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CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Methoxyflurane for Acute Pain in the Emergency Department: A Review of Clinical Effectiveness, Cost-Effectiveness and Guidelines

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Context and Policy Issues

Methoxyflurane is an analgesic and a muscle relaxant previously used for anesthesia, until its withdrawal and discontinuation due to concerns regarding nephrotoxicity and renal impairment.[1] Methoxyflurane in inhaler form (brand name: Penthrox) was recently approved for marketing authorization by Health Canada for the indication of the short-term relief of moderate to severe acute pain in adult trauma patients.[2,3] Currently, it is also approved for use in Australasia in subanesthetic levels (low-dose) to provide emergency pain relief for trauma-related injuries, and has been used in this setting for the past 30 years.[1,4] It is self-administered through a portable handheld inhaler, wherein the patient inhales 3 mL of vaporized methoxyflurane at either 0.2% to 0.4% concentrations, or 0.5% to 0.7% concentrations when the inhaler air diluter hole is covered.[1]

Minor adverse events can occur with the use of methoxyflurane, such as nausea, dizziness and somnolence.[1] Generally, it appears to have a good safety profile when used at low concentrations.[1] Compared to other analgesics (such as opioids) the positive safety profile and the possibly lower potential for abuse makes methoxyflurane an attractive treatment option for acute pain.[1] Additionally, as intravenous sedation and other analgesics are often costly and labour intensive, a method of analgesia that is lower-cost is of interest.[5] The use of methoxyflurane in the emergency setting is of potential interest to stakeholders.

The aim of this review is to evaluate the clinical effectiveness, cost-effectiveness, and evidence-based guidelines regarding the use of low-dose methoxyflurane for acute pain in the emergency department.

Research Questions

1. What is the clinical effectiveness of methoxyflurane (Penthrox) for moderate to severe acute trauma and/or procedural pain in emergency department patients?
2. What is the cost-effectiveness of methoxyflurane (Penthrox) for moderate to severe acute trauma and/or procedural pain in emergency department patients?
3. What are guidelines informing the use of methoxyflurane (Penthrox) for moderate to severe acute trauma and/or procedural pain in emergency department patients?

Key Findings

One randomized controlled trial was identified regarding the use of methoxyflurane for pain from minor to moderate trauma in the emergency department. Overall, the study was well conducted, with appropriate randomization and blinding, as well as clearly reported inclusion and exclusion criteria, intervention, and comparator. Methoxyflurane was effective for pain relief when compared with placebo, and adverse events were primarily mild and transient. No studies were identified that compared methoxyflurane to an active comparator such as an alternative analgesic; the effectiveness of methoxyflurane compared with existing analgesics in the emergency department is uncertain. Additionally, no evidence-

based guidelines or cost-effectiveness studies were identified, so no conclusions can be made regarding guidance on use or comparative costs.

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 July 19, 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 the emergency department
Intervention	Low-dose, inhaled methoxyflurane (marketed in Canada as Penthrox) used as monotherapy or in combination with other analgesics
Comparator	Inhaled nitrous oxide; 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) or harm (e.g., potential for misuse/abuse and/or diversion, safety) Q2: Cost-effectiveness Q3: Evidence-based guidelines and/or recommendations
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations, evidence-based 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. Articles were also excluded if they were performed in a setting other than the emergency department of a hospital, including in the pre-hospital setting (e.g., ambulance).

Critical Appraisal of Individual Studies

The included randomized study was critically appraised using the Downs and Black checklist.[6] Summary scores were not calculated for the included study; rather, a review of the strengths and limitations was described.

Summary of Evidence

Quantity of Research Available

A total of 164 citations were identified in the literature search. Following screening of titles and abstracts, 136 citations were excluded and 28 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search. Of these potentially relevant articles, 28 publications were excluded for various reasons, while 1 publication met the inclusion criteria and was included in this report. Appendix 1 describes the PRISMA flowchart of the study selection. Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Additional details regarding the characteristics of the included publications are provided in Appendix 2.

Study Design

The included study was a randomized controlled trial (RCT) with a subgroup analysis of the adult population.[7] This subgroup analysis was pulled from a larger study published in 2014.[8]

Country of Origin

The included RCT was conducted at six emergency departments (EDs) across the United Kingdom.[7]

Patient Population

The patient population for the sub-group analysis of the included RCT was patients over the age of 18 years (N = 203) reporting to the emergency department with minor to moderate trauma.[7] "Trauma" included physical wounds or injuries, such as fractures, lacerations, burns, and contusions. Trauma was categorized as "minor to moderate", and all participants were required to have a pain score of greater than or equal to 4 and less than or equal to 7 on the numerical rating scale (NRS) at the time of admission to the ED. The NRS is a subjective pain rating, on a 0 to 10 scale, and scores of 4 to 7 include mild to moderate pain.[7]

Interventions and Comparators

The intervention was an inhaler containing 3 mL methoxyflurane which was self-administered by the patients, or administered with assistance from a nurse. A second dose of 3 mL inhaled methoxyflurane was available upon request of the patient. Each inhaler contained enough medication to provide approximately one hour of pain relief, used intermittently. Inhalers contained a "diluter hole", which, if covered, provided a higher concentration of medication. Patients were allowed to cover the diluter hole at their discretion.[7]

The comparator was an identical inhaler containing placebo (5 mL sterile normal saline), with one drop of methoxyflurane on the outside of the inhaler to disguise the scent difference between methoxyflurane and placebo. A second 5 mL inhaler was also available upon request of the patient.[7] As methoxyflurane is denser than saline, a 5 mL volume was chosen for the placebo solution to disguise the weight difference and maintain blinding.

Rescue medications (paracetamol, or intravenous, intranasal, or oral opioids) were available for all patients at any time, and patients' pain intensity was not measured after receipt of rescue medication.[7]

Outcomes

The primary outcome for the included RCT was pain, measured by the 100 mm visual analogue scale (VAS, in which 0 is no pain and 100 is the worst imaginable pain), at 5, 10, 15, 20 and 30 minutes after initiation of medication. VAS ratings were recorded every 30 minutes thereafter until discharge, or until rescue medication was given.[7]

Secondary outcomes included the use of rescue medication within 20 minutes of treatment (binary scale, yes or no), time until request of rescue medication, time to first reported pain relief, number of inhalations before first reported pain relief, global medication performance (GMP; range from poor to excellent), and adverse events (both treatment and non-treatment related).[7] In addition, the use of a second inhaler, use of the diluter hole, the time between the first and second inhaler, and the Glasgow coma score (GCS) were recorded. The GCS is a measure of consciousness of a patient, from a range of 3 to 15. Mild to no impairment of consciousness is classified as a GCS of 13 to 15.

Summary of Critical Appraisal

The included RCT was well conducted, and overall, the study was of high quality. The original RCT[8] had appropriate randomization of intervention using stratified blocks by age (adolescent/adult) and centre. Therefore, when using the adult subgroup,[7] randomization was preserved. Additionally, both patients and assessors were blinded to allocated intervention, with one drop of methoxyflurane placed on the outside of the placebo inhaler, and equal weights of medication placed in the inhaler to preserve blinding. An intention-to-treat analysis for clinical effectiveness was performed to protect the randomization sequence.[7]

Not all between-group comparisons were statistically tested (such as baseline characteristics), so differences in some outcomes are not clear. For example, the differences in pain overall were tested, but not reported on at all time points, and no safety data were tested statistically. Note that the power calculation of 150 patients required per arm was originally estimated for the original publication,[8] and the authors did not intend for the subgroup analysis to be sufficiently powered to detect some differences in treatment effects.[7] Despite having fewer than 150 patients per treatment arm, the study was adequately powered as evidenced by detection of statistically significant differences.

Summary of Findings

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Clinical Effectiveness of Methoxyflurane

Pain was measured using VAS, at baseline, and at 5, 10, 15, 20 and 30 minutes after initiation of medication. The estimated treatment effect of methoxyflurane compared with placebo was –17.4 mm (95% confidence interval [CI] –22.3 to –12.5 mm) across measurement time points, which was statistically significant ($P < 0.0001$). This was after adjustment for baseline VAS score and time by treatment interaction (which was significant, $P < 0.0004$). The mean change in VAS was numerically greater for methoxyflurane at all

time points (although the results at 30 minutes were not reported). The greatest comparative estimated treatment effect occurred at 15 minutes post-initiation of medication (least squares mean difference = –21.0 mm, 95% CI –26.8 to –15.3 mm). At any time point, 82.4% of patients and 52.5% of patients reported pain relief in the methoxyflurane group and placebo group, respectively. This indicates a high placebo effect of the inhaler, but despite this, methoxyflurane was still significantly more effective in relieving patients' pain.[7]

Fewer patients in the methoxyflurane group (16; 15.7%) required rescue medication for pain relief compared to patients in the placebo group (47; 46.5%).The median time to first pain relief was 5 minutes in the methoxyflurane group, and 20 minutes in the placebo group. The hazard ratio (methoxyflurane versus placebo) for time to first pain relief was 2.32, with a 95% CI of 1.63 to 3.30 ($P < 0.0001$). Overall, the group receiving methoxyflurane had a greater decrease in VAS score, and a quicker time to pain relief than the placebo group.[7]

Additionally, fewer patients in the methoxyflurane group (36.3%) covered the diluter hole in the inhaler when compared with the placebo group (42.6%), but this difference was not tested statistically. More patients in the methoxyflurane group requested a second inhaler (24.5%) compared with patients in the placebo group (14.9%).[7]

Within 20 minutes, rescue medication was requested in 2.0% of patients in the methoxyflurane group and 22.8% of patients in the placebo group. This was a statistically significant difference ($P < 0.0003$), where among the methoxyflurane group the odds of the patient requesting rescue medication within 20 minutes were 93% lower than the odds of a patient requesting rescue medication in the placebo group (odds ratio: 0.07; 95% CI 0.02 to 0.29).[7]

There were numerically fewer adverse events in the placebo group (41 total; 15 treatment-related) then the methoxyflurane group (64 total; 43 treatment-related). The most common adverse events were headache, dizziness, and somnolence, which occurred in both groups. All other adverse events occurred in less than 5% of patients in either treatment group. The adverse events were transient in nature and no severe adverse events were reported. Cardiovascular and respiratory function parameters remained within ± 5 heartbeats per minute and 14 to 15 breaths per minute. Changes in blood pressure remained within ± 6 mmHg. The Glasgow coma score remained at 15 for all patients, with the exception of two patients who recorded a score of 14 at one or more time points. There were no renal or liver concerns.[7]

Cost Effectiveness of Methoxyflurane

No studies were identified regarding cost-effectiveness data for methoxyflurane for patients in the ED; therefore, no summary can be provided.

Guidelines

No guidelines were identified regarding methoxyflurane for patients in the ED.

Limitations

One of the limitations regarding the body of evidence for the use of methoxyflurane in the emergency department is the lack of studies specifically addressing the use of this drug in that setting. Although there were studies exploring the use of methoxyflurane (Appendix 5), the majority of them were in a pre-hospital (ambulance) setting, or in a tertiary care setting.

Within the included RCT, the majority of the patients included were White, limiting generalizability to other races. Additionally, there were no comparisons of methoxyflurane to an active comparator, such as nitrous oxide, opiates, or other analgesics. Although comparison to a placebo inhaler helped to maintain blinding, this limits the usability of the results, as it does not provide information on how methoxyflurane performs in relation to already used alternatives. Additionally, there was a high placebo effect recorded in the present study.

No evidence-based guidelines or cost-effectiveness studies were identified. This gap in research prevents any conclusions regarding currently recommended use or cost-effectiveness of the intervention.

Conclusions and Implications for Decision or Policy Making

One high quality randomized controlled trial was identified regarding methoxyflurane use in the emergency department. Methoxyflurane through a self-administered inhaler provided greater pain relief than placebo for patients with minor to moderate trauma and moderate pain in the emergency department. There were numerically more adverse events in the methoxyflurane group compared with the placebo group. The majority of adverse events associated with the medication were minor.

No studies were identified in which methoxyflurane was compared to an active control; therefore, the effectiveness of methoxyflurane compared with existing analgesics in the emergency department is uncertain. No evidence-based guidelines or cost-effectiveness studies were identified.

Overall, one randomized controlled trial found methoxyflurane to be more effective in relieving pain related to minor to moderate trauma in the emergency department when compared with a placebo control, despite a high placebo response.

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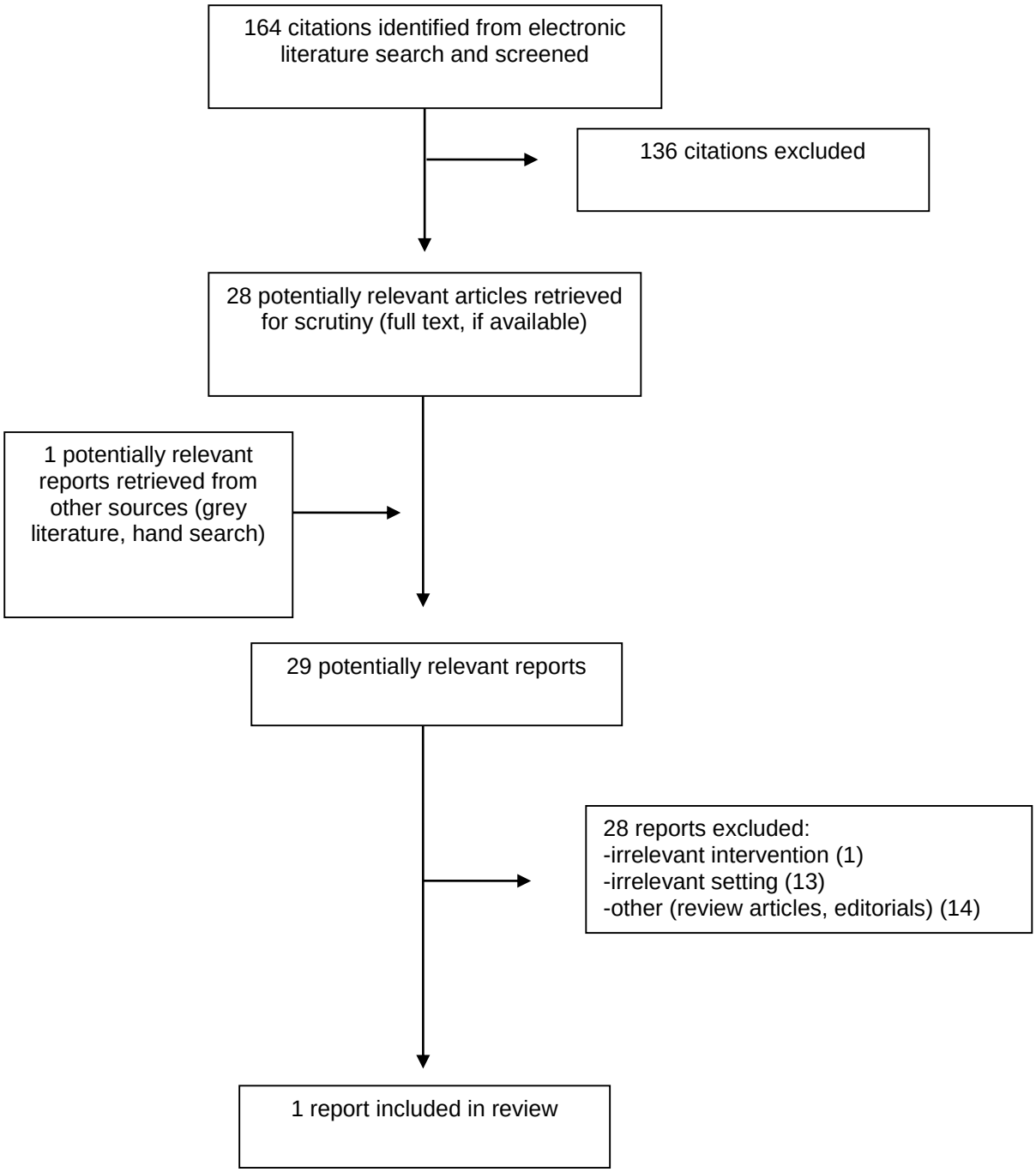
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of the Included Primary Clinical Study

First Author, Publication Year, Country	Study Design, Statistical testing	Population Characteristics	Intervention and Comparator(s)	Primary and Secondary Clinical Outcomes, Length of Follow-up
Coffey et al. 2016[a] **UK**	RCT, subset analysis (adults only) Repeated-measures ANOVA, intent-to-treat Safety measure presentation descriptive, no statistical testing	Pain score of ≥ 4 and ≤ 7 measured with numerical rating scale at time of admission **Adult subset** n = 203[7] LTF = 23 (12 methoxyflurane, 11 placebo) Age, mean (SD) • 36.7 (13.9) Gender, n (%) *Methoxyflurane:* • Male: 53 (52.0) • Female: 49 (48.0) *Placebo:* • Male: 51 (50.5) • Female: 50 (49.5) Race, n (%) *Methoxyflurane:* • White: 99 (97.1%) • Asian: 1 (1.0%) • Black 2 (2.0%) *Placebo:* • White: 96 (95.0%) • Asian: 2 (2.0%) • Black 2 (2.0%) Baseline VAS pain, mean (mm) Methoxyflurane = 66.2 Placebo = 65.5	3 mL Methoxyflurane inhaler (second 3 mL inhaler available upon request of patient) (n = 102) 5 mL placebo inhaler (second 5 mL placebo inhaler available upon request of patient) (n = 101)	Pain intensity using 100 mm VAS Use of rescue medication within 20 minutes of treatment (binary scale, yes or no) Time until request of rescue medication Time to first reported pain relief Number of inhalations before first reported pain relief Level of consciousness (GCS)Assessment of GMP Adverse events Follow-up of 5, 10, 15, 20, 30 minutes, and then every 30 minutes thereafter until discharge or rescue medication administration 14 ± 2 day follow-up visit for safety information

ANOVA = analysis of variance; GCS = Glasgow coma scale; GMP = global medication performance; LTF = lost to follow-up; RCT = randomized controlled trial; UK = United Kingdom; VAS = visual analogue scale.

[a] Coffey et al. 2016[7] is a subgroup analysis of adult patients from the STOP! RCT[8]

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of the Primary Clinical Study using the Downs and Black checklist[6]

Strengths	Limitations
Coffey et al. 2016[7a]	
• The hypothesis and aim of the study are clearly stated • Main (primary and secondary) outcomes clearly described within text • Clearly defined exclusion and inclusion criteria • Intervention of interest and placebo-control clearly described, including administration method • Power calculation performed prior to initiation of study • Assembly and dispensing of study medication and placebo inhalers performed by one independent (uninvolved with study conduct or interpretation), unblinded research team member • Randomization plan prepared by independent statistician • Randomization performed using sealed envelopes with no identifying characteristic apart from randomization number • Main study findings clearly described in table and text format • Extensive adverse events table, including adverse events considered unrelated to treatment • Assessments performed by a blinded research nurse • Randomization stratified by centre and age, so subgroup analysis appropriate • Participants were blinded, and participants receiving placebo had one drop of active treatment placed on placebo inhaler to disguise smell differences • Same length of follow-up for all patients • Intention-to-treat analysis performed for efficacy data (no imputation of data – if follow-up data missing, “no change” from baseline recorded) • Baseline VAS pain score and time by treatment accounted for in analysis	• Other confounders or covariates (aside from baseline VAS score and time by treatment interaction) not listed nor accounted for in analysis • Although subjectively similar, no statistical between-group testing of baseline characteristics, so unclear whether patients in intervention and placebo groups were statistically different (however, this is of minimal concern due to appropriate randomization) • No statistical testing performed on safety outcomes, only descriptive, and no statistical comparisons for some within-group comparisons

VAS = visual analogue scale.

[a] Some methodology information received from original publication, Coffey et al. 2014[8]

Appendix 4: Main Study Findings and Authors' Conclusions

Table 4: Summary of Findings of Included Primary Clinical Study

Main Study Findings	Authors' Conclusion
Coffey et al. 2016[7]	
Adult subgroup **VAS pain score/intensity** • Methoxyflurane, mean (mm), [SD]: ○ Baseline: 66.2 [16.6] ○ Baseline (median): 68 • Methoxyflurane, adjusted mean change from baseline (mm), ○ Overall (averaged across time points?): –29.0 ○ 5 minutes: –20.7 ○ 10 minutes: –27.4 ○ 15 minutes: –33.3 ○ 20 minutes: –34.8 • 84 patients (82.4%) experienced pain relief • Placebo, mean (mm), [SD]: ○ Baseline: 65.5 [18.1] ○ Baseline (median): 70 • Placebo, adjusted mean change from baseline (mm): ○ Overall: –11.6 ○ 5 minutes: –8.0 ○ 10 minutes: –11.1 ○ 15 minutes: –12.3 ○ 20 minutes: –15.2 ○ 53 patients (52.5%) experienced pain relief • Estimated between-group treatment effect (mm, [95% CI]): ○ Overall: –17.4 (–22.3 to –12.5) ○ 5 minutes: – 12.6 (–17.0, –8.3) ○ 10 minutes: –16.3 (–21.4 to –11.1) ○ 15 minutes: – 21.0 (–26.8 to –15.3) ○ 20 minutes: –19.7 (–26.0 to –13.3) ○ Time by treatment interaction, *P* < 0.0004 • Mean change in VAS ○ 5, 10, 15, 20 minutes: Methoxyflurane significantly higher change in VAS compared with placebo (*P* = NR) **Time to first pain relief** • Hazard Ratio: 2.32; (95% CI, 1.63 to 3.30) *P* < 0.0001 • Median time ○ Methoxyflurane (min, 95% CI): 5 (NC) ○ Placebo (min, 95% CI): 20 (10.0 to NC) • Number of patients with first pain relief after X inhalations; methoxyflurane, placebo:	*"Methoxyflurane significantly reduced pain intensity compared with placebo."* (p. 2019) *"The results of this study confirm that methoxyflurane is a highly effective analgesic for adult patients in the ED setting. There was a highly significant difference between the methoxyflurane and placebo groups (p < 0.0001) in the analysis of the VAS pain intensity score at all-time points tested, despite a considerable 'placebo effect'."* (p. 2026)

Main Study Findings	Authors' Conclusion
○ No relief: 16 (15.7%), 47 (46.5%) ○ 1 inhalation: 1 (1.0%), 0 ○ 2 inhalations: 6 (5.9%), 2 (2.0%) ○ 3 inhalations: 11 (10.8%), 7 (6.9%) ○ 4 inhalations: 19 (18.6%), 3 (3.0% ○ 5 inhalations: 8 (7.8%), 8 (7.9%) ○ 6 inhalations: 9 (8.8%), 7 (6.9%) ○ 7 inhalations: 4 (3.9%), 1 (1.0%) ○ 8 inhalations: 10 (9.8%), 4 (4.0%) ○ 9 inhalations: 4 (3.9%), 4 (4.0%) ○ 10 inhalations: 9 (8.8%), 9 (8.9%) ○ >10 inhalations: 5 (4.9%), 9 (8.9%) **Second inhaler** • Methoxyflurane: 25 (24.5%) requested a second inhaler • Placebo: 15 patients (14.9%) requested a second inhaler **Median time between first and second inhalers** • Methoxyflurane: 54 mins (range 30 to 120 minutes) • Placebo: 50 min (range 20 to 72 minutes) **Number of patients covering diluter hole (i.e., resulting in greater agent concentration)** • Methoxyflurane: 37 (36.3%) • Placebo: 43 (42.6%) **Rescue medication** • 2.0% of methoxyflurane treated patients used rescue medication within 20 minutes • 22.8% of placebo patients used rescue medication within 20 minutes ○ OR: 0.07, 95% CI 0.02 to 0.29; *P* = 0.0003 • Prior to censoring, rescue medication use lower in methoxyflurane group (11.8%) compared with placebo group (38.6%) • Time to request rescue medication longer in methoxyflurane group ○ HR: 0.23, 95% CI 0.12 to 0.44; P < 0.0001 ○ Estimated median time to request uncalculatable **GMP** • GMP rating significantly better in methoxyflurane group ○ P < 0.0001 for all comparisons (patient assessment, physician assessment and nurse assessment; ordinal logistic regression) **Safety** Treatment emergent AEs, n (%): • Methoxyflurane: 64 (62.7%) ○ Treatment-related[a]: 43 (42.2%) • Placebo: 41 (40.6%) ○ Treatment-related[a]: 15 (14.9%) AEs, number of patients (%), methoxyflurane, placebo • Headache: 20 (19.6%), 13 (12.9%) • Dizziness: 37 (36.3%), 11 (10.9%) • Somnolence: 5 (4.9%), 1 (1.0%) • All other AEs < 5% of patients in either treatment group[b]	

Main Study Findings	Authors' Conclusion
• One patient (from intervention group) experienced serious AE of a lower respiratory tract infection, but was unrelated to study medication • No severe AEs reported • Heart rate remained within ± 5 heartbeats per minute • Breathing rate remained within 14 to 15 breaths per minute • Changes in blood pressure remained within ± 6 mmHg GCS • 15 for all patients at all time points, except 2 patients • 2 patients recorded a score of 14 (one at 10, 20 and 30 min and one at 30 min only)	

AE = adverse events; CI = confidence interval; GCS = Glasgow coma score; GMP = global medication performance; HR: hazard ratio; NC = not calculable; NR = not reported; OR: odds ratio; RR = risk ratio; SMD = standardized mean difference; VAS = visual analogue scale.

[a] determined to be related to treatment via investigator's causality assessment

[b] other AEs reported (in both groups, either treatment-related or -unrelated) included: ear and labyrinth disorders, gastrointestinal disorders, general disorders and administration site conditions, infections and infestations, injury, poisoning and procedural complications, investigations, musculoskeletal and connective tissues disorders, nervous system disorders, psychiatric disorder, reproductive system and breast disorders, respiratory, thoracic and mediastinal disorders, skin and subcutaneous tissue disorders, and vascular disorders.

Appendix 5: Additional References of Potential Interest

Protocols

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Alternative Setting

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