and ranking of these four pharmacological alternatives. Pharmacologically, combining nitrous oxide with opioids in a single network is justified because nitrous oxide acts as a partial opioid receptor agonist and its effects are reversed by naloxone, confirming involvement of the opioid system.

Condition being studied Labour pain is one of the most intense forms of acute pain. Effective pain relief is essential for maternal comfort and the normal progress of labour. Epidural analgesia is the gold standard, but in some cases it is contraindicated (coagulopathies, infections, spinal abnormalities, patient refusal). In these situations, the main alternatives remain systemic opioids (remifentanil, fentanyl, meperidine) and inhaled nitrous oxide (N_2O). Despite many years of use, the comparative efficacy and safety of these methods have not been definitively established. No studies exist that directly compare all four methods simultaneously. This network meta-analysis allows such a comparison for the first time.

METHODS

Search strategy The search was conducted in 7 databases: PubMed, Europe PMC, ScienceDirect, Dimensions, Wiley Online Library, WHO ICTRP, and BASE, covering the period from January 1, 1989, to March 25, 2026. The search strategy was adapted for each database using queries that included the following English terms: (remifentanil[Title/Abstract] OR fentanyl[Title/Abstract] OR pethidine[Title/Abstract] OR meperidine[Title/Abstract] OR "nitrous oxide"[Title/Abstract]) AND ("labour"[Title/Abstract] OR "labor"[Title/Abstract] OR "obstetric"[Title/Abstract] OR "childbirth"[Title/Abstract]) AND (randomized[Title/Abstract] OR randomised[Title/Abstract] OR "randomized controlled trial"[Publication Type]) NOT (epidural[Title/Abstract] OR spinal[Title/Abstract] OR "combined spinal"[Title/Abstract] OR CSE[Title/Abstract] OR regional[Title/Abstract] OR "patient-controlled epidural"[Title/Abstract] OR PCEA[Title/Abstract]). In addition, an automated "snowball" method was applied by screening the reference lists of the included studies and relevant systematic reviews.

Participant or population Parturients (pregnant women in labour) requesting systemic analgesia for pain relief during childbirth, in whom epidural (neuraxial) analgesia is contraindicated or unavailable. Setting: Hospital labour wards (any country, any level of care).

Intervention Non-regional pharmacological methods of labour pain relief: remifentanil, fentanyl, pethidine/meperidine, and nitrous oxide (N_2O).

Comparator Any of the above-mentioned agents (direct or indirect comparisons within the network).

Study designs to be included Randomised controlled trials (RCTs) and randomised cross-over studies.

Eligibility criteria RCTs (including cross-over studies) evaluating the efficacy and safety of systemic labour analgesia were included if they reported at least one of the following outcomes: pain intensity (VAS), maternal satisfaction, adverse events (nausea, desaturation, pruritus), delivery-related outcomes (spontaneous vaginal delivery, instrumental delivery), or neonatal outcomes (Apgar score, umbilical artery pH, naloxone use, NACS, breastfeeding initiation). The following interventions were considered: remifentanil (PCA), fentanyl (IV, SC, intranasal), meperidine (IV, IM), and nitrous oxide (inhalation). Nitrous oxide is a standard comparator in NMA (partial opioid receptor agonist).The choice of interventions was determined by the availability of direct comparisons, not by regulatory approval status. Studies were excluded if they used neuraxial analgesia (epidural, spinal), had an ineligible design (systematic reviews, cohort studies, letters to the editor, animal studies), or lacked a relevant comparator. No restrictions on language, publication date, or publication status were applied.

Information sources PubMed, Europe PMC, ScienceDirect, Dimensions, Wiley Online Library, WHO ICTRP, BASE.

Main outcome(s) 1. Pain intensity at 1 hour after drug administration measured by the Visual Analogue Scale (VAS, 0–10 cm). Effect measure – Mean Difference (MD). 2. Maternal satisfaction with labour pain relief (scale 0–10). Effect measure – Mean Difference
(MD). 3. Apgar score at 5 minutes < 7. Effect measure – Odds Ratio(OR).

Additional outcome(s) 1. Frequency of nausea. Effect measure – Odds Ratio (OR).
2. Frequency of desaturation (SpO_2 <95%, binary outcome). Effect measure – Odds Ratio (OR).

3. Frequency of spontaneous vaginal delivery (binary outcome). Effect measure – Odds Ratio (OR).
4. Frequency of instrumental delivery: obstetric forceps, vacuum-assisted fetal extraction (binary outcome). Effect measure – Odds Ratio (OR).
5. Mean umbilical artery pH. Effect measure – Mean Difference (MD).
6. Frequency of naloxone administration in newborns. Effect measure – Odds Ratio (OR).
7. Frequency of pruritus (itching). Effect measure – Odds Ratio (OR).
8. Duration of labour. Effect measure – Mean Difference (MD).
9. Breastfeeding initiation – Mean Difference (MD)
10. Neurologic and Adaptive Capacity Score (NACS), 0–40 points.

Data management Study management was performed using the Mendeley Desktop reference manager (Elsevier, v1.19.8, 2020), and review management was conducted using RAYYAN.

Quality assessment / Risk of bias analysis The risk of bias in individual studies will be assessed using the Cochrane RoB 2 tool. Two reviewers will independently evaluate five domains: randomisation, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results. Each study will be rated as "low risk", "some concerns", or "high risk". The overall certainty of evidence for the primary and secondary outcomes will be assessed using GRADE as operationalised in CINeMA (Confidence in Network Meta-Analysis). Six domains will be evaluated: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence. The contribution matrix will be used to account for the influence of each study on network estimates. Certainty will be rated as "high", "moderate", "low", or "very low". The CINeMA web application (cinema.ispm.ch) will be used.

Strategy of data synthesis A Bayesian network meta-analysis (NMA) will be conducted using the MetaInsight web application (R/Stan). A random-effects model will be used. Meperidine is proposed as the reference intervention, being the most extensively studied obstetric analgesic. For continuous outcomes (pain intensity, satisfaction, umbilical artery pH), the mean difference (MD) with 95% credible intervals (CrI) will be calculated. For binary outcomes (nausea, desaturation, caesarean section, Apgar score <7, etc.), the odds ratio (OR) with 95% CrI will be used. Heterogeneity will be assessed using I^2 and τ^2. Network inconsistency will be evaluated using the node-splitting approach. A sensitivity analysis using meta-regression will be performed to assess the impact of the route of meperidine administration on the primary outcome (pain at 1 hour). The certainty of evidence will be rated using CINeMA. Results will be presented as league tables and forest plots. Ranking of interventions will be reported using SUCRA (Surface Under the Cumulative Ranking Curve) probabilities. If NMA is not feasible (e.g., sparse network, no closed loops), only descriptive summaries will be provided.

Subgroup analysis Subgroup analyses (e.g., by parity, dose regimen) will be considered if sufficient data are available; otherwise not performed.

Sensitivity analysis Sensitivity analysis will be performed using meta regression to assess the impact of the route of meperidine administration (intramuscular, intravenous, patient controlled analgesia) on the primary outcome (pain at 1 hour). A sensitivity analysis excluding high risk-of-bias studies will be performed only if the network connectivity is preserved.

Language restriction There are no language restrictions.

Country(ies) involved Russian Federation.

Other relevant information Review as recommended by PRISMA NMA, 2015.

Keywords Labor analgesia; Remifentanil; Fentanyl; Meperidine; Nitrous oxide; Patient-controlled analgesia; network meta-analysis.

Dissemination plans The results of this network meta-analysis will be published in a peer-reviewed scientific journal in accordance with the PRISMA-NMA guidelines.

Contributions of each author

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