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REVIEW ARTICLE

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Inhaled analgesics for the treatment of prehospital acute pain—A systematic review

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Abstract

Background: Many prehospital emergency patients receive suboptimal treatment for their moderate to severe pain. Various factors may contribute. We aim to systematically review literature pertaining to prehospital emergency adult patients with acute pain and the pain-reducing effects, adverse events (AEs), and safety issues associated with inhaled analgetic agents compared with other prehospital analgesic agents.

Methods: As part of an initiative from the Scandinavian Society of Anaesthesia and Intensive Care Medicine, we conducted a systematic review (PROSPERO CRD42018114399), applying the PRISMA guidelines, Grading of Recommendations Assessment, Development, and Evaluation (GRADE), and Cochrane methods, searching the Cochrane Library, Epistemonikos, Centre for Reviews and Dissemination, PubMed, and EMBASE databases (updated March 2024). Inclusion criteria were the use of inhaled analgesic agents in adult patients with acute pain in the prehospital emergency care setting. All steps were performed by minimum of two individual researchers. The primary outcome was pain reduction; secondary outcomes were speed of onset, duration of effect, and relevant AEs.

Results: We included seven studies (56,535 patients in total) that compared inhaled agents (methoxyflurane [MF] and nitrous oxide [N_2O]) to other drugs or placebo. Study designs were randomized controlled trial (1; $n = 60$), randomized non-blinded study (1; $n = 343$), and randomized open-label study (1; $n = 270$). The remaining were prospective or retrospective observational studies. The evidence according to GRADE was of low or very low quality. No combined meta-analysis was possible. N_2O may reduce pain compared to placebo, but not compared to intravenous (IV) paracetamol, and may be less effective compared to morphine and MF. MF may reduce pain compared to paracetamol, ketoprofen, tramadol, and fentanyl. Both agents may be associated with marked but primarily mild AEs.

Conclusion: We found low-quality evidence suggesting that both MF and N_2O are safe and may have a role in the management of pain in the prehospital setting. There is low-quality evidence to support MF as a short-acting single analgesic or as a bridge to IV access and the administration of other analgesics. There may be occupational health issues regarding the prehospital use of N_2O.

KEYWORDS

acute pain, adverse drug event, emergency medical services, EMS, methoxyflurane, nitrous oxide, occupational health, prehospital emergency care

Editorial Comment

This systematic review presents available evidence for prehospital acute pain management by inhalational agents. The certainty of evidence was low, and the review highlights the need for sufficiently sized randomized trials in this area, although the environmental impact of using inhalational agents in emergency settings must be considered.

1 | BACKGROUND

A substantial proportion of prehospital emergency patients receive suboptimal treatment for their severe pain.[1–5] The term oligoanalgesia may be defined as "underuse of analgesics in the face of valid indication"[6] or "inadequate treatment of pain."[7] In prehospital emergency care, oligoanalgesia seems to be frequent and is still a substantial problem.[1,3,5,7,8]

Various factors may contribute to insufficient pain relief in this setting. Some groups of patients seem to be at higher risk of experiencing oligoanalgesia than others—it appears to be more common in patients with gynecological and obstetric pain,[1,7] as well as pain in trauma and non-cardiac disease patients.[1] The experience of the prehospital care provider may also be a factor.[3] Berben et al. found that lack of formal pain evaluation and less familiarity with the analgesic drugs may play a role.[8] In our experience, other factors may also contribute, such as difficulties in establishing intravenous (IV) access, time constraints, fear of adverse events (AEs), and restrictive protocols in emergency medical services (EMS).

If the lack of IV access is a reason for oligoanalgesia, inhaled analgesic agents may be an alternative. Indeed, nitrous oxide mixed with oxygen 50%:50% (N_2O) and methoxyflurane (MF) have been used for several decades. N_2O probably exerts its analgesic effect over the N-methyl-D-aspartate (NMDA) receptor,[9] and it has been used prehospital in some countries.[10] It is unclear to what extent it is currently used worldwide for prehospital emergency patients, but it has been investigated in recent studies.[11,12] MF is a volatile anesthetic of the de-alkyl esters group[13] and has been used since the 1980s in Australia.[14] It was approved by the European Medicines Agency (EMA) in 2018.[13]

Only a few studies have been performed investigating the effectiveness and safety of inhaled analgetic agents in the prehospital setting. To our knowledge, no adequate systematic reviews addressing prehospital use have been published. The aim of this systematic review is to establish the knowledge base for the effectiveness and safety for inhaled analgesics in prehospital emergency care. Our clinical questions are: in adult prehospital patients with acute pain, what is the pain-reducing effect, what are the AEs and are there other safety issues associated with inhaled analgetic agents compared with other modes of prehospital pain management?

2 | METHODS

This systematic review was a part of an initiative by the Scandinavian Society of Anaesthesia and Intensive Care Medicine (SSAI) to publish evidence-based guidelines for prehospital pain management. The research group has published systematic reviews investigating the prehospital use of opioids, ketamine, and femoral nerve blocks.[15–17] The systematic reviews were registered in PROSPERO (registration number CRD42018114399) as a protocol for all the publications for this series. All reviews were performed according to the Cochrane Handbook for systematic reviews of interventions[18] and the PRISMA 2020 guidelines.[19]

The Population, Intervention, Comparison, and Outcomes items for this systematic review were:

1. Population: Adult patients with acute pain in the prehospital emergency care setting
2. Intervention: Inhaled analgesics
3. Comparison: Other analgesics or placebo
4. Outcomes:
   - Primary outcome: pain reduction
   - Secondary outcomes: speed of onset; duration of effect; relevant AEs, such as mortality, morbidity, anaphylaxis, nausea and vomiting, hypotension, respiratory failure, loss of airway patency, emergence phenomena; safety issues for healthcare providers.

The literature searches were performed by an experienced research librarian. The searches were last updated in March 2024. The following databases were searched: the Cochrane Library, Epistemonikos, Centre for Reviews and Dissemination, PubMed, and EMBASE. The full search strategy for PubMed for this review can be found in Table S1. The searches were restricted to adult patients and a prehospital setting.

Our primary outcome was reduction in pain intensity (Numeric Rating Scale [NRS; 0–10 or 1–10]; Visual Analogue Scale [VAS; 0–100 or 0–10], Verbal Numerical Pain Score [VNPS; 0–10], etc.) Secondary outcomes were speed of onset, duration of effect, and relevant AE. There is no international definition of AE agreed upon. Hence, all AEs reported in the included studies have been included in our review. Examples of reported AE include nausea/vomiting, unintended sedation, hypoventilation, and hypotension. Suspecting that there may be a scarcity of published papers on the subject, we aimed to include randomized controlled trials (RCTs), non-randomized controlled studies, cohorts with control groups, interrupted time series, and controlled before- and after-studies if applicable. Regarding AEs and safety issues, we also included case series and case reports as AE may be infrequent.

No restriction on the publication date was imposed. Only publications in English or Scandinavian languages were included. This is a deviation from the PROSPERO protocol. However, it is in concordance with the methodology applied in the previous publications in this series.

All identified publications were imported into the COVIDENCE software for systematic reviews (Veritas Health Innovation, Melbourne, Australia). For the evaluation of Risk of Bias (RoB), we applied the Cochrane Effective Practice and Organisation of Care (EPOC) criteria.[20] Due to the expected low number of applicable publications, we chose EPOC which allows for inclusion of non-RCTs, as well as reports on AEs. All steps of inclusion/exclusion, RoB evaluation, and data extraction were performed by two assessors independently and conflicts were resolved through discussion or involvement of a third assessor. We searched the bibliography of the included studies manually for further includable studies.

We extracted data and summarized these according to the data identified. Where appropriate, we conducted meta-analyses, alternatively we reported data descriptively. We conducted sensitivity analyses for effect and safety for different patient groups where there were enough information and homogeneity for it to be feasible. Dichotomous outcomes were presented as risk ratio (RR) with 95% confidence intervals (95% CIs). Continuous outcomes were presented as mean differences between the groups (MD) with 95% CI. Where different scales were used to measure the same outcome, we calculated standardized mean difference (SMD) with 95% CI.

We used Review Manager (version 5.4.1, The Cochrane Collaboration, 2020) to calculate 95% CI when not reported.

To rate the certainty of the evidence, we applied the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology.[21,22]

3 | RESULTS

3.1 | Inclusion of studies

We identified 3792 reports through systematic searches and assessed 2787 unique reports for eligibility (after duplicate removal). Of the potentially relevant reports included for full-text review, seven studies were finally included (Figure 1). The seven studies included a total of 56,535 patients. One study was an RCT ($n = 60$), one a randomized non-blinded study ($n = 343$), and one a randomized open-label study

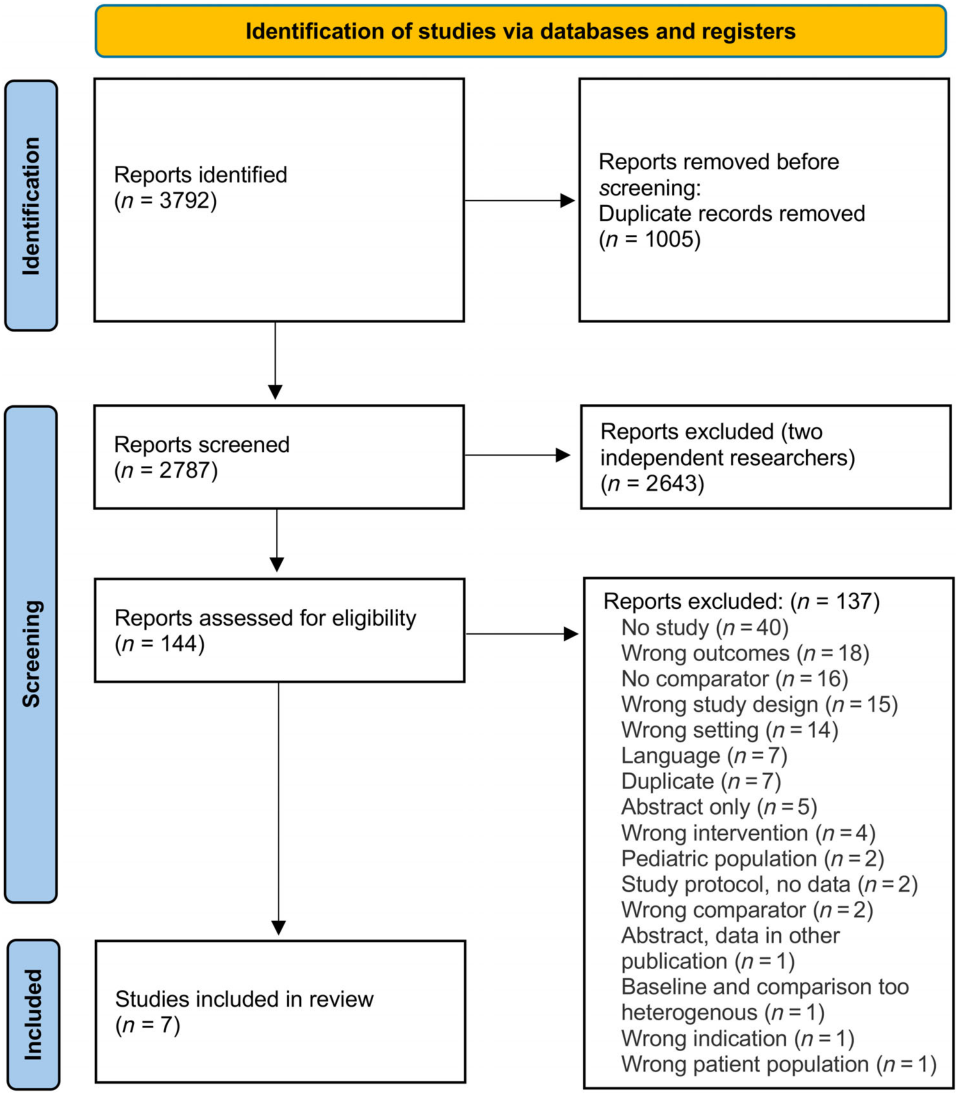

FIGURE 1 PRISMA flow chart of included and excluded reports with reasons.

($n = 270$). The remaining were prospective or retrospective observational studies. Although case series without any comparator group were excluded, 13 were used for AE evaluation.

3.2 | Risk of bias of included studies

RoB for the included studies where either of the two inhaled analgesics were compared to other agents or placebo, and with pain reduction as an outcome measure. One RCT had low RoB,[11] but most of the studies had moderate[23,24] or high RoB (Figure 2).

3.3 | GRADE

We found the certainty of the evidence for the outcomes from the seven included studies to be low or very low. The GRADE summary of the findings table can be found in Table S2.

3.4 | The included studies

The characteristics of the seven included studies are summarized in Table 1.

3.5 | Results of the different comparisons

The results of the different comparisons, including AEs, are summarized in Table 2. Forest plots may be found in Figures S1–S3.

3.5.1 | AEs in other studies

Studies with no comparator have not been reported above.[10,13,28–38] Below, we summarize the AE reported in these studies. No serious AEs were reported (Table 3).

Study (reference)	Random sequence generation	Allocation concealment	Baseline outcome measurements similar	Baseline characteristics similar	Incomplete outcome data	Knowledge of the allocated interventions adequately prevented during the study	Protection against contamination	Selective outcome reporting	Other risks of bias
Braybrook et al. 2023 (25)	x	x	x	x	+	x	x	+	+
Ducassé et al. 2013 (11)	+	+	+	+	+	+	+	+	+
Johnston et al. 2011 (26)	x	x	x	x	x	x	?	+	+
Lim et al. 2020 (23)	+	+	+	+	+	x	+	+	?
Mercadante et al. 2019 (24)	+	+	+	+	+	x	+	+	x
Middleton et al. 2010 (14)	x	x	+	+	x	x	x	?	?
Smith et al. 2022 (27)	x	x	?	x	+	x	x	+	+

+: low risk of bias; ?: unclear risk of bias; X: high risk of bias

FIGURE 2 Risk of bias of the included studies.

3.5.2 | Safety and occupational health

We identified four studies that reported N_2O concentrations in ambulances in different situations.[39–42] Two studies found N_2O concentrations to be above the threshold limit value defined by The National Institute for Occupational Safety and Health.[40,41,43] One identified study reported exposure to MF in ambulance personnel.[44]

3.5.3 | Cost

Smith et al. analyzed the cost of a single dose per patient of the four substances in their study.[27] This included expenses for the necessary equipment in the estimate. The estimates per dose per patient were as follows: inhaled N_2O British pounds (GBP) 6.60; IV morphine GBP 7.70; IV paracetamol GBP 7.87; inhaled MF GBP 18.89.

4 | DISCUSSION

We included seven reports of various study designs comparing MF or N_2O to other drugs or placebo suggesting that both MF and N_2O are safe and may have a role in the management of pain in the prehospital setting. The certainty of the evidence was rated as low to very low. We found no evidence of serious AEs. However, some report a rather large proportion of milder AEs. There may be occupational health issues regarding the prehospital use of N_2O.

4.1 | Nitrous oxide

We identified only one eligible study comparing N_2O to placebo.[11] The pain reduction achieved was moderate, clinically important and in accordance with previous in-hospital studies.[45–47] The reported proportion of AEs during N_2O administration varies considerably from low to substantial. Faddy et al. investigated the safety profile of N_2O reported in in-hospital studies.[48] They found no significant difference in risk of AEs when comparing N_2O with placebo. The apparent differences in our findings may be due to different definitions and registrations. However, we cannot exclude the possibility that receiving N_2O in a moving ambulance may enhance the risk of nausea.

4.2 | Methoxyflurane

MF appears to have a rapid onset of action compared to IV-administered analgesics.[24] This may be because time spent on a

TABLE 1 Characteristics of included studies.

Author (reference) year	Study design	Setting	Comparison(s)	Outcome measures
Braybrook et al.[25] 2023	Retrospective cohort (n = 536; MF = 130, IV fentanyl 77, IN fentanyl 12, PO paracetamol 28)	Australia. EMS; mountain bikers and hikers	MF vs. IV fentanyl, IN fentanyl, PO paracetamol	• Median pain reduction (VNRS; %; IQR) • Meaningful pain reduction (MPR; ≥25% from the initial pain score)
Ducassé et al.[11] 2013	Randomized, double-blind, multicenter (n = 60, 30 in each group)	France. Advanced EMS responders; trauma patients, moderate pain (NRS 4–6)	N_2O vs. placebo, medical air	• Proportion of patients with NRS <3 at 15 min • AE
Johnston et al.[26] 2011	Retrospective observational chart review of randomly selected cases (n = 1024)	Australia. EMS paramedics; patients in visceral pain, i.e., abdominal-, renal-, or cardiac pain	MF vs. IN fentanyl, or in combination	Pain reduction (VAS) at 5 min and on arrival at hospital
Lim et al.[23] 2020	Prospective, randomized, non-blinded cross-over study (n = 343)	Singapore. EMS providers; patients in musculoskeletal pain, NRS ≥3	MF vs. IM tramadol	Proportion of NRS reduction ≥3 at 5, 10, 15, 20, and >20 min
Mercadante et al.[24] 2019	Randomized, open-label multicenter study (n = 270)	Italy. EMS providers; patients in moderate (NRS 4–6) or severe pain (NRS ≥7)	MF vs. IV morphine in severe pain; MF vs. IV paracetamol or IV ketoprofen in moderate pain	Change in pain score (VAS 0–100) at 3, 5, and 10 min
Middleton et al.[14] 2010	Retrospective observational registry review (n = 52,046)	Australia. EMS paramedics; patients in any moderate or severe pain (NRS ≥5)	MF vs. IN fentanyl vs. IV morphine	Reduction in initial pain score of ≥30%
Smith et al.[27] 2022	Prospective, non-randomized observational study (n = 2256)	England. EMS providers; trauma patients in moderate (VNPS 4–6) or severe (7–10) pain	N_2O vs. IV morphine vs. IV paracetamol	• Pain (VNPS) at 0 and 30 min • Time to VNPS ≤5 • Time to least pain • Cost

Abbreviations: AE, adverse event; IM, intramuscular; IN, intranasal; IV, intravenous; n, number of patients enrolled; N_2O, N_2O and O_2 (50%–50%); NRS, Numeric Rating Scale (0–10); PO, per os, oral; VAS, Verbal Analogue Scale (0–10); VAS (0–100), Visual Analogue Scale (0–100); VNPS, Verbal Numerical Pain Score (0–10).

TABLE 2 Results, different comparisons.

Comparison Study (reference)	Outcome measures	Result	Certainty of the evidence (GRADE)[a]	Comment
N_2O vs. placebo (medical air; MA)				
Ducassé et al.[11]	Proportion of patients with NRS <3 at 15 min	N_2O: 67%, MA: 23%, Δ = 40% (95% CI = 17%–63%) RR = 2.50 (95% CI 1.31–4.77) in favor of N_2O	⊕⊕◯◯ Low	
	AE	All AE pooled: N_2O: 1/30, MA: 3/30 RR 29.0 (95% CI = 1.77–475.35) in favor of MA	⊕⊕◯◯ Low	AE: nausea
N_2O vs. IV paracetamol				
Smith et al.[27]	Pain reduction (VNPS) after 30 min	Mean difference −0.20 (95% CI = −0.60 to 0.20) inconclusive	⊕◯◯◯ Very low	MD calculated from data in the publication
	AE	Not reported		
N_2O vs. IV morphine				
Smith et al.[27]	Pain reduction (VNPS) after 30 min	Mean difference 1.10 (95% CI = 0.80–1.40) in favor of IV morphine	⊕◯◯◯ Very low	MD calculated from data in the publication
	AE	Not reported		
N_2O vs. MF				
Smith et al.[27]	Pain reduction (VNPS) after 30 min	Mean difference 2.00 (95% CI = 1.62–2.38) in favor of MF	⊕◯◯◯ Very low	
	Estimated duration in severe pain (VNPS >5)	MF: 10.54 min (95% CI = 9.16–11.91) N_2O: predicted that VNPS ≤5 would not be reached	⊕◯◯◯ Very low	
	Time to least pain	MF: 26.94 min (95% CI = 25.50–28.38) N_2O: 44.96 min (95% CI = 40.07–49.84)	⊕◯◯◯ Very low	
	AE	MF: mild to moderate in 32/429 (6.7%) patient MF episodes N_2O: not reported	⊕◯◯◯ Very low	AE: Cough, dizziness, drowsiness, dry mouth, feeling abnormal, headache, altered mood, nausea, altered taste, anxiety, oral discomfort, paresthesia
MF vs. standard analgesic treatment (SAT; IV paracetamol or IV ketoprofen)				
Mercadante et al.[24]	VAS (0–100) reduction at 3 min	Mean difference 3.62 (95% CI 0.75, 6.49) in favor of MF	⊕⊕◯◯ Low	
	VAS (0–100) reduction at 5 min	Mean difference 5.74 (95% CI = 1.79–9.69) in favor of MF	⊕⊕◯◯ Low	
	VAS (0–100) reduction at 10 min	Mean difference 8.53 (95% CI = 3.86–13.20) in favor of MF	⊕⊕◯◯ Low	
	AE	RR 5.75 (95% CI = 2.04–16.18) in favor of SAT	⊕◯◯◯ Very low	AE: Euphoric mood, somnolence, nausea, feeling abnormal, pyrexia, vertigo, presyncope, bronchitis, diplopia, dizziness, feeling drunk, headache, oral discomfort, sedation

TABLE 2 (Continued)

Comparison Study (reference)	Outcome measures	Result	Certainty of the evidence (GRADE)[a]	Comment
MF vs. IV paracetamol				
Smith et al.[27]	VNPS reduction at 30 min	Mean difference 1.80 (95% CI = 1.56–20.4) in favor of MF	⊕◯◯◯ Very low	
	Estimated duration in severe pain (VNPS >5)	MF: 9.66 min (95% CI = 8.32–11.00) Paracetamol: 37.53 min (95% CI = 24.64–50.42)	⊕◯◯◯ Very low	
	Time to least pain	MF: 27.07 min (95% CI = 25.58–28.55) Paracetamol: 45.77 min (95% CI = 39.67–51.87)	⊕◯◯◯ Very low	
	AE	MF: mild to moderate in 32/429 (6.7%) patient MF episodes Paracetamol: not reported	⊕◯◯◯ Very low	AE: Cough, dizziness, drowsiness, dry mouth, feeling abnormal, headache, altered mood, nausea, altered taste, anxiety, oral discomfort, paresthesia
MF vs. PO paracetamol				
Braybrook et al.[25]	Median pain reduction (MPR)	MF: 25% (IQR 0–50); PO paracetamol: 0% (IQR 0–43)[a]	⊕◯◯◯ Very low	
	Meaningful pain reduction (MPR)	RR 1.44 (95% CI = 0.85–2.44) inconclusive	⊕◯◯◯ Very low	
	AE	Not reported		
MF vs. IM tramadol				
Lim et al.[23]	Proportion of NRS reduction ≥3 at 5 min	RR 1.98 (95% CI = 1.39–2.84) in favor of MF	⊕⊕◯◯ Low	
	Proportion of NRS reduction ≥3 at 10 min	RR 2.34 (95% CI = 1.10–5.00) in favor of MF	⊕⊕◯◯ Low	
	Proportion of NRS reduction ≥3 at 15 min	RR 1.76 (95% CI = 0.43–7.23) inconclusive	⊕⊕◯◯ Low	
	Proportion of NRS reduction ≥3 at 20 min	RR 0.12 (95% CI = 0.01–2.16) inconclusive	⊕⊕◯◯ Low	
	Proportion of NRS reduction ≥3 at >20 min	RR 0.65 (95% CI = 0.54–0.79) in favor of tramadol	⊕⊕◯◯ Low	
	AE	MF: 74/167 (44.3%) Tramadol: 11/176 RR 7.09 (95% CI = 3.90–12.88) in favor of tramadol	⊕⊕◯◯ Low	MF: Nausea and vomiting, drowsiness and dizziness, headache, throat irritation and cough
MF vs. IV morphine				
Middleton et al.[14]	Proportion of patients with ≥30% pain reduction	OR 0.31 (95% CI = 0.29–0.33) in favor of morphine	⊕⊕◯◯ Low	
	AE	Not reported		

(Continues)

TABLE 2 (Continued)

Comparison Study (reference)	Outcome measures	Result	Certainty of the evidence (GRADE)[a]	Comment
Mercadante et al.[24]	Pain reduction at 3 min	Mean difference 3.73 (95% CI = 0.08–7.38) in favor of MF	⊕⊕◯◯ Low	Scale: VAS (0–100)
	Pain reduction at 5 min	Mean difference 8.63 (95% CI = 3.10–14.16) in favor of MF	⊕⊕◯◯ Low	Scale: VAS (0–100)
	Pain reduction at 10 min	Mean difference 4.25 (95% CI = −2.91 to 11.41) no difference	⊕⊕◯◯ Low	Scale: VAS (0–100)
	AE	RR 5.75 (95% CI = 2.04–6.18) in favor of morphine/standard analgesics treatment	⊕◯◯◯ Very low	AE: Euphoric mood, somnolence, nausea, feeling abnormal, pyrexia, vertigo, presyncope, bronchitis, diplopia, dizziness, feeling drunk, headache, oral discomfort, sedation
Smith et al.[27]	VNPS reduction at 30 min	Mean difference 0.90 (95% CI = 0.53–1.27) in favor of MF	⊕◯◯◯ Very low	
	AE	6.7% of cases in MF group, not reported for IV morphine	⊕◯◯◯ Very low	AE: Cough, dizziness, drowsiness, dry mouth, feeling abnormal, headache, altered mood, nausea, altered taste, anxiety, oral discomfort, paresthesia
MF vs. IN fentanyl				
Middleton et al.[14]	Proportion of patients with ≥30% pain reduction	Adjusted OR 0.36 (95% CI = 0.33–0.39) in favor of IN fentanyl	⊕◯◯◯ Very low	
	AE	Not reported		
Johnston et al.[26]	Pain reduction at 5 min	Mean difference −0.40 (95% CI = −0.68 to −0.12) in favor of MF	⊕◯◯◯ Very low	
	Pain reduction at arrival at hospital	Mean difference 0.70 (95% CI = 0.20–1.20) in favor of IN fentanyl	⊕◯◯◯ Very low	
	AE	Not reported		
Braybrook et al.[25]	Median pain reduction (%; IQR)	MF: 25 (0–50); IN fentanyl 28 (10–62)	⊕◯◯◯ Very low	Does not compare the different analgesics; 95% CI or *p* values not reported
	Meaningful pain reduction (MPR)	RR 1.03 (95% CI = 0.57–1.86) inconclusive	⊕◯◯◯ Very low	
	AE	Not reported		
MF vs. IV fentanyl				
Braybrook et al.[25]	Median pain reduction (%; IQR)	MF: 25 (0–50); IV fentanyl 50 (29–63)[a]	⊕◯◯◯ Very low	
	Meaningful pain reduction (MPR)	RR 0.64 (95% CI = 0.52–0.78) in favor of IV fentanyl	⊕◯◯◯ Very low	
	AE	Not reported		

Abbreviations: Δ, Difference; 95% CI, 95% confidence interval; IQR, interquartile range; MA, medical air; MD, mean difference; N_2O, N_2O and O_2 (50%–50%); NRS, Numeric Rating Scale (0–10); OR, odds ratio; RR, relative risk; VAS, Verbal Analogue Scale (0–10); VAS (0–100), Visual Analog Scale (0–100); VNPS, Verbal Numerical Pain Score (0–10).

[a]Full GRADE summary of findings table in Supporting Information.

TABLE 3 AE reported in N_2O or MF studies without a comparison.

Study (reference)	Number of patients	AE (%) all pooled	AE types
N_2O			
Andolfatto et al.[28]	60	20.0	Feeling of unreality, dizziness, nausea, fatigue, general discomfort, mood, change, hallucination, headache
Baskett[10]	305	21.0	Nausea, drowsiness, amnesia
Donen et al.[30]	240	68.1	Drowsiness, dizziness, vertigo, nausea, numbness, headache, amnesia
Johnson et al.[32]	200	15.5	Dizziness, nausea, drowsiness, lightheadedness
McKinnon[33]	72	90.3	Drowsiness, giddiness, nausea, amnesia, sleep
Peterson et al.[34]	Not reported	54.0	Lightheadedness, numbness, dizziness, slurred, speech, drowsiness, nausea, confusion
Stewart et al.[35]	1201	20.6	Dizziness, lightheadedness, nausea, vomiting excitement, numbness
Thal et al.[36]	47	23.4	Lightheadedness, drowsiness, nausea, vomiting
Wigley[37]	113	8.8	Nausea, vomiting
Wright et al.[38]	94	58.5	Lowering of consciousness level, vomiting, drowsiness, dryness of mouth, nausea
MF			
Buntine et al.[29]	83	10.8	Nausea, euphoria, dizziness, headache, hallucinations, sore throat, lip paresthesia
Johansson et al.[31]	32	15.6	Nausea
Trimmel et al.[13]	109	59.6	Dizziness, confusion, feeling drunk, disgusting taste, sedation, nausea

Abbreviations: AE, adverse event; MF, methoxyflurane; N_2O, N_2O and O_2 (50%–50%).

primary IV access is omitted. However, the effect of IV-administered analgesics may be more long-lasting.[14,23,24,26] One of the studies reported a maximum OR for reduction of pain (VAS) as 8.5 versus the comparator,[24] representing an NRS reduction of 0.85.

Lim et al. found that at 20 min, none of the patients given MF experienced a pain reduction of NRS ≥3, whereas at over 20 min, the corresponding proportion was 47%.[23] This may be due to a second dose of MF.

An in-hospital RCT published by Coffey et al. found that MF may be "an efficacious, safe, and rapidly acting analgesic" for the treatment of acute pain in an emergency department.[49] The in- and prehospital populations may experience different AEs—nausea and dizziness—due to motion during evacuation and transport. To our knowledge, no study has systematically compared the in-hospital AE to those identified prehospital.

In a recently published review, Fabbri et al. concluded that MF had advantages compared to standard-of-care analgesics.[50] The included studies were not solely prehospital, and the findings may not be transferable. The authors conducted neither RoB nor GRADE assessments. In addition, three of the authors were employees of a retailer of MF. Acknowledging these limitations, their findings were in accordance with ours.

We did not identify any serious AE or safety issues related to MF. Middleton et al. do not report AE but state that "methoxyflurane is associated with few AE in the prehospital setting."[14] In a systematic review, Allison et al. found that MF seemingly gives only mild to moderate AEs. In addition, the concentration of MF in the working environment seems acceptable. However, these authors find it remarkable that there are no set limits for occupational exposure to MF in several countries.[51]

Based on our findings, MF may have a role in prehospital management of moderate to severe pain, including as a bridge to IV access and administration of longer-lasting analgesics. A barrier to utilization may be the relatively high cost of MF, a price almost double that of IV morphine and IV paracetamol.[27,52]

4.3 | Limitations and discussion of methods

The PROSPERO protocol covers all systematic reviews from our group pertaining to acute prehospital pain management. Safety issues related to occupational health are not applicable to other reviews than the present. Hence, this study diverges from the protocol in this aspect.

We have restricted our inclusion to studies performed in the prehospital setting. Arguably, the same agents should have similar effects across settings. However, EMS healthcare providers may differ from in-hospital providers in education and numbers; the time constraint is often more accentuated, most patients do not have an IV access on arrival, and the motion during extraction may be considerably larger accentuating, for example, fracture pain. Furthermore, motion during transport may lower the threshold for opioid-induced motion sickness.[53] This might also be the case for N_2O and MF.

We further restricted inclusion to adults across all our systematic reviews as we assumed there would be few valid pediatric studies. However, the alleviation of pain may be even more relevant in pediatric prehospital care. Children may suffer more and longer due to problems with IV access due to pain and lack of cooperation. Abebe et al. recently published a systematic review filling this gap. They concluded that IN fentanyl and MF seem to be preferred agents.[54]

The strength of this current systematic review lies in the rigorous and transparent methodology, including the systematic and broad literature search and independent duplication of all steps.

4.4 | General discussion

Non-pharmacological pain management should be the foundation for treatment of all patients in pain, including stabilization and reduction of fractures.

Berben et al. highlight the problem of having only a fraction of patients assessed systematically with an objective scale, for example, NRS or VAS.[8] All EMS services should collect and report pain assessments to help providers focus on the alleviation of pain and to continuously monitor the adequacy of pain treatment.

The feasibility of using inhaled analgesics and especially MF may improve prehospital pain treatment. Further, inhaled analgesics may be utilized as a bridge to IV access and further analgesia with other modalities. MF may also be used in remote settings.

There is an international drive to reduce greenhouse gas emissions, including N_2O and anesthetic gasses.[55,56] Hence, there may be environmental issues associated with both agents.

There were few studies identified and the supporting evidence is weak. However, the research interest in the field seems to be growing, and one RCT is ongoing.[57] Hopefully, there will be more studies in the future, both RCTs and well-designed prospective observational studies depicting both effect and safety of inhaled analgesics.

A multitude of outcome measures makes it difficult to compare results across studies. A core outcome set should be established,[58] and a universal dataset for prehospital pain research is called for.

5 | CONCLUSION

In this systematic review, we found low-quality evidence suggesting that both MF and N_2O are safe and may have a role in the management of pain in the prehospital setting. There is low-quality evidence to support MF as a short-acting single analgesic or as a bridge to IV access and the administration of other analgesics. There may be occupational health issues regarding the prehospital use of N_2O.

AUTHOR CONTRIBUTIONS

All authors have been part of the identification of the PICO question and read the submitted manuscript and the revision thereof. PKH has been leading the process, conducted the literature searches, screened and excluded/included publications, performed RoB and GRADE evaluation and drafted the manuscript and conducted the revisions. MR has screened and excluded/included publications, performed RoB and GRADE evaluation and co-authored the manuscript. KDF has screened and excluded/included publications and co-authored the manuscript. LRo has screened and excluded/included publications and co-authored the manuscript. LRa has co-authored the manuscript. JK has co-authored the manuscript. RL has co-authored the manuscript. PK has co-authored the manuscript. MS has co-authored the manuscript. VM has co-authored the manuscript. GEV has been the group's methods expert, assisting in all questions regarding method and co-authored the manuscript.

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DATA AVAILABILITY STATEMENT

All data are extracted from the included publications. Hence, a data repository does not exist.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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