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Review

Methoxyflurane as a volatile anesthetic and its place in modern pain management: a narrative review

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Abstract

Background: **Methoxyflurane ($C_3H_4Cl_2F_2O$, Penthrox), introduced initially as a volatile anesthetic in the 1960s, was later discontinued as a general anesthetic due to nephrotoxicity. However, recent studies have highlighted its significant analgesic properties at subanesthetic doses. This literature review explores the evolution of methoxyflurane from a general anesthetic to a widely used analgesic, focusing on its current applications, safety profile, environmental impact and regulatory aspects.**
Methods: **PubMed, Embase, and Cochrane Library were searched in July 2024 for articles related to methoxyflurane.**
Results: **Effectiveness: Methoxyflurane offers rapid and effective pain relief. Its self-administration feature by inhalation provides significant advantages in situations where time-sensitive pain management is critical.**
Safety: The safety profile of methoxyflurane is favorable, with only mild, transient side effects such as dizziness and nausea. No significant long-term renal or cardiovascular complications have been observed at subanesthetic doses. Environmental Impact: Compared to other volatile anesthetics, methoxyflurane has a low global warming potential, due to its short atmospheric lifetime and low radiative efficiency.
Conclusion: **Methoxyflurane has proven to be a potent and effective analgesic, particularly in emergency and trauma care. Furthermore, its lower environmental impact compared to other anesthetics aligns with growing sustainability goals in healthcare. Despite its benefits, further research is necessary to address gaps in its use for vulnerable populations, such as children and pregnant women, and to explore its broader clinical applications and ecological footprint.**

Mesh Kewords: **Methoxyflurane, Acute pain, Anesthesia, inhalation, Impact, environmental.**

Introduction

Methoxyflurane has long been recognized for its anesthetic and analgesic properties, making it a valuable tool in the medical field. Initially introduced in the 1960s as an inhalational anesthetic, methoxyflurane was widely used for general anesthesia. However, due to concerns about dose-dependent nephrotoxicity and the arrival of newer anesthetic agents with better safety profiles, its use in clinical anesthesia declined significantly by the early 1980s[1].

Despite its withdrawal from general anesthesia, methoxyflurane was later identified as having potent analgesic properties at subanesthetic doses, making it particularly useful in emergency and prehospital settings[2].

Today, methoxyflurane is widely used as a rapid-acting, self-administered analgesic in Australia, New Zealand, Europe, and beyond[1]. Its noninvasive delivery and fast onset make it ideal for acute pain management in trauma and minor surgical procedures[3].

However, alongside the renewed clinical interest in methoxyflurane, there has been growing awareness and concern about the

This is an original review. It has not been published before, nor is it being considered for publication elsewhere. All listed authors have read the article and agree to its content. They declare no funding or conflicts of interest. Ethical approval was not required as this review did not involve patient data.

What is already known on this topic

⇒ Methoxyflurane was initially used as a volatile anesthetic but discontinued due to nephrotoxicity.
⇒ It is now used as an analgesic at subanesthetic doses, particularly in emergency and trauma care.
⇒ It has a low environmental impact compared to other volatile anesthetics.

What this review adds

⇒ Overview of its pharmacokinetic and pharmacodynamic properties
⇒ Comprehensive assessment of its clinical safety and efficacy across various medical settings
⇒ Evaluates its environmental footprint and explores future research directions regarding sustainability and regulations.

How this review might affect research, practice or policy

⇒ Promotes methoxyflurane as a viable, sustainable analgesic alternative in emergency settings, potentially influencing clinical practice and pain management protocols.
⇒ Encourages further research into its use in vulnerable populations like children and pregnant women, where data is currently limited.
⇒ Supports the development of guidelines for methoxyflurane's use, with a focus on balancing patient care with environmental impact.

environmental impact of modern healthcare. The healthcare sector, including anesthesia and critical care, contributes significantly to greenhouse gas emissions due to resource-intensive and high-tech operations[4]. The environmental impact of methoxyflurane is a significant consideration, as all volatile anesthetics are classified as greenhouse gases to varying degrees, and their release into the atmosphere contributes to both ozone layer depletion and global warming[5].

Understanding the balance between methoxyflurane's clinical benefits and environmental impact is crucial for making informed decisions about its use. This literature review aims to synthesize existing knowledge on methoxyflurane and its clinical application, assess its role in ozone depletion, and compare its environmental footprint with other anesthetic agents. This comprehensive evaluation is essential for developing strategies that optimize patient care while minimizing environmental harm.

Methods

A literature search was conducted in July 2024 using the following databases: PubMed, Embase and Cochrane Library. The search terms included:

- ("Methoxyflurane") AND ("history" OR "uses" OR "applications" OR "mechanism of action" OR "pharmacologic characteristics" OR "chemical properties" OR "climate change" OR "atmospheric" OR "ozone" OR "alternatives")
- ("Volatile anesthetics") AND ("climate change" OR "atmospheric" OR "ozone" OR "climate")
- ("Methoxyflurane") AND ("gynecology" OR "dermatology" OR "trauma" OR "emergency" OR "procedural" OR "pediatrics" OR "urology" OR "colonoscopy")

Search terms such as 'sedation' and 'analgesia' were intentionally excluded to maintain a specific focus on methoxyflurane's current use and environmental implications rather than focusing on its analgesic or sedative roles, which have been extensively covered in existing literature.

Figure 1 shows a flowchart of the methods for exclusion of articles.

Articles published before 2009 were excluded to reflect contemporary discussions of methoxyflurane's reintroduction and evolving environmental considerations, despite its widespread clinical use ceasing in the 1980s. The search yielded 144 PubMed, 378 Embase, and 156 Cochrane Library articles. After removing duplicates and title screening, 154 remained.

Abstract screening excluded 96 articles due to irrelevant topics, study protocols, case reports, language barriers, or lack of full text. Studies from journals with an impact factor below one were also excluded.

After full-text review of 58 articles, 25 were excluded for relevance or quality issues. Specific outcome measures for inclusion were not predefined during initial screening. Articles were excluded based on relevance to the review's focus areas (e.g., environmental effects, historical context, procedural applications) to maintain thematic consistency. Ultimately, 33 articles were included.

Ethical approval was not required as this review did not involve patient data.

Pharmacokinetics and Pharmacodynamics of Methoxyflurane

Pharmacokinetics

Methoxyflurane is a halogenated ether and volatile anesthetic agent. Its pharmacokinetics involves absorption, distribution, metabolism, and

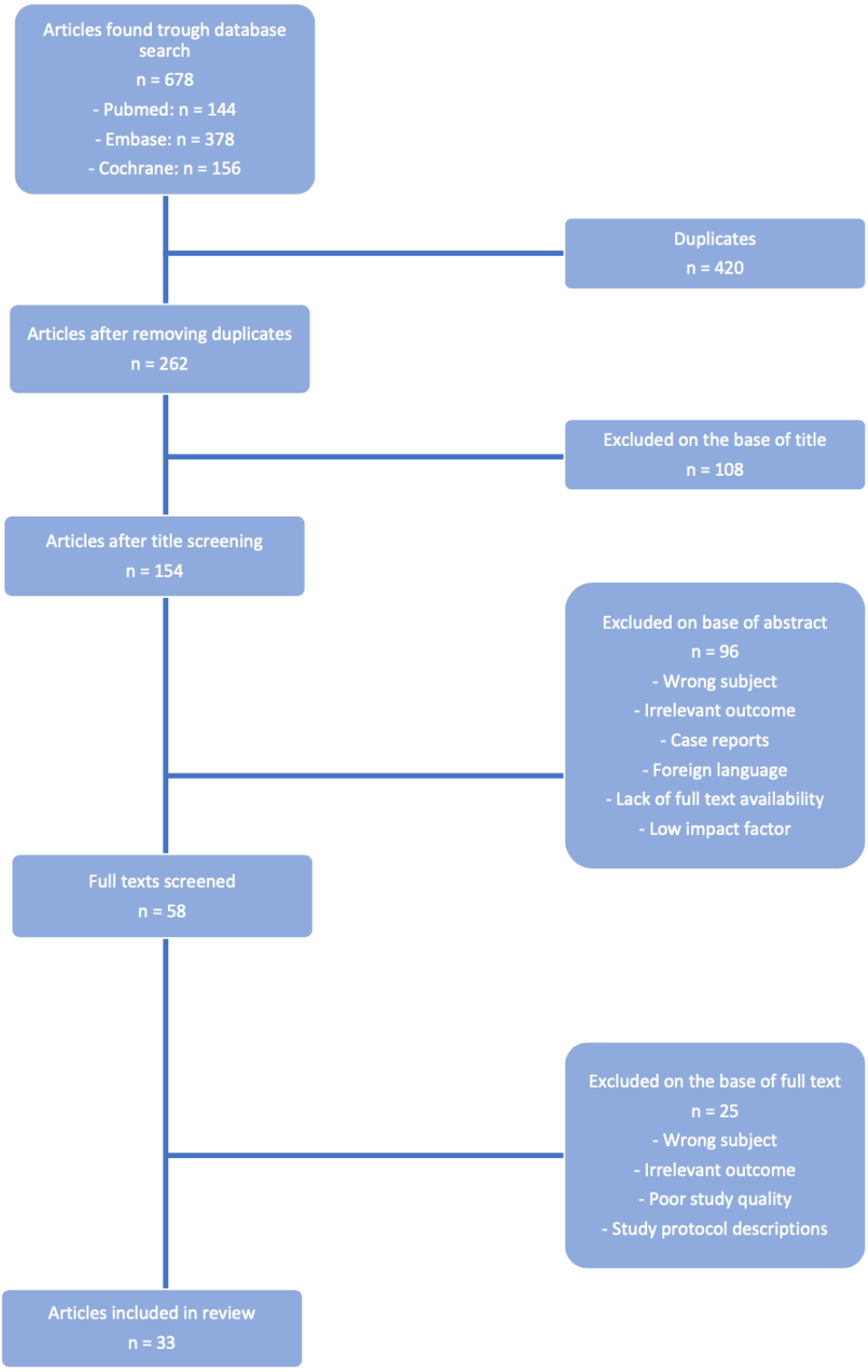

Fig. 1 — Flowchart of method of exclusion of articles.

excretion, with key features related to its solubility and metabolism. Figure 2 shows the structure of different volatile anesthetics.

Absorption and Onset of Action

Methoxyflurane is administered via inhalation and has a high blood-gas partition coefficient of approximately 12. This means it equilibrates slowly between the alveoli and the bloodstream. While it provides effective pain relief within minutes, achieving full anesthetic effects takes longer, making it less suitable for induction in surgical anesthesia[6].

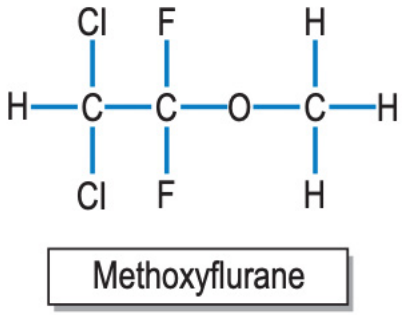

Fig. 2 — Structure of methoxyflurane[7].

Distribution

Once in the bloodstream, methoxyflurane is distributed throughout the body. Its high lipid solubility results in significant accumulation in fatty tissues, prolonging its duration of action[7].

Metabolism and Elimination

Unlike other modern inhaled anesthetics, methoxyflurane is extensively metabolized in the liver by cytochrome P450 enzymes, particularly CYP2E1 and CYP2A6. During metabolization, free fluoride, oxalic acid, difluoromethoxyacetic acid, and dichloroacetic acid are released. The kidneys primarily excrete free fluoride and oxalic acid, which cause kidney damage at concentrations higher than those used for analgesia[6].

The extensive metabolism and high lipid solubility mean that methoxyflurane has a prolonged half-life, and its elimination from the body is slow, taking several days to weeks for complete clearance[7].

Pharmacodynamics

Anesthetic and analgesic effects

The exact mechanism of action for volatile anesthetics is complex and not yet fully understood. Methoxyflurane likely exerts its effects by enhancing inhibitory neurotransmission through GABAA and glycine receptors, while inhibiting excitatory neurotransmission through nicotinic acetylcholine and glutamate receptors. GABAA receptor involvement is common among volatile anesthetics, leading to neuron hyperpolarization, reduced excitability, and resulting in both analgesia and anesthesia[1].

Methoxyflurane is a highly potent inhalation anesthetic, as reflected by its high oil-gas partition coefficient and low MAC value. However, its slow onset, prolonged recovery times, and potential nephrotoxicity have limited its use for anesthesia. At sub-anesthetic concentrations, methoxyflurane provides effective analgesia, with pain relief typically reported within four minutes. While its high blood-gas partition coefficient contributes to slower overall equilibration with the brain — delaying anesthetic induction — its lipophilicity and localized effects at peripheral and central nervous system sites may underlie the relatively prompt onset of analgesia at lower doses. Furthermore, the high blood-gas solubility leads to prolonged retention in the body, allowing analgesic effects to persist into the recovery period[1].

Therapeutic dosing

Methoxyflurane is administered for analgesia via a handheld inhaler, typically in doses of 3 mL per inhaler. Clinical guidelines recommend a maximum dose of 6 mL per day and 15 mL per week to avoid cumulative toxicity, particularly nephrotoxicity related to fluoride ion release. Consecutive daily use is not advised. Each 3 mL dose provides effective analgesia for approximately 20–30 minutes, with additional inhalers permitted if required, provided maximum limits are not exceeded. Methoxyflurane is self-administered under medical supervision, allowing patients to titrate the dose to their pain intensity while maintaining a favorable safety profile at these sub-anesthetic exposures[17].

Cardiovascular effects

When used for general anesthesia, methoxyflurane has been shown to decrease cardiac output, mean arterial pressure and systemic vascular resistance, while increasing heart rate. However, another study noted only an initial decrease in myocardial contractility. In smaller analgetic doses, significant adverse hemodynamic effects are generally absent. While methoxyflurane is licensed for moderate to severe pain after trauma, it is contraindicated in patients with significant cardiovascular instability. However, a more recent study suggests it may be a safe alternative in trauma patients with potential bleeding[8].

Renal effects

The primary concern with methoxyflurane has been nephrotoxicity, historically reported with higher doses during deep anesthesia. This renal damage is likely due to methoxyflurane's metabolism in the liver and kidneys, leading to the release of fluoride ions. However, clinical experience and laboratory evidence suggest low, effective analgesic doses do not pose a significant risk of renal adverse events. Specifically, the Penthrox inhaler, delivering up to 6 mL/day and 15 mL/week (0,59 MAC-hours), results in exposure well below the nephrotoxic threshold (2 MAC-hours), supporting the conclusion that analgesic doses of methoxyflurane do not pose a risk of nephrotoxicity[9].

Comparison with Desflurane, Sevoflurane, and Nitrous Oxide

Table I shows the differences between, desflurane, sevoflurane, nitrous oxide and methoxyflurane.

Onset of Action

Desflurane and sevoflurane, with low blood-gas partition coefficients (0.42 and 0.65), have faster onset and offset than methoxyflurane. Nitrous oxide, with an even lower coefficient (0.46), offers rapid onset and recovery, making it ideal for short procedures. Methoxyflurane, though slower due to its higher partition coefficient of 12, provides a rapid onset of analgesia because of its high potency[10].

Solubility and duration of action

Methoxyflurane is the most lipophilic inhaled anesthetic, characterized by a high oil-gas partition coefficient and an exceptionally high blood-gas partition coefficient (approximately 12). This high solubility in blood and fat contributes to its prolonged duration of action and accumulation in adipose tissue. While this property results in delayed anesthetic induction and prolonged recovery at higher doses, methoxyflurane delivers effective analgesia at sub-anesthetic concentrations.

The relatively prompt onset of analgesic action, despite its high blood-gas solubility, is thought to result from its high potency and rapid interaction with peripheral and central nervous system targets at low doses. Additionally, its lipophilicity may facilitate early distribution to effect sites involved in analgesia before achieving concentrations necessary for full anesthesia. The analgesic effects are sustained over time due to its slow elimination, with the agent remaining in fat stores and gradually redistributing[11].

In contrast, desflurane and sevoflurane have lower lipid solubility, resulting in rapid onset and short duration of action[10]. Desflurane, with the lowest blood-gas partition coefficient (0.42), allows for the fastest equilibration and recovery, followed closely by sevoflurane (0.65). Nitrous oxide, with an even lower solubility in both blood and fat, provides a rapid onset and offset, making it especially suitable for brief outpatient procedures requiring minimal recovery time[11].

Metabolism and Toxicity

As the most lipophilic inhaled anesthetic, methoxyflurane undergoes the most biotransformation at an estimated 70% of the drug administered[10].

Desflurane and sevoflurane undergo minimal metabolism (less than 5%), reducing the risk of toxic metabolites. Nitrous oxide is not metabolized and is exhaled unchanged, though chronic exposure can lead to vitamin B12 deficiency[7].

Methoxyflurane was withdrawn from the market due to renal failure, linked to plasma fluoride levels over 50 µmol/l. Sevoflurane also raises fluoride concentrations, even higher than 50 µmol/l, but no cases of related renal dysfunction have been reported. The key difference is that methoxyflurane's fluoride is produced in the kidneys, causing direct renal damage, while sevoflurane's renal metabolism is much lower, reducing fluoride exposure[12].

Environmental impact

Like all volatile anesthetics, methoxyflurane has an environmental impact due to its role in ozone depletion and climate change. All heteronuclear gases (possessing more than one type of atom (e.g. CO2, H2O) and some homonuclear molecules (e.g. ozone (O3)) are infrared active, meaning they vibrate, rotate or stretch in the presence of infrared radiation. Molecular absorption, and later emission, of infrared light leads to heat retention, described by the term global warming potential (GWP). The GWP of a volatile anesthetic is determined by its atmospheric lifetime and radiative efficiency[13]. Methoxyflurane has a relatively short atmospheric lifetime of approximately 39 to 54 days, significantly lower than other volatile anesthetics. The GWP of methoxyflurane is 3.0 over a 100-year horizon, making it one of the least impactful

Table I. — Comparison of Characteristics of Different Volatile Anesthetics.

Inhalation agent	Blood-gas partition coefficient @ 37°C [10]	Oil:gas partition coefficient @ 37°C [10]	Approximate MAC volumes (%/vol) [10] MAC: 30-55y old at 1 atm	Approximate rate of metabolism (%) [7]	Global warming potential (GWP100) [13]
Isoflurane	1.4	97	1.17	0.17	510
Desflurane	0.45	19	6.0	0.02	2,540
Sevoflurane	0.65	53	2.0	2.0	130
Methoxyflurane	11	950	0.2	50	3.0
Nitrous oxide	0.47	1.3	104	0.004	265

volatile anesthetics in terms of greenhouse gas emissions. Because of its short atmospheric lifespan and low GWP values, methoxyflurane is unlikely to have a profound atmospheric impact[14].

Next to its GWP, methoxyflurane's overall environmental impact can be calculated by carrying out a life cycle impact assessment (LCIA). LCIA provides a more comprehensive analysis of a drug's environmental footprint, accounting for factors beyond carbon emissions. Studies indicate that methoxyflurane is 117.7 times better from a climate change perspective than using 30 minutes of Entonox (a mixture of nitrous oxide and oxygen). Furthermore, methoxyflurane is administered via a handheld inhaler rather than a piped gas system, which reduces waste and leakage. Reports suggest that NHS hospitals experience significant nitrous oxide losses, up to 95% of the total annual volume leaking from gas pipelines, further exacerbating their environmental footprint[15].

When considering environmental sustainability in anesthesia, reducing the use of high-GWP agents such as desflurane and nitrous oxide is a key strategy. Anesthetists can minimize their carbon footprint by practicing low-flow anesthesia, avoiding desflurane, isoflurane and nitrous oxide when possible, and incorporating regional and total intravenous anesthesia (TIVA) techniques. Although nitrous oxide remains a primary contributor to ozone depletion and global warming, its use far exceeds that of methoxyflurane despite methoxyflurane's far smaller carbon footprint[15]. Figure 3 shows the comparison between methoxyflurane and nitrous oxide. Given that the use of inhaled anesthetics contributes approximately 0.1% of global warming, equivalent to the emissions of 1 million U.S. cars, even small reductions in their use can have significant environmental benefits[13].

In summary, methoxyflurane's unique pharmacokinetic and pharmacodynamic properties make it a potent analgesic but with limitations as an anesthetic due to its slow onset, prolonged duration, and potential for toxicity. Furthermore, due to its low GWP, methoxyflurane can play an essential role in sustainable analgesia. Desflurane, sevoflurane, and nitrous oxide, with their more favorable solubility profiles and faster kinetics, are preferred in many anesthetic applications where rapid control of anesthesia is essential.

Clinical use of Metoxyflurane

Anesthesiology & outpatient procedures

Methoxyflurane is increasingly used as an inhaled analgesic for outpatient procedures due to its rapid onset, ease of self-administration, and effective control of moderate pain. Unlike traditional anesthetics, methoxyflurane is administered via a handheld inhaler, allowing patients to adjust their analgesia throughout the procedure. Its administration causes mild sedation and temporary psychomotor impairment, which resolve quickly after inhalation stops, allowing patients to return to normal activities without the risks associated with deep sedation. New low-dose formulations, such as Penthrox, have proven effective in ambulatory settings where intravenous access or full sedation is not ideal[17].

Gastroenterology

Methoxyflurane is increasingly used in gastroenterology, particularly for managing pain during colonoscopies.

Fig. 3 — Environmental impact of methoxyflurane versus nitrous oxide[16].

A prospective, randomized study across three endoscopic centers in Australia compared methoxyflurane to intravenous midazolam and fentanyl for colonoscopy. There were no differences between the groups in VAS pain scores or STAI Y-1 anxiety scores during or immediately after the procedure, procedural success rate, incidence of hypotension, tachycardia, time to reach the caecum, or polyp detection rate. However, 10 patients (8%) in the Penthrox group required additional intravenous sedation. Notably, patients using only Penthrox had faster recovery times, awoke more quickly, and were ready for discharge sooner than those given intravenous sedation[18].

Another study on post-colonoscopy care after a 15-minute methoxyflurane inhalation observed a temporary, slight decline in psychomotor function among healthy volunteers, with full recovery within 30 minutes after inhalation. These findings suggest that patients using inhaled methoxyflurane for conscious analgesia during outpatient procedures like colonoscopy can safely resume tasks requiring high psychomotor skills, such as driving and working, on the same day[19].

Urology

Methoxyflurane has been studied as an analgesic option for a variety of urologic procedures. In the context of transrectal ultrasound-guided prostate biopsy (TRUSB), two studies have evaluated its efficacy and safety. A multicenter, placebo-controlled, double-blind, randomized phase 3 trial involving 420 men undergoing their first TRUSB found that mean pain scores were slightly lower in the methoxyflurane group compared to the placebo group. However, the difference was not statistically significant. Methoxyflurane was associated with improved comfort, overall experience, and willingness to undergo repeat biopsies. In contrast, it also resulted in higher scores for drowsiness and dizziness without a significant increase in severe adverse events[20]. In a smaller single-center study of 64 patients, median VAS pain scores were 2.0, 2.4, and 3.0 during digital rectal examination (DRE), probe insertion, and needle biopsy, respectively, with the Penthrox inhaler. Patients who had previously experienced periprostatic infiltrative local anesthesia (PILA) reported better pain relief with PILA than with the Penthrox inhaler during a needle biopsy[21]. These findings suggest methoxyflurane is a safe and effective analgesic in urologic procedures, with particular utility in office-based settings where sedation is limited.

Gynecology

Methoxyflurane has been effective in managing pain during hysteroscopy and other gynecological procedures. A 2024 UK observational study assessed the use and side effects of Penthrox for various intrauterine interventions. Nearly all participants found the device easy to use, with over 95% of procedures successfully completed and more than 90% of women indicating they would choose Penthrox for pain control in future procedures[22].

A 2024 single-center, double-blind RCT compared methoxyflurane to a placebo during hysteroscopy. Results showed that methoxyflurane significantly reduced pain for both diagnostic and operative hysteroscopies. It was well-tolerated, with no reported adverse events[23].

Dermatology

Methoxyflurane is a valuable analgesic option for many outpatient dermatology procedures. While injections of local anesthetics effectively manage pain during many dermatologic procedures, some cases may require additional pain control to enhance patient comfort. It's essential to consider both patient- and procedure-specific factors. Pediatric patients, individuals with chronic pain or procedural anxiety are more likely to experience pain during dermatologic procedures. Additionally, specific procedures may not be optimally managed with local anesthetic alone due to factors such as limited efficacy, large treatment areas, high dosage requirements, or contraindications, including allergies to local anesthetics[24].

Additional case studies involving methoxyflurane for minor surgical procedures, such as burn dressing changes and vacuum-assisted closure (VAC) dressings, reported effectives pain management. Ninety-one dressing changes were successfully completed across 41 patients, reinforcing methoxyflurane's effectiveness in these settings[25].

The reintroduction of methoxyflurane in outpatient care emphasizes its unique advantages as a non-opioid, inhalable analgesic. Clinical studies support its safety and effectiveness at low doses, providing reliable pain relief without the drawbacks of traditional anesthesia, such as intravenous access or prolonged recovery. Its rapid onset and patient-controlled dosing make it especially useful in brief interventions, where minimal side effects and fast recovery are essential. These attributes highlight methoxyflurane's potential as a practical solution across diverse medical specialties.

Emergency room & trauma settings

Methoxyflurane has found renewed utility as an analgesic agent in emergency medicine,

particularly for acute trauma pain. Administered via a compact handheld inhaler, this low-dose formulation provides effective pain relief through self-administration, making it highly versatile for pre-hospital and emergency room use.

Efficacy

Methoxyflurane has been extensively studied for its efficacy in managing pain in emergency settings, with multiple trials highlighting its rapid and effective analgesic properties. The STOP trial, a double-blind RCT conducted in six UK sites in 2014, enrolled 300 patients aged 12 years or older with minor trauma. Patients received either 3 mL of methoxyflurane or 5 mL of placebo. The primary endpoint, change in pain intensity on the Visual Analogue Scale (VAS) from baseline, showed significant pain reduction with methoxyflurane compared to placebo at all time points. The median time to first pain relief for the methoxyflurane group was 4 minutes. This compares favorably with a median time to onset of meaningful pain relief of 11 min with intranasal fentanyl, 16 minutes with oromucosal fentanyl, and 5 minutes with intravenous morphine sulfate. The most significant treatment effect was observed 15 minutes after administration, with an adjusted mean difference of −18.5 mm favoring methoxyflurane. These findings confirmed methoxyflurane's rapid onset of action and significant analgesic superiority over placebo in trauma-related pain[9].

The MEDITA trial was conducted in 15 emergency units across Italy. This randomized, open-label study included 270 adults with limb trauma and pain scores of ≥4 on the Numeric Pain Rating Scale (NRS). Patients were randomized to receive methoxyflurane or standard analgesic treatment (SAT), which included intravenous morphine for severe pain (NRS ≥ 7) or paracetamol/ketoprofen for moderate pain (NRS 4–6). Methoxyflurane significantly reduced pain intensity on the VAS at 3, 5, and 10 minutes, with adjusted mean treatment differences favoring methoxyflurane across all pain severities. The median onset of pain relief was 9 minutes for methoxyflurane and 15 minutes for SAT. Practicality of methoxyflurane treatment was rated ''Excellent'', ''Very Good'' or ''Good'' by 90% of clinicians vs. 64% for SAT. This trial reinforced methoxyflurane's rapid and effective pain relief, even when compared to potent intravenous analgesics like morphine[26].

The INMEDIATE trial, published in 2020, further supported methoxyflurane's efficacy. It was the first randomized, active-controlled, multicenter trial of methoxyflurane in the emergency setting in Europe. It evaluated its efficacy in patients with trauma-related moderate-to-severe pain (NRS ≥ 4). It compared methoxyflurane with standard analgesia, which included intravenous first-step analgesics and opioids. Methoxyflurane consistently demonstrated more significant reductions in pain scores at all time points. Additionally, patient and clinician satisfaction were notably higher with methoxyflurane; 77% of patients and 72% of clinicians rated it as exceeding expectations, compared to 38% and 19% for standard treatments. Furthermore, this trial also showed that the median time to first pain relief was significantly shorter for methoxyflurane than standard analgesic treatment (3 versus 10 minutes). This trial highlighted methoxyflurane's advantages in trauma-related pain, offering both effective pain relief and high satisfaction[27].

The RAMPED trial, a phase 4 randomized study, expanded methoxyflurane's scope by including patients with severe, nontraumatic pain. Unlike previous studies focused on trauma, this trial involved 120 patients presenting to the emergency department with severe pain (NRS ≥ 8) from various causes, including renal colic, intra-abdominal infections, and chronic back pain exacerbations. Methoxyflurane was compared to standard analgesia, with the primary outcome being a ≥ 50% reduction in pain scores at 30 minutes. While only 10% of methoxyflurane patients achieved the primary outcome compared to 5% in the standard care group ($p = 0.49$), methoxyflurane consistently provided more significant pain reduction at all time points, with higher proportions of patients experiencing substantial drops in pain scores at 15, 30, 60, and 90 minutes. These findings highlight methoxyflurane's potential for nontraumatic pain management and suggest its applicability across a broader spectrum of painful conditions[28].

Together, these trials establish methoxyflurane as an effective and versatile analgesic in emergency settings, capable of delivering rapid pain relief with high patient and clinician satisfaction across various pain severities and etiologies.

Adverse effects

In multiple studies, Methoxyflurane has demonstrated a favorable safety profile, with adverse events typically mild, transient, and predictable based on its pharmacological properties.

A large-scale cohort study of 135 770 patients (13% treated with methoxyflurane in prehospital settings) found no differences in heart rate, renal or hepatic disease, cancer, or diabetes between treated and untreated patients during follow-ups up to 14 years[29].

Similarly, a retrospective study of 1 024 patients reported no adverse events when methoxyflurane was used as a sole agent, unlike intravenous

fentanyl, which was associated with hypotension in some cases[30].

The STOP and INMEDIATE trials also reported no serious AEs, with the latter confirming no renal or hepatic impairment or abnormal blood test results during follow-up, supporting the safety of low dose methoxyflurane[9,27].

Although the MEDITA trial noted a higher incidence of mild AEs in methoxyflurane-treated patients (17% vs. 3%), all were non-serious, as shown in Table II[26].

Additionally, a randomized crossover study in hypovolemic volunteers found no significant changes in cardiac output, stroke volume, or arterial pressure, suggesting that methoxyflurane may be suitable for polytrauma patients[8].

These findings collectively support the safety of low-dose methoxyflurane for pain relief in emergency and prehospital settings.

Methoxyflurane is an effective option for analgesia in emergency rooms and prehospital settings. It offers rapid pain relief within minutes, making it ideal for time-sensitive situations. Its inhalational delivery bypasses the need for intravenous access, reducing delays and benefiting patients with difficult or compromised vascular access. Additionally, self-administration enables patients to control their pain relief, which is especially useful during transport or in busy emergency departments. When used at analgesic doses, methoxyflurane is well-tolerated and does not cause significant side effects, further highlighting its advantages over standard analgesic options.

Worldwide authorization of Metoxyflurane

Methoxyflurane has been used the longest in Australia and New Zealand since 1975 31. It is approved for emergency pain relief via self-administration in hemodynamically stable trauma patients and for monitored analgesia during surgical procedures, such as dressing changes[32,33].

In Europe and the United Kingdom, the European Medicines Agency (EMA) granted methoxyflurane marketing authorization in 2015 for the short-term relief of moderate to severe acute pain associated with trauma or interventional medical procedures in conscious adult patients[34]. After that, further national approvals expanded its availability, and today, methoxyflurane remains authorized for adult patients in many European countries[35].

Since July 2018, Canada has approved it for the short-term relief of moderate to severe acute pain in conscious adults[36].

It is also authorized in Guatemala, South Africa, Taiwan, the United Arab Emirates, Hong Kong,

Table II. — Adverse effects reported in the MEDITA trial[26].

Number of patients (%)	Methoxyflurane (N = 135)		Standard analgesic treatment (N = 135)	
	All AEs	Related AEs *	All AEs	Related AEs *
Any adverse events	23 (17.0)	17 (12.6)	4 (3.0)	2 (1.5)
Euphoric mood	5 (3.7)	5 (3.7)	0	0
Somnolence	4 (4.0)	4 (4.0)	0	0
Nausea	3 (2.2)	3 (2.2)	1 (0.7)	0
Dysgeusia	3 (2.2)	3 (2.2)	0	0
Feeling abnormal	3 (2.2)	3 (2.2)	0	0
Pyrexia	2 (1.5)	0	0	0
Vertigo	2 (1.5)	2 (1.5)	0	0
Presyncope	1 (0.7)	0	2 (1.5)	1 (0.7)
Bronchitis	1 (0.7)	0	0	0
Diplopia	1 (0.7)	1 (0.7)	0	0
Dizziness	1 (0.7)	1 (0.7)	0	0
Feeling drunk	1 (0.7)	1 (0.7)	0	0
Headache	1 (0.7)	0	0	0
Oral discomfort	1 (0.7)	1 (0.7)	0	0
Sedation	1 (0.7)	1 (0.7)	0	0
Vomiting	0	0	2 (1.5)	1 (0.7)
Constipation	0	0	1 (0.7)	0
Hyperhydrosis	0	0	1 (0.7)	0
Hypotension	0	0	1 (0.7)	1 (0.7)
Pruritis	0	0	1 (0.7)	0

Data are presented as number (%) of patients. Adverse events (AEs) are presented by MedDRA preferred term in decreasing order of frequency in the methoxyflurane group, follow by the standard analgesic treatment group
* Events considered possibly or probably related to study treatment by the investigator.

Saudi Arabia, and Singapore[37,38]. The maximum daily dose is generally 6 mL, with a weekly limit of 15 mL, and consecutive daily administration is not recommended.

In the United States, the FDA determined in 2005 that methoxyflurane was associated with se and irreversible nephrotoxicity, concluding that the risks outweighed its potential benefits. As a result, it was withdrawn from the market for safety reasons, and new clinical studies would be required before its reintroduction[39]. Figure 4 shows the countries where methoxyflurane has been authorized to use.

Use in children

Methoxyflurane may be used in children in Australia and New Zealand, but only at the minimum effective dose, as prolonged exposure in animal studies has shown potential neurodevelopmental risks[32].

In other countries, its use is not authorized for pediatric use[36,40].

However, the EMA has authorized a randomized, double-blind, multicenter, placebo-controlled study to evaluate the safety and efficacy of methoxyflurane for the treatment of acute pain in children and adolescents from 6 to less than 18 years of age presenting to an emergency department with minor trauma. The use of methoxyflurane in pediatric patients may become an option in the future[41].

Use during pregnancy

Methoxyflurane is categorized as a Class C drug in Australia and New Zealand, indicating that it may cause reversible fetal harm without causing malformations. Its use is advised against in compromised fetuses and should be approached with caution in pregnancy[32].

In Canada, methoxyflurane is not indicated for use during pregnancy or the peripartum period, including labor. All general anesthetics, including methoxyflurane, carry the potential for central nervous system and respiratory depression in newborns, warranting careful consideration when used in pregnancy[36].

Conclusion

Methoxyflurane, introduced as a volatile anesthetic in the 1960s, has evolved into a valuable analgesic at subanesthetic doses. No longer used for general anesthesia due to nephrotoxicity, its potent, rapid pain relief has established its role in modern emergency and trauma care.

This review highlights its self-administration capability, non-invasive delivery, and favorable safety profile, with clinical trials reporting only mild, transient adverse effects when used appropriately. Large studies further reinforce its reliability in acute pain management.

The growing awareness of the healthcare sector's environmental footprint highlights the importance of optimizing methoxyflurane's use, ensuring that clinical benefits are maximized while minimizing its ecological impact. Internationally, methoxyflurane is widely accepted in Australia, New Zealand, and Europe for managing acute pain from trauma and procedures.

Knowledge gaps remain regarding its use in pediatric and pregnant populations, warranting further research. Methoxyflurane also shows promise as a lower-impact alternative to nitrous oxide, and future studies should continue evaluating both its clinical applications and ecological footprint.

In summary, methoxyflurane is a rapid, effective, and increasingly important analgesic with a favorable safety and environmental profile, well-suited to modern emergency medicine.

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The authors agree to share the data reported in this study upon reasonable request. Interested parties may contact the main author, Esther Bossuyt, for further details on the conditions for data access.

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