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CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Methoxyflurane in Pre-Hospital Settings: A Review of Clinical Effectiveness, Cost-Effectiveness and Guidelines

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	November 9, 2018
Report Length:	16 Pages

CADTH

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Cite As: Methoxyflurane in Pre-Hospital Settings: A Review of Clinical Effectiveness, Cost-Effectiveness and Guidelines. Ottawa: CADTH; 2018 Nov. (CADTH rapid response report: summary with critical appraisal).

ISSN: 1922-8147 (online)

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Context and Policy Issues

Methoxyflurane (Penthrox) was approved by Health Canada in April 2018 as short-term relief of moderate to severe pain associated with trauma or interventional procedures.[1,2] It is an inhaled analgesic that has a quick onset of action, providing immediate pain relief.[3] It is supplied as a 3 mL bottle solution of 99.9% methoxyflurane liquid and patients may inhale up to two bottles in a single administration.[2]

Methoxyflurane is relatively safe and changes in vital signs following methoxyflurane administration, such as heart rate, blood pressure, and respiratory rate, are usually associated with pain relief; therefore, its use would not affect patient examination.[3]

The Canadian Agency for Drugs and Technologies in Health (CADTH) previously reviewed the clinical effectiveness, cost-effectiveness, and evidence-based guidelines for the use of low-dose methoxyflurane for acute pain in the emergency department.[4] One randomized controlled trial was identified in the emergency setting for the use of methoxyflurane in patients with moderate to severe pain and demonstrated it is effective compared to placebo.[4] Given the ease of administration of inhaled methoxyflurane, a review of appropriate use in a pre-hospital setting to provide quick pain relief to patients is needed.

The objective of this review is to evaluate the clinical effectiveness, cost-effectiveness, and evidence-based guidelines for the use of low-dose methoxyflurane for the management of moderate to severe pain associated with trauma or procedures in the pre-hospital setting.

Research Questions

1. What is the clinical effectiveness of methoxyflurane for the management of moderate to severe pain associated with acute trauma and/or procedural pain in pre-hospital settings?
2. What is the cost-effectiveness of methoxyflurane for the management of moderate to severe pain associated with acute trauma and/or procedural pain in pre-hospital settings?
3. What are guidelines informing the use of methoxyflurane for the management of moderate to severe pain associated with acute trauma and/or procedural pain in pre-hospital settings?

Key Findings

Two systematic reviews were identified regarding the use of inhaled methoxyflurane as an analgesia for pain in the pre-hospital setting; however, neither of the systematic reviews provided a summary statistic, thus it is difficult to determine the magnitude of benefits of this agent in this particular population. Two primary studies were identified, both of which were retrospective observational studies. One was a safety study and inhaled methoxyflurane appeared to be safe and well tolerated. The other study suggested it was less effective for pain relief in this setting when compared to intravenous morphine or intranasal fentanyl.

No relevant cost-effectiveness studies or evidence-based guidelines were identified for the use of methoxyflurane for the management of moderate to severe pain associated with

acute trauma and/or procedureal pain in pre-hospital setting; therefore, no conclusions can be made.

Given the limited availability and low quality of evidence, the effectiveness and use of inhaled methoxyflurane in the pre-hospital setting remains uncertain.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including Ovid Medline, Embase, PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases and a focused Internet search. No methodological filters were applied to limit retrieval by publication type. The search was limited to English language documents published between January 1, 2008 and October 10, 2018.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult patients (i.e., ages ≥18 years) with moderate to severe acute trauma and/or procedural pain in pre-hospital settings (exclusions will include obstetric, inpatient usage and/or indications other than trauma/procedural)
Intervention	Low-dose, inhaled methoxyflurane (marketed in Canada as Penthrox) used as monotherapy or in combination with other analgesics
Comparator	Inhaled nitrous oxide [N_2O 50:50 with oxygen (marketed as Entonox)]; ketamine; oral or injectable analgesics; oral or injectable sedatives; placebo
Outcomes	Q1: Clinical effectiveness i.e., benefit (e.g., reduction in pain; use of rescue medication; reduction in analgesics/sedative use; reduced time to onset of analgesia) and/or harm (e.g., potential for misuse/abuse and/or diversion; safety) Q2: Cost-effectiveness Q3: Evidence-based guidelines and/or recommendations
Study Designs	Systematic reviews, meta-analyses, randomized controlled trials, economic evaluations, non-randomized studies, guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2008. Guidelines with unclear methodology and conference abstracts were also excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using the AMSTAR 2 tool[5] and non-randomized studies were critically appraised using the Downs and Black checklist.[6] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

Summary of Evidence

Quantity of Research Available

A total of 168 citations were identified in the literature search. Following screening of titles and abstracts, 146 citations were excluded and 22 potentially relevant reports from the electronic search were retrieved for full-text review. 17 potentially relevant publications were retrieved from the grey literature search for full text review. Of these potentially relevant articles, 35 publications were excluded for various reasons, and four publications met the inclusion criteria and were included in this report. These comprised two systematic reviews and two non-randomized studies. Appendix 1 presents the PRISMA[7] flowchart of the study selection.

Summary of Study Characteristics

Additional details for each individual study are presented in Appendix 2.

Study Design

Two systematic reviews evaluated the use of methoxyflurane in a pre-hospital setting and were published in 2017[8] and 2010.[9] One systematic review included five studies, two of which were reviews of literature, one placebo controlled trial and retrospective observational trial.[8] The other systematic review included 21 studies, one of which, a prospective observational study, evaluated the use of methoxyflurane in the pre-hospital setting.[9] Between the two systematic reviews, the literature searches covered from 1946 to September 2016.[8,9]

Two relevant primary studies were identified from the literature search.[10,11] Both were retrospective cohort studies and were published in 2010.[10,11] One study evaluated the safety of methoxyflurane by evaluating the composite outcome of hospital admission and death.[10] Middleton et al. conducted a retrospective comparative study assessing effective analgesia, which was defined as pain reduction of at least 30% of initial pain score.[11]

Country of Origin

The investigators of both of the systematic reviews were from United Kingdom.[8,9] The two non-randomized studies were from Australia.[10,11]

Patient Population

In one of systematic reviews, adult patients with pain associated with trauma who were treated by the Search and Rescue Helicopter were included.[8] The second systematic review included patients who needed pain relief in the pre-hospital setting and excluded studies that did not include numerical values.[9]

One of the primary clinical studies included patients who were serviced by the Western Australian Ambulance Service and were transported by an ambulance to the hospital between 1990 to 2000.[10] Middleton et al. included patients aged 16 to 100 who have moderate to severe pain and were treated by paramedics from the Ambulance Service of New South Wales.[11]

Interventions and Comparators

One of the systematic reviews included studies that compared methoyxflurane to placebo[8] while the other systematic reviewed included all studies that included pain relief for pre-

hospital settings; however, the study of interest that was included assessed methoxyflurane for pain relief.[9]

In the study by Jacobs et al., patients who received methoxyflurane 0.3% were compared to those who did not receive methoxyflurane.[10] The other primary study compared patients who received methoxyflurane 0.2% to 0.4% administered with a handheld inhaler to those who received intravenous morphine or intranasal fentanyl.[11] The intravenous morphine was dosed initially at 5 mg and then followed by 2.5 to 5.0 mg every two minutes as needed with a maximum of 0.5 mg/kg.[11] The intranasal fentanyl was initially dosed at 900 mcg and then followed by 60 to 120 mcg every five minutes as needed with no maximum.[11]

Outcomes

The outcomes that were considered by the systematic reviews include the following: visual analogue pain score,[8,9] adverse events[8,9], occupational safety,[8] onset of action[9], ventilation[9], and sedation.[9]

Jacobs et al. conducted a safety study and evaluated a composite outcome of hospital admission and death[10] with a minimum follow-up of four years and up to 14 years while the primary outcome for the other primary study was whether or not effective analgesia was achieved which was defined to be a pain reduction of at least 30% from initial pain.[11]

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Systematic Reviews

Both of the systematic reviews were designed a priori; however, neither had duplicate study selection and extraction.[8,9] Both of them had a comprehensive literature search including grey literature and a full list of included articles was provided but not the articles that were excluded.[8,9] The characteristics of the included studies were provided for both systematic reviews.[8,9] The quality of the included studies was included in the systematic review by Griffiths et al.[8] and not in the one by Park et al.[9] making it difficult to assess whether or not the conclusion was formulated appropriately. The method to combine the findings for the both systematic reviews seemed reasonable. [8,9] Only one of the studies assessed the likelihood of publication bias[8] while it was not done in the other systematic review.[9] Conflict of interest was included in both systematic reviews.[8,9] There are limitations with the methodology of these systematic reviews which may limit the certainty of the results and findings.

Primary Studies

Both of the included primary studies were retrospective comparative studies and are non-randomized trials that can introduce systematic bias that may overestimate the magnitude of the benefits and reduce the certainty of the outcome. [10,11] The objectives and outcomes of interest was clearly described in the study. [10,11] Large sample size was included in both studies;[10,11] however, one study included patients with varying types in pain including trauma, acute, abdominal pain, inflammatory musculoskeletal pain, cardiac pain and renal colic[10] while the other study had a lot of missing data and was only able to include 42% of the population of interest.[11] There was no age restriction on the patients for one of the studies.[10] The dose for methoxyflurane is unclear for both studies.[10,11] The statistics and analyses appear to be appropriate for both studies.[10,11] Although the conflict of interest was

provided for one of the studies,[10] the study was funded by the manufacturers of methoxyflurane but they were not involved in the design, analysis, interpretation of results nor preparation of the study.[10] No declaration of conflict of interest was provided for the other primary study.[11]

Summary of Findings

Appendix 4 presents further detail regarding main study findings and authors' conclusions.

Clinical Effectiveness of Methoxyflurane

No summary statistic was provided for one of the systematic reviews but based on the included studies, methoxyflurane was found to provide pain relief in the pre-hospital setting with minimal adverse effects and no concerns for occupational exposure.[8] In another systematic review, the use of methoxyflurane provided pain relief based on pain scores and at 20 minutes, the mean pain score was 33/100.[9] Methoxyflurane was well tolerated and the most common adverse events included increased sedation, nausea, euphoria, dizziness, headache, hallucination, sore throat, and lip paraesthesia.[9] Based on the available evidence, methoxyflurane does appear to be effective and safe as an analgesic option for patients with pain in a pre-hospital setting.[8-11] However, it is worth noting that this is based on low quality evidence and more well-designed randomized controlled trials would provide more high quality evidence regarding the use of methoxyflurane.

As for a composite outcome of death and hospitalizations, the observational study did not demonstrate any increase in risk.[10] One observational study demonstrated that intravenous morphine, intranasal fentanyl, and inhaled methoxyflurane were all associated with effective analgesia, as defined by a 30% reduction from initial pain, in 81.8%, 80.0%, and 59.1% of patients respectively.[11] This indicates that intravenous morphine is the most effective and the adjusted odds ratio compared with morphine is 0.86 (95% CI 0.78 to 0.94) and 0.31 (95% CI 0.29 to 0.33) for intranasal fentanyl and inhaled methoxyflurane respectively.[11]

Cost-Effectiveness of Methoxyflurane

No studies were identified regarding the cost-effectiveness of methoxyflurane for patients in a pre-hospital setting; therefore, no summary can be provided.

Guidelines

No evidence-based guidelines were identified regarding the use of methoxyflurane for patients in a pre-hospital setting.

Limitations

Although the methods of the systematic reviews were well described, there is a paucity of high quality evidence for the use of inhaled methoxyflurane in the pre-hospital setting. In addition, the systematic reviews did not provide a summary statistic, making it difficult to know the magnitude of benefit with the use of inhaled methoxyflurane for pain relief. The authors of both systematic reviews have identified the limited evidence and call for further research in this area. [8,9]

One of the major limitations for one of the primary studies is that it was funded by the manufacturers of methoxyflurane.[10] In addition, both of these studies are retrospective observational studies and no randomized controlled trial was identified for this setting.[10,11]

Without randomized controlled trials, it is difficult to be certain of the true effects and the magnitude of benefit of methoxyflurane for the management of moderate to severe pain in the pre-hospital setting.

Since no relevant cost-effectiveness studies or evidence-based guidelines were identified, there is limited evidence to inform clinical decisions.

Conclusions and Implications for Decision or Policy Making

A total of four relevant studies were identified in the search including two systematic reviews[8,9] and two retrospective studies.[10,11]

The available evidence indicates that inhaled methoxyflurane may be effective for providing analgesia effects for pain associated with trauma in a pre-hospital setting. However, it may not be as effective as other options, including intravenous morphine or intranasal fentanyl. In general, methoxyflurane was found to be well-tolerated, with minimal adverse effects.

No relevant cost-effectiveness studies or evidence-based guidelines were identified. Therefore, no conclusions regarding the cost-effectiveness or recommended use can be provided. The limited evidence indicates that further research comparing inhaled methoxyflurane to other options is needed in the pre-hospital setting in order to determine its place in therapy in this setting.

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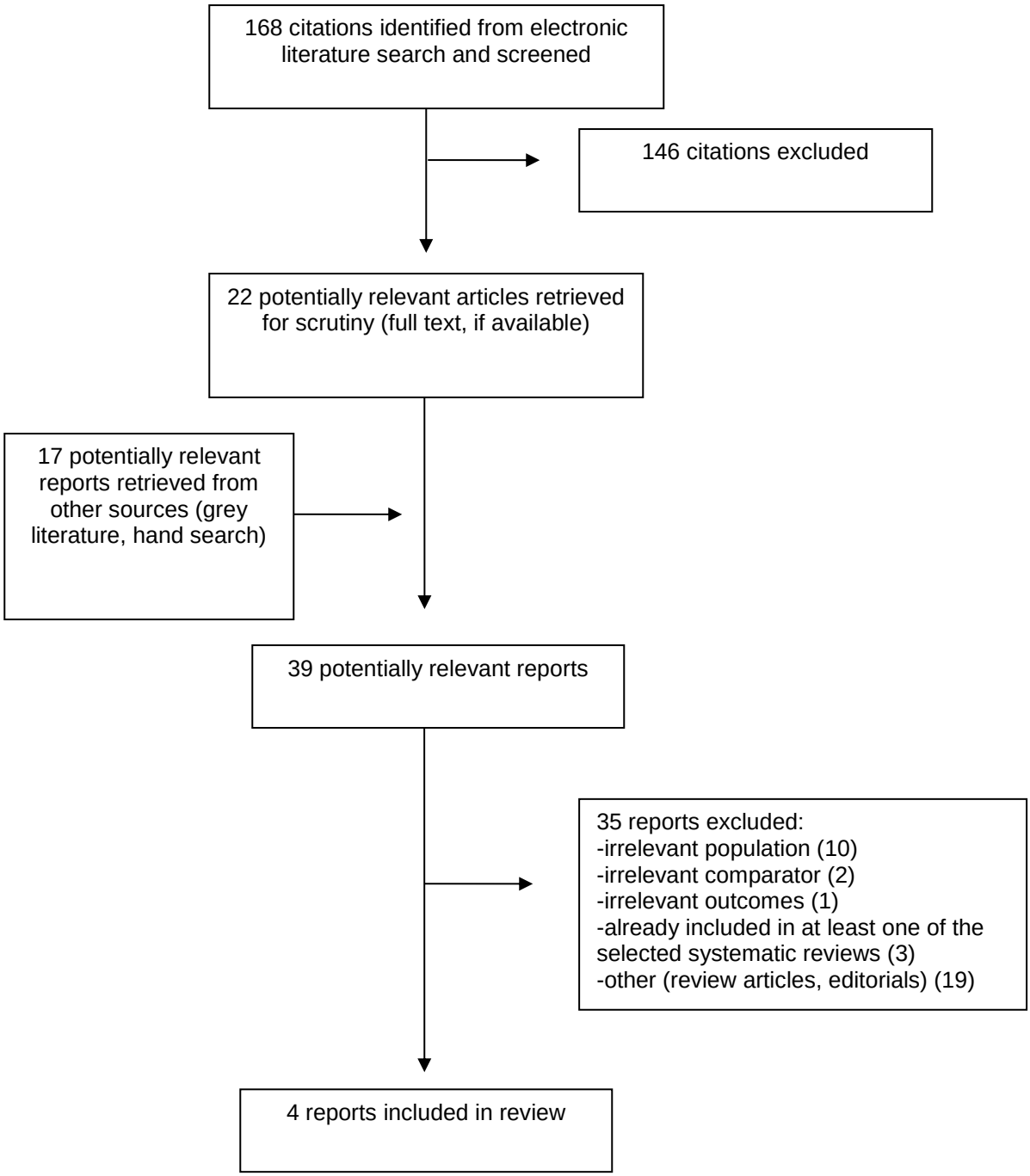
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Griffiths 2017[8] **United Kingdom**	Systematic review of the literature from 2006 to September 2016 5 studies were included: • 2 reviews of literature including one systematic review of the literature and one electronic database search with set inclusion/exclusion criteria • 1 double blinded, multicenter, placebo controlled trial (N = 204) • 2 retrospective non-randomized, non-blinded observational study (N = 83 and N = 19235)	Pain associated with trauma in adults	Methoxyflurane Placebo	Visual analogue pain score, adverse events, occupational safety
Park 2010[9] **United Kingdom**	Systematic review of the literature;1946 to November 2009 Any study, of any design, including efficacy or adverse events of pre-hospital analgesia in adults were included up to November 2009 21 studies were included, 1 specifically for methoxyflurane – a prospective observational study of 83 patients	Patients needing pre-hospital pain relief 83 patients	methoxyflurane	Analgesia, onset of action, ventilation, sedation, adverse events Up to 20 minutes post administration

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Jacobs 2010[10] **Australia**	retrospective cohort of patients from 1990 to 2000	• Patients who were serviced by the Western Australian Ambulance Service and transported by ambulance to hospital from 1990 to 2000 with follow-up to December 31, 2004 • patients who received methoxyflurane compared with those who did not receive methoxyflurane	• intervention: methoxyflurane (0.3%) • comparator: did not receive methoxyflurane	Composite outcome: hospital admission or death Follow-up: minimum 4 years up to 14 years
Middleton 2010[11] **Australia**	Retrospective comparative study from January 1, 2004 to November 30, 2006	Adults • age 16 to 100 inclusively • moderate to severe pain • treated by paramedics from the Ambulance Service of New South Wales	Intervention: inhaled methoxyflurane with a concentration of 0.2% to 0.4% was administered with a handheld inhaler Comparators: • Intravenous morphine dosed at 5 mg initially, followed by 2.5 to 5.0 mg every 2 minutes as needed up to a maximum of 0.5 mg/kg • Intranasal fentanyl dosed at 900 mcg, followed by 60 to 120 mcg, every 5 minutes (no maximum)	Primary outcome: effective analgesia defined as a reduction in initial pain score of ≥ 30%

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[5]

AMSTAR Item		Griffiths et al. 2017[8]	Park et al., 2010[9]
Was an a priori design provided?		+	+
Was there duplicate study selection and data extraction?	Selection	X	X
	Extraction	X	X
Was a comprehensive literature search performed?		+	+
Was the status of publication (i.e. grey literature) used as an inclusion criteria?		+	+
Was a list of studies (included and excluded) provided?	Included	+	+
	Excluded	X	X
Were the characteristics of the included studies provided?		+	+
Was the scientific quality of the included studies assessed and documented?		+	X
Was the scientific quality of included studies used appropriately in formulating conclusion?		+	?
Were the methods used to combine the findings of studies appropriate?		+	+
Was the likelihood of publication bias assessed?		+	X
Was conflict of interest included?		+	+

Legend: + = Yes, X = No, ? = Unclear

Table 5: Strengths and Limitations of Clinical Studies using Downs and Black[6]

Strengths	Limitations
Jacobs, 2010[10]	
• Objectives and outcomes of interest were clearly stated. • Large, population based study. • Comparative study with those who did not receive the drug. • Long duration of follow-up to evaluate potential long-term outcomes (up to 14 years). • Methods were clearly described. • Statistics and analyses appear to be appropriate for this type of population study. • Conflicts of interest declared and although the manufacturers of methoxyflurane funded the study, they had no input into the design, analysis, and interpretation of results or preparation of the publication.	• Retrospective comparative study. • Non-randomized study, it can introduce bias. • Some data is missing. Data inaccuracies may also influence the outcome of this study. • Patients who were not admitted to hospital were excluded as data would not have been available for them. • Included patients of different types of pain (trauma, acute abdominal pain, inflammatory musculoskeletal pain, cardiac pain and renal colic. • No restriction on the age of the patients. • Not able to assess the actual dose of methoxyflurane. • Only descriptive results were provided in text. • Funded by the manufacturers of methoxyflurane in Australia.
Middleton, 2010[11]	
• Clearly stated the objectives and the outcomes of interest for the study. • The intervention and comparators were clearly described. • Large sample size • Comparative (active placebo) study • Patients included were appropriate for the study question. • Numeric pain scale is reasonable for evaluating pain outcomes. • Analyses and statistics appear to be appropriate for the study type. • Results were clearly described in the text and also presented clearly in the tables.	• Retrospective comparative review • Non-randomized study, it can introduce bias • Effective analgesia is arbitrarily defined • Lots of missing data, 100,000 eligible cases but pain scores was only recorded for 55,666 patients (only 42% were included) • Dose of analgesia given is not known • Considered combination use of analgesic medications but did not include what the combination was • Not possible to determine the appropriateness of the analgesic choice • No declaration for conflict of interest.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Griffiths, 2017[8]	
• Five included studies reviewed the efficacy of methoxyflurane: • No summary statistic was provided for the five studies. • All five studies concluded that methoxyflurane could provide analgesic effects. • Some of the studies only provided descriptive benefits of methoxyflurane as an analgesic. • Seven studies were included that evaluated the safety of methoxyflurane: • No summary statistic was provided for the seven studies. • Two of the indicated the adverse events were mild and transient. • Four studies concluded methoxyflurane did not increase the risk of nephrotoxicity. • One study concludes there was no evidence of hepatotoxicity. • One study concluded there were no clinically significant changes for blood pressure and respiratory rate. • One study did not identify any increased likelihood of suffering diseases of interest following the use of methoxyflurane. • Three studies evaluated occupational safety associated with the administration of methoxyflurane. • Two studies concluded there was no causal link between administration of methoxyflurane and occupational health. • One study concluded personnel may experience headaches, nausea, vomiting, and skin irritation if patients use methoxyflurane in the back of an ambulance without a filter.	*"Penthrox appears to be an efficacious and safe analgesic. It overcomes the barriers associated with using traditional analgesics during* [Search and Rescue Helicopter] *SARH missions and would be indicated for a significant number of the casualties rescued by UK* [United Kingdom] *SARH crews. It is currently in use by the Irish CG* [coast guard] *SARH crews and has been administered successfully in Australia millions of times over several decades. It is recommended that the UK SARH paramedic cadre adopts Penthrox into their analgesic formulary. This would enable further trials comparing Penthrox to its comparators in the SARH context."* p. 114[8]
Park, 2010[9]	
• Mean pain scores of 33/100 mm 20 minutes after administration in 83 patients. • Recorded adverse events of methoxyflurane (total 83 patients): 29 experienced increased sedation, 7 experienced nausea, 3 experienced euphoria, 2 experienced dizzy, 1 experienced headache, 1 experienced hallucinations, 1 experienced sore throat and lip paraesthesia	*"There is no obvious guidance from the evidence available. More, better, and better thought out research is needed, and this review suggests some ways in which that could be achieved; publication of surveys and audits of appropriate quality would help. Given the paucity of information and the extreme variation in patients, providers, and environments, the pragmatic advice would be to take heed of the title of Ella Fitzgerald's 1939 song: "T'aint what you do (It's the way that you do it)", and then find ways of doing it better."* p. 299[9]

mm = millimeter

Table 7: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Jacobs, 2010[10]	
• Total cohort consisted of 135,770 patients and 17,629 (13%) received at least one dose methoxyflurane. • In patients that received methoxyflurane, no increased risk was observed.	*"…this study suggests that there is no evidence, that the use of Methoxyflurane in the pre-hospital setting as currently recommended, is associated with an increased likelihood of the Ischaemic Heart Disease, Diabetes, Cancer, Renal or Hepatic disease in patient's receiving this agent."* p. 12[10]
Middleton, 2010[11]	
• N = 42,844 (12,955 for morphine alone, 3,778 for fentanyl alone, 19,235 for methoxyflurane alone, 6,876 for combination) • Median age 51 (interquartile range: 34 to 72) • Percentage of patients achieving effective analgesia (≥30% reduction in initial verbal numeric rating scale): • Morphine: 81.8% • Fentanyl: 80.0% • Methoxyflurane: 59.1% • Combination: 80.0% • Adjust OR (95% CI) for effective analgesia (≥30% reduction in initial verbal numeric rating scale) compared to morphine (reference): • Fentanyl: 0.86 (0.78 to 0.94) • Methoxyflurane: 0.31 (0.29 to 0.33) • Combination: 0.84 (0.78 to 0.91)	*"Inhaled methoxyflurane, IN fentanyl, and IV morphine are all effective analgesic agents in the out-of-hospital setting. Morphine and fentanyl are significantly more effective analgesic agents than methoxyflurane. Morphine appears to be more effective than IN fentanyl; however, the benefit of IV morphine may be offset to some degree by the ability to administer IN fentanyl without the need for IV access. Morphine is the preferred analgesic for adult patients with moderate to severe pain where IV access can be readily achieved."* p. 446[11]

CI = confidence interval; OR = odds ratio