SUPPLEMENTARY MATERIALS

UPDATED EUSEM GUIDELINE: MANAGEMENT OF ACUTE PAIN IN EMERGENCY SETTINGS

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Introduction

The updated EUSEM guidelines provide comprehensive recommendations for both adult (≥16 years) and paediatric (≥1–≤15 years) populations. The principles of the recommendations are predicated on multimodal pain management strategies using a 'traffic light' system for pain severity integrated with the CERTA (Channels-Enzymes-Receptors Targeted Analgesia) and WHO analgesic ladder approach (Figure S1). (1, 2) Key recommendations include systematic pain assessment using validated tools, consideration of multiple administration routes (oral, intranasal, inhaled, intravenous, nerve blocks), and patient-specific approaches addressing characteristics such as age, ethnicity, comorbidities, and special populations. The guidelines prioritize non-opioid and multimodal analgesia while reserving opioids for appropriate cases, emphasizing training, education, and regular audit to optimize patient outcomes across European emergency settings.

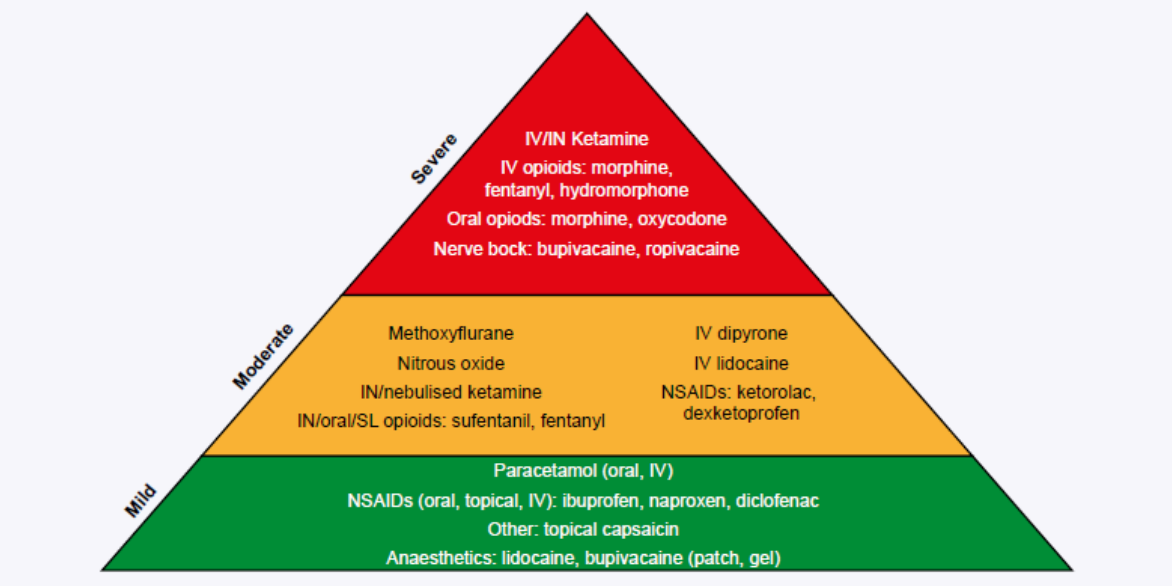
These Supplementary Materials provide additional information to support the published guidelines and focus on the role of:

1. Guiding principles for acute pain management in emergency settings
2. Protocol development and audit to support acute pain management implementation
3. Multimodal strategies to manage acute pain
4. Pain assessment in optimizing patient care
5. Non-pharmacological approaches to acute pain management
6. Approach to pharmacological management of acute pain in emergency settings
7. Route of administration of analgesia in the emergency setting
8. Pharmacological options in acute pain management
9. Patient characteristics and comorbidities that impact the administration and considerations for analgesia in emergency settings

Additional information on the literature search protocols undertaken, grading criteria for identified publications, and summaries of all data pertaining to pharmacological options for the guidelines (both 2020 and 2025) are included in Tables S1–S4.

For further information, please also refer to the full guideline handbook available on the EUSEM website (https://eusem.org/images/251210_EUSEM_European_Pain_Initiative_Guidelines_Updated_Oct_2025.pdf).

Figure S1. Overview of the step-wise management of pain according to pain severity that outlines the placement of analgesics from the CERTA approach (adapted from Cisewski et al. 2019) (1)



IN, intranasal; IV, intravenous; NSAIDs, non-steroidal antiinflammatory drugs; SL, sublingual

Management of acute pain in the prehospital and hospital settings

1. Guiding principles

To provide the flexibility required in busy, diverse emergency settings EUSEM recommendations have been based on an agreed set of guiding principles:

- Effective analgesia education in pain assessment and management for clinicians, nurses, and paramedics in emergency settings is crucial for addressing oligoanalgesia and improving patient outcomes with standardized training and effective protocols. Effective education needs to be underpinned by regular training for all emergency personnel to ensure effective and timely intervention.
- Development of manageable and effective multimodal acute pain management protocols for all emergency personnel to mitigate uncontrolled pain.
- Evaluation by clinicians of how patient distress is contributing to a patient's pain experience - acknowledge it, address it empathically, and demonstrate a willingness to understand their experience.

- Documentation of patient pain intensity pre- and post-interventions. Baseline and regular pain assessments should be undertaken and documented using tools applicable to the individual in pain. Unidimensional scales such as Numerical Rating Scale (NRS) and Visual Analogue Scale (VAS) remain the norm, but EUSEM recommends the consideration of multidimensional pain scales such as the Brief Pain Inventory (BPI) short form to capture additional facets of the patient's experience.
- Effective, documented communication with patients and their caregivers to set realistic expectations for their pain management, gaining their input through shared decision-making and exploring 'success' in relation to pain control.
- If pharmacological analgesia is required, ensure that there are no contraindications to medications before administration and ensure that all medications administered are clearly documented.
- First-line analgesia should be determined by the patient's baseline pain and pain reassessed at a pre-determined interval, with analgesic escalation or de-escalation as required with multimodal analgesia using CERTA principles in line with the established WHO analgesic ladder. (1, 2)
- Consider the route of analgesic administration, determining choice based on pain severity, patient characteristics, staff training levels, and clinical urgency rather than defaulting to a traditional IV opioid approach.
- Ensure all patients being discharged to home are given effective post-discharge information and analgesia.
- Audit emergency pain management practice at least annually to determine efficacy and areas for improvement.

2. Protocol development and audit

EUSEM recommend that within individual emergency settings it is essential to develop pain management protocols that include pain assessment and management strategies that can be audited and evaluated over time to improve patient outcomes.

Standardized, multimodal acute pain protocols in ED and pre-hospital care improve time to analgesia, analgesic adequacy and patient satisfaction without compromising diagnostic accuracy or safety. (3, 4) Implementation studies and meta-analyses show protocol-based care reduces door-to-analgesia times by ~30–40 minutes and increases pain score reductions without impairing diagnostic accuracy in conditions such as acute abdominal pain. (4)

Core approaches in a pain management protocol are effective, consistent and repeated pain assessment and management of pain within a multimodal framework.

Barriers and challenges to effective protocol development include organisational and infrastructure factors such as: oligoanalgesia, diagnostic overshadowing, limited pain education, workload, protocol non-adherence, lack of feedback data, incomplete documentation, and underuse of structured protocols. (5-7)

Development of protocols can optimise patient care and provide opportunities including significant improvements in pain assessment, shortened time to first dose of analgesia and appropriate opioid use. (3, 7) Effective protocols also provide opportunities for nurse- or paramedic-initiated analgesia with the possibility for decision-support prompts in electronic records, and simulation-based education programmes. (3, 7) Protocols enable tailored pre-hospital algorithms (including intranasal options and paediatric-specific pathways) and standardized handover between emergency services personnel and the ED driving continuity of care across the entire emergency trajectory

Audit of protocols and their implementation is a key quality improvement tool in both EDs and pre-hospital settings, systematically reviewing current care against explicit standards and enabling targeted interventions to enhance the assessment and management of acute pain. (8, 9) Audit of pain assessment and management can reveal common issues such as incomplete pain score documentation and under-treatment, prompting targeted education and policy changes that improve patient outcomes. Audit should be undertaken at least annually.

Protocols drive improved pain control which is associated with higher satisfaction, better functional recovery and no increase in adverse events when protocols embed monitoring, dose titration and reassessment loops in both ED and pre-hospital settings.

3. Multimodal management

EUSEM recommends pain management within a multimodal, multidisciplinary framework that embraces opioid stewardship. This approach needs to integrate non-pharmacologic, and procedural interventions, involving collaboration among healthcare professionals.

Multimodal analgesia combines diverse interventions to target pain through different mechanisms, and can reduce opioid consumption, shorten ED length of stay, and improve pain outcomes without increasing adverse effects. (10-12) Core components of an effective multimodal analgesia approach should include pharmacological agents, (11, 13) non-pharmacological methods including immobilisation, splinting and psychological interventions,

(7, 8) and opioid stewardship, reserving opioids for severe pain in appropriate patients with protocols emphasising low-dose, short-duration use. (7, 13)

A multimodal approach to analgesia should consider psychological interventions such as the sharing of information about the procedure and what the patient might expect to feel during it, (14, 15) and distraction techniques such as the use of imagery, music and relaxation. (16-18) A range of data exists that explores the role of nurse-initiated interventions in the ED setting suggesting that analgesia implemented early by a range of personnel is feasible and effective. (19-23)

4. Pain assessment: a treatment imperative

Assessment of pain is a treatment imperative, and poor assessment of pain can lead to oligoanalgesia and worse patient outcomes. (24) Analgesia may be desired by patients at lower pain scores than those considered by physicians, whilst others reporting high pain scores may eschew analgesia. (25) The practicalities of pain assessment in emergency settings and patients' needs and expectations means a re-evaluation of analgesic success may be required with a threshold of 50% reduction in pain score only poorly reflective of the patient's experience. (25)

EUSEM recommends it is prudent to consider including the use of multidimensional pain assessment tools in the emergency setting, with examples such as the McGill Pain Questionnaire and BPI suggested for use over the Visual Analogue Scale (VAS) or Numeric Rating Scale (NRS). (26)

It is recommended that all patients receive a baseline assessment of pain on arrival to Emergency Services in the prehospital setting or on arrival to the ED immediately and, as a minimum, within 15 minutes.

All patients should have their pain reassessed regularly. Frequency of reassessment should be determined by baseline pain score and route of administration of first-line analgesia.

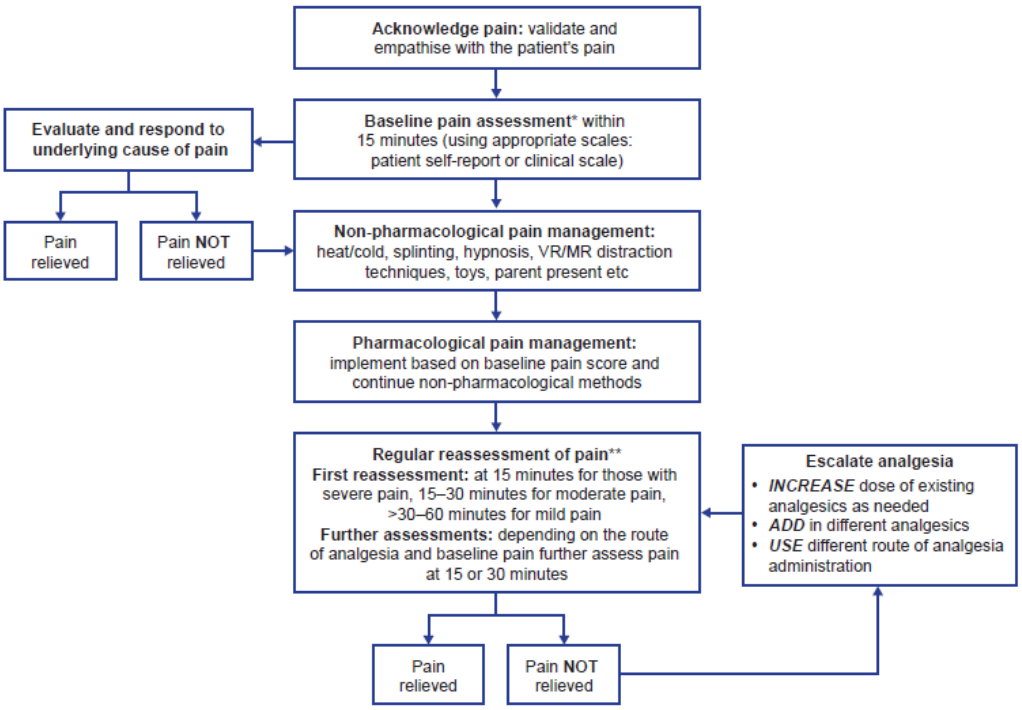
- For patients in severe pain the first reassessment of pain should take place within 15 minutes of first-line analgesia being implemented.
- For patients with moderate pain the first reassessment of pain should take place within 30 minutes of first-line analgesia being implemented.

It is recommended that physicians consider fast onset inhaled or intranasal (IN) analgesia in patients with moderate or severe pain for immediate administration as other routes of analgesia are being established. These include IN/nebulized ketamine, (27-34) IN opioids

such as fentanyl (35-37) and sufentanil, (38-40) inhaled methoxyflurane (41-47) or nitrous oxide. (48-50)

The proposed pathway for patients in pain in emergency settings is shown in Figure S2.

Figure S2. Managing pain in emergency settings: patient pathway



MR, mixed reality; VR, virtual reality.
**Pain assessment: where possible use patient self-report. Consider the pain scoring tool used to ensure it meets the needs of the patient, particularly those who are unable to self-report effectively such as children and those with cognitive impairment. Where possible use tools that are multidimensional but easy to implement in a busy emergency environment.*
***Pain reassessment: time of reassessment is determined by the degree of baseline pain and analgesic options adopted.*
ADULTS & CHILDREN: consider first reassessment of pain as follows: for severe baseline pain at 15 minutes, baseline moderate pain 15–30 minutes and >30–60 minutes for mild pain. On reassessment, if pain reduction is not evident then escalate analgesia and reassess. Route of analgesia administration should also be considered. For IV, IN and SL administration reassess pain score at 15 minutes. For IM and PO administration assess pain at 30 minutes.

5. Non-pharmacological approaches to acute pain management

Whilst non-pharmacological management of pain in emergency settings remains unchanged from previous recommendations, incorporation of newer technologies should be considered.

(51) Psychological interventions such as the sharing of information about the procedure and what the patient might expect to feel during it are an imperative. (14, 15) Establishing patient trust, especially in children, has been shown to be effective in gaining their cooperation and enabling implementation of analgesia, (52, 53) Distraction techniques such as the use of imagery, music and relaxation, may be most appropriate to acute pain in the ED, (16-18) although robust clinical evidence specific to this setting is currently lacking.

Since 2020, rapid, technological advances have emerged including modified reality (MR), virtual reality (VR) and artificial intelligence (AI) and should be considered for patients where resources allow. VR has emerged as a promising non-pharmacological intervention for acute pain management in EDs and prehospital settings. A review by Viderman and colleagues evaluated all current evidence and demonstrated that VR can be successfully employed to control pain, including acute, perioperative, periprocedural and chronic. (54) A Swiss ED study demonstrated significant pain reduction (median NRS 4.5 to 3.0, $p<0.001$) and anxiety reduction (median NRS 4.0 to 2.0, $p<0.001$) following 20-minute VR sessions in 52 adult patients with traumatic and non-traumatic pain. Systematic reviews confirm VR's effectiveness across medical procedures, with 83% of studies reporting decreased pain intensity compared to controls. (55, 56) Modern standalone VR headsets (e.g. Oculus Quest 2) overcome previous implementation barriers, making emergency and prehospital deployment feasible. High user satisfaction, good tolerability, and minimal side effects support VR’s integration into multimodal acute pain protocols.

5. Pharmacological approach

The pharmacological approach to acute pain management in emergency settings has also evolved. EUSEM have integrated the CERTA approach and pyramid (Channels-Enzymes-Receptors Targeted Analgesia) into updated recommendations aligned with an adapted pain ladder from WHO. It is hoped that this approach means guidelines will retain relevance across all healthcare systems for the longer term, regardless of drug availability and encourage physicians to think holistically about every individual patient. (1, 2) An overview of the CERTA approach adopted for these guidelines is shown in Figure S1.

6. Considering the route of administration for analgesia

When considering analgesic medication, route of administration should be evaluated based on pain severity, patient characteristics, staff training levels, and clinical urgency rather than

defaulting to traditional IV opioid approaches. Choice should meet the needs of the individual patient and the required speed of onset for analgesia.

- The oral route is preferred where possible as it requires minimal specialized training and represents the simplest, most cost-effective approach to analgesic delivery. Typically reliable in most cases, it does have a slower onset to effect than IV.
- Topical analgesia/anaesthesia should be limited to superficial wounds and lacerations and other local pain but is particularly useful for paediatric patients requiring onward analgesia using more invasive routes of administration or for patients who have a fear of needles. Onset to effect is slow requiring 30–60 minutes for effect.
- Intranasal administration requires basic training in nasal anatomy, proper device positioning, and dosing calculations. With a fast onset to effect it is particularly valuable for paediatric patients, those with difficult IV access, or situations requiring rapid non-invasive analgesia. Contraindications include nasal obstruction, bleeding disorders, or facial trauma affecting nasal passages.
- Sublingual (SL) or buccal administration requires minimal training focusing on proper tablet/film placement, patient positioning, and swallowing avoidance. Onset to effect of drugs like SL fentanyl peaks at 15–30 minutes, and 15 minutes for drugs like buccal paracetamol. SL and buccal dosing is suitable for conscious patients and is particularly valuable in patients unable to swallow but requiring faster analgesic onset than oral medications. SL and buccal administration is contraindicated in those with oral lesions, altered mental state that prevents cooperation and in those with severe xerostomia.
- Nebulized or inhaled analgesia requires training in device setup, dosing calculations, and patient positioning. Nebulized or inhaled analgesics are suitable for conscious patients with intact respiratory function, but are contraindicated in respiratory depression, pneumothorax, otitis or patient altered mental state. Nitrous oxide has long been a backbone for analgesia with an onset to effective within 20 seconds with peak effect at 3–5 minutes and immediate reversibility upon discontinuation. Nebulized fentanyl shows onset within 5–10 minutes with sustained effect. Inhalation of methoxyflurane using the specific Penthrox® inhaler is a quick, well tolerated and effective method of analgesia for conscious patients without any changes in consciousness, circulation and respiration. The use of methoxyflurane has been well established in adults within Europe. (57, 58) Efficacy has also been established in children in Australia and one European study demonstrating efficacy. (59, 60) The MAGPIE trial evaluating methoxyflurane in children, (61) is yet to formally be

published, but results from 240 children aged 6–18 years in Ireland with moderate-to-severe pain had faster and greater reductions in pain than those treated with placebo. These results have culminated in approval for use in children in Ireland. (62) Despite this robust evidence base, the lack of formal regulatory approval for paediatric use of Penthrox in wider Europe remains a significant barrier, but should be considered for those children able to cope with instruction, without facial injuries.

- IV administration has a fast onset, with reliable outcomes and is excellent for fast and precise, titratable analgesia but may be less practical in out of hospital settings and requires advanced training in venipuncture techniques, sterile procedures, and recognition of complications including infiltration and phlebitis. Analgesic onset is within 10 minutes depending on the medicine (e.g. opioids, ketamine). Limitations include difficulty establishing access in hypovolemic, paediatric, or technically challenging patients.
- Ultrasound guided nerve blocks are gaining traction in emergency settings, but require extensive training including ultrasound image interpretation, needle manipulation skills, local anaesthetic pharmacology, and complication management. Nerve blocks demonstrate onset within 5–15 minutes depending on technique and agent used, with duration of 6–12 hours. Nerve blocks are indicated for moderate-to-severe pain or specific traumatic injuries as well as specific anatomical pain patterns, patients requiring prolonged analgesia and those intolerant of systemic opioids. Nerve blocks are contraindicated in those with infection at the injection site, coagulopathy or patient refusal.

7. Pharmacological options for emergency settings

When considering pharmacological analgesia assess each patient for contraindications for all drugs planned for use, including simple analgesics. For each planned analgesic, consult the Summary of Product Characteristics for each medication available in your country or from the European Medicines Agency (EMA) as required, for further information and an overview of drug-drug interactions.

A detailed overview of studies supporting the use of pharmacological analgesia used in the emergency setting is provided in Table S3 and a detailed overview of non-pharmacological studies has been previously published. (51)

EUSEM suggests a series of guiding considerations for pharmacological prescribing:

- Do not use intravenous (IV) opioids in combination with other IV opioids because of the risks of sedation and respiratory depression.
- When administering opioids ensure that naloxone is available for reversal and ready to use as required if clinically significant sedation or respiratory depression occurs.
- Only prescribe second-line NSAID analgesia (e.g. diclofenac or ketorolac) in patients who have not received previous NSAIDs e.g. ibuprofen.
- When combining strong analgesics such as ketamine with opioids, to decrease the risk of respiratory depression consider strategies that provide ketamine first (up to the maximum permitted dose) and then titrate opioids to appropriate analgesia rather than the other way around.

Codeine and tramadol are not included as part of EUSEM recommendations because of their significant pharmacological limitations, safety concerns and availability of superior alternative medications. However, it is recognized that in some countries the use of codeine or tramadol for acute pain is advocated and, in these instances, local recommendations should be considered. However, codeine is contraindicated in children. For countries where codeine or tramadol are advocated EUSEM suggests users refer to specific national or institutional guidance.

Given the variety of medication availability across Europe, the EUSEM recommendations have been developed with a range of flexible alternative options to meet the needs of individual institutions and settings. Before using these recommendations, it is incumbent on

the user to review their analgesic choices against the needs and characteristics of their individual patient.

8. Understanding specific patient characteristics and comorbidities that impact acute pain management

EUSEM recommends consideration of patient characteristics when exploring analgesia, including those unrelated to the patient's pain. Research highlights systemic biases, communication barriers, and protocol gaps that exacerbate risks for certain groups. These disparities often lead to prolonged suffering, increased complications, and long-term health consequences. Consider each patient as an individual and adjust management and clinical thinking accordingly.

Children

Understanding the issues and biases that exist when confronted with the child in pain in emergency settings is important to optimise care. There are disparities in the delivery of analgesia to children as noted in a range of studies due to ethnicity, age and pain type. (60, 63-66)

It is recommended that pharmacological management of pain in children contains both non-opioid and opioid agents as well as non-pharmacological methods as appropriate. In children, the use of IN and inhaled medications such as IN fentanyl and inhaled nitrous oxide or methoxyflurane may be useful as single drugs or in combination with other analgesics. (67) These medications are well tolerated, easy and fast to administer with rapid onset and short duration of action. and would seem to be drugs of choice, but both require patient cooperation and may not be suitable for those with facial trauma. (67) Inhaled methoxyflurane has very recently been approved for use in children in Ireland, (62) and but currently it remains off-label in wider Europe.

Older adults and elderly patients

Providing effective analgesia to older patients is a common challenge faced by emergency physicians. Older patients have been shown to be at greater risk of oligoanalgesia, (68, 69) and in the ED are up to 20% less likely to receive treatment than younger patients. (70) Analgesia should be selected based on patient-specific risks and patient preferences. Whilst there is a need to consider age and polypharmacy when choosing analgesia for elderly

patients it should be noted that for many analgesic treatment options efficacy and safety are comparable in younger and older patients.

Patients with kidney disease

Pain is highly prevalent in patients with chronic kidney disease (CKD) and those presenting with renal complications, and poorly managed pain in this group is linked to decreased quality of life and survival. (71, 72) Assessment must consider the cause, severity, and type of pain, as well as the patient's level of kidney function and concurrent comorbidities. (71, 73)

For all patients, particularly those with reduced drug clearance, a multimodal, stepwise approach to analgesia must be adopted. First-line approaches should emphasise non-pharmacological and non-opioid interventions wherever possible. (72-74) Analgesic selection and dosing must account for reduced renal clearance, comorbidities, and potential drug interactions.

Patients with liver disease

Acute pain is common in patients with liver disease – affecting up to 80% of people with liver disease – but management is complicated by impaired liver function, altered pharmacokinetics, comorbidities (such as coagulation disorders and encephalopathy), and elevated risk of drug toxicity. (75-78) Pain aetiology, severity, liver disease stage, and risk of hepatic encephalopathy must guide analgesic selection and dosing. (75, 77)

Non-pharmacological interventions and a multimodal analgesic strategy should be prioritized to reduce reliance on medications with hepatic metabolism. (75) A tailored patient-centric approach is essential and a multidisciplinary approach including hepatology and pain specialists should be considered. (75) One of the greatest limitations of medication selection in those with liver disease is the reduction in hepatic clearance of certain medications, which most often leads to increased drug exposure.

Patients with sickle cell disease and sickle cell crisis

Acute pain crises (vasoocclusive episodes, VOC) are the most common reason for emergency visits in sickle cell disease (SCD). (79-81) There are no objective measures for pain severity in SCD, so management relies on the patient's report of pain and previous effective regimens – their report of pain should be considered gold standard. (82) Whenever

possible, use individualized pain protocols based on what has previously worked for the patient as these have potential to improve pain scores, length of stay in the ED and time to first opioid analgesia. (83)

Pregnancy

Analgesic prescribing during pregnancy is challenging, with the general rule being to avoid any medication, and whilst many analgesics may be considered safe to use there are specific considerations to be noted. (84) Non-pharmacological treatment should always be considered before analgesic medications are used. Paracetamol is regarded as safe in all three trimesters and is the analgesic of choice for pregnant patients with no risks noted for congenital abnormalities or spontaneous abortion. (85) NSAIDs, in particular ibuprofen, are best avoided but can be used in the second trimester (85) but should be avoided in the third trimester because of the risk of premature closure of the ductus arteriosis. (86) Evidence for opioids in pregnancy is largely limited to pregnant patients abusing opioids, which is associated with adverse neonatal outcomes. Short-term use of opioids for pain in pregnancy does not, however, appear to be problematic for patients or foetuses. (8, 84) Although nitrous oxide is not absolutely contraindicated in pregnancy it should be used with caution as it can have maternal and foetal side effects, most data confine the use of nitrous oxide to labour pain rather than emergency pain or for termination of pregnancy. (87-89)

Ethnic minorities

Patients from ethnic minorities may be underserved with respect to effective pain control in prehospital settings (63) and are less likely to receive opioids or ketamine. (90) Across the spectrum of analgesia prescriptions, people of an ethnic minority were significantly less likely to receive opioid analgesia. (91-94) All studies are from the US where the opioid crisis has accelerated in a different way to Europe. European data are lacking, and further research would be welcomed. However, understanding and exploring individual and institutional biases should be considered to prevent sub-optimal analgesia in those from ethnic minorities and to evaluate possible impact on pain management.

Pain management in neurodivergent people

Pain perception is a complex process and individuals with neurodivergence including those with autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD) and Tourette syndrome can experience increased pain sensitivity and may exhibit an atypical response to pain although data on this phenomena are limited. (95-97) Further, people with neurodivergent conditions such as ASD may struggle to communicate their pain and need for analgesia. (98) To optimise assessment and management of pain in people with ASD clinicians might consider:

- Environmental modifications
- Adjustments of language to the patient
- Time and patience with patients
- Inviting input from others
- Using measures and assessment scales appropriate for use in ASD such as Quantitative Sensory Testing. (95)

All of these modifications and an understanding of neurodivergence and its impact on pain perception and presentation require education of parents, caregivers and also healthcare professional staff.

Patients receiving opioids for chronic pain

Any patient in receipt of analgesia for chronic pain conditions presenting with new acute pain needs to be assessed on a case-by-case basis to ascertain the cause. Data supporting the use of opioids in the ED for treatment of acute exacerbation of chronic, non-cancer pain demonstrate higher likelihood of harm rather than benefit. (99) In patients currently receiving opioids, the amount of opioid used daily prior to the onset of the new pain must be determined and adequate doses of opioid need to be prescribed to treat baseline pain in combination with short-acting opioids to address the new acute pain. (8, 100) Opioid analgesics should not be routinely used in the ED for chronic non-cancer pain with a notable exception of VOC crisis of SCD. (99)

Acute pain management in patients with opioid misuse disorder

Managing acute pain in patients with opioid use disorder (OUD) or those receiving opioid substitution therapy (OST) poses significant clinical challenges, often leaving patients undertreated. (101) Whilst data to support analgesia in these patients is limited, a recent

systematic review suggests the use of oral clonidine, IM haloperidol and midazolam with IV morphine or IV lidocaine may improve pain outcomes. (102)

Patients need assurance that their pain will be assessed and managed appropriately as they may be anxious about stigmatisation and denial of analgesia. Inadequate treatment of pain in patients on opioid replacement therapy (e.g. methadone or buprenorphine/naloxone) commonly leads to disruptive behaviour by angry and frightened patients who then may discharge themselves against medical advice, often to the detriment of their health.

Drug-seeking behaviour

There will be occasions when patients presenting with a chief complaint of pain may raise suspicions of drug seeking behaviour. A careful history and patient review are required to balance the risk of supplying drugs inappropriately with denying effective analgesia to patients with genuine pain. Until more information is available, unless there is strong evidence to the contrary, an assumption must be made that the patient is in real pain and appropriate analgesia supplied. (8, 103) In patients addicted to opioids who are reporting genuine pain, consider the use of non-opioid approaches such as steroid injections, radiofrequency neurotomy, nerve blocks or non-pharmacological approaches. (104)

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Table S1. Literature search parameters from 1st January 2020 to 30th May 2025

Database	Search
Pubmed/Embase/ Cochrane Limits: none Methodologic filter: none	"Emergency medicine" OR "Emergency nursing" OR "Emergency medical services" OR "Emergency room" OR Emergency department" OR Pre-hospital OR prehospital AND pain AND analges*
	(("Emergency department" OR Pre-hospital OR prehospital AND pain AND analges*) AND (intravenous[Title/Abstract]))
	(("Emergency department" OR Pre-hospital OR prehospital AND pain AND analges*) AND (intranasal[Title/Abstract]))
	"Emergency department" OR Pre-hospital OR prehospital AND pain AND analges*
	"Emergency medicine" OR Pre-hospital OR prehospital AND pain AND ibuprofen
	"Emergency medicine" OR Pre-hospital OR prehospital AND pain AND paracetamol
	"Emergency medicine" OR Pre-hospital OR prehospital AND pain AND NSAIDs
	"Emergency medicine" OR Pre-hospital OR prehospital AND pain AND metamizole
	"Emergency medicine" OR Pre-hospital OR prehospital AND pain AND nitrous oxide
	"Emergency medicine" OR Pre-hospital OR prehospital AND pain AND methoxyflurane
	"Emergency medicine" OR Pre-hospital OR prehospital AND pain AND fentanyl
	"Emergency medicine" OR Pre-hospital OR prehospital AND pain AND morphine
	"Emergency medicine" OR Pre-hospital OR prehospital AND pain AND opioids
	"Emergency medicine" OR Pre-hospital OR prehospital AND pain AND opioids OR fentanyl OR morphine
	"Emergency medicine" OR Pre-hospital OR prehospital AND pain AND ketamine
	"Emergency medicine" OR "Emergency nursing" OR "Emergency medical services" OR Pre-hospital OR prehospital AND pain AND analges*
	"Acute pain" AND Analges* AND wound* OR injur* AND "pain therapy" AND Pre-hospital OR prehospital AND "Emergency medicine" OR "Emergency nursing" OR "Emergency medical services"
	"pre-hospital" OR prehospital AND pain AND analges*
	"pre-hospital" OR prehospital AND pain
	Analges* OR "therapy" AND "acute pain" OR pain AND "pre-hospital" OR prehospital
	Analges* OR "therapy" AND "acute pain" AND "pre-hospital" OR prehospital
	Analges* OR "therapy" AND "acute pain" AND emergency OR "pre-hospital" OR prehospital
	Analges* OR "therapy" AND "acute pain" AND emergency OR "pre-hospital"
	Analges* OR "therapy" AND "acute pain" AND "intravenous" OR "intranasal" OR "inhaled" OR "intramuscular"
	Analges* OR "therapy" AND "acute pain"
	Analges* AND "acute pain"

Table S2. Inclusion and exclusion criteria for reviewed data

Inclusion	Exclusion
RCTs Clinical trials without randomisation e.g. open label, observational, retrospective Meta analyses Case series/case-controlled studies Systematic reviews English language	Individual case reports Treatment methods not found in the ED e.g. acupuncture After 30 May 2025 Publication not in English

RCTS, randomised clinical trials

Table S3. GRADE approach adopted for evidence reviewed for bias and graded accordingly.[3]

IA	Evidence from meta-analysis of randomised controlled trials with a very low risk of bias
IB	Evidence from at least one randomised controlled trial with a low risk of bias
1C	Evidence from meta-analysis of randomised controlled trials with a high risk of bias
IIA	Evidence from at least one controlled study without randomisation with low risk of confounding bias and high probability that the relationship is causal
IIB	Evidence from at least one other type of quasi-experimental study with low risk of confounding or bias and a moderate probability that the relationship is causal
III	Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies high risk for potential bias or confounding and a risk that the relationship identified is not causal
IV	Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both

Table S4. Overview of included studies
Cited references for the table below are shown at the end of the supplement

Therapy	Route of administration	Overview of study/data	Level of evidence
NITROUS OXIDE			
	Inhaled	**Thal et al. 1979**[2] Of 47 patients with abdominal or chest pain, MSK trauma or burns treated by a mobile unit, 44 (93.6%) achieved partial or complete pain relief with nitrous oxide.	IV
	Inhaled	**Ducassé et al. 2013**[3] In patients with moderate acute pain being transported by ambulance, 67% of 30 patients treated with nitrous oxide had NRS ≤3 at 15 minutes versus 27% of 30 patients treated with medical air (p<0.001).	IB
	Inhaled	**Herres et al. 2016**[4] Significant reductions in mean pain scores at 20 minutes, sustained to 60 minutes, were reported in 85 patients in the ED with moderate-to-severe pain who self-administered nitrous oxide.	IIB
PARACETAMOL			
	Oral	**Lyrtzis et al. 2011**[5] Patients with acute ankle sprain were randomised to receive oral paracetamol (n=45) or oral diclofenac (n=45). There was more ankle oedema in the diclofenac group at Day 3 but not at Day 0, but no difference in pain reduction between groups.	III
	Oral	**Bondarsky et al. 2013**[6] In a double-blind RCT of adult ED patients with acute MSK pain randomised to oral paracetamol (n=30), oral ibuprofen (n=30) or combination (n=30), pain scores decreased over the 1-hour study period for all groups, with no significant differences between groups in terms of pain reduction or need for rescue analgesics.	IB
	Oral	**Buccelletti et al. 2014**[7] In patients with localised traumatic or inflammatory pain of the extremities treated with oral paracetamol and codeine (n=87) or oral ketorolac (n=113), paracetamol and codeine was equivalent to ketorolac in non- and post-traumatic pain, but superior in acute, fracture and muscular pain.	IIB

Therapy	Route of administration	Overview of study/data	Level of evidence
	Oral	**Ridderikhof et al. 2018[8]** Patients with acute blunt minor MSK extremity trauma randomised to oral paracetamol (n=182), oral diclofenac (n=183) or combination therapy (n=182) showed no significant differences in NRS reduction at 90 minutes, either at rest or with movement.	IB
	IV	**Craig et al. 2012[9]** Patients with isolated limb trauma and in moderate-to-severe pain were randomised to IV paracetamol (n=27) or IV morphine (n=28). There were no significant differences between groups in terms of analgesic effect at any time point measured or rescue analgesia required, but there were significantly more adverse reactions in the morphine group.	IIB
	IV	**Zare et al. 2014[10]** In patients with acute bone fracture randomised to IV morphine (n=74) or IV paracetamol plus oral oxycodone (n=79), pain scores were lower in the morphine group at 10 minutes, but similar at later time points. Nausea and itching were seen significantly more frequently in the oxycodone/paracetamol group.	IB
	Mixed (oral, IV)	**Dijkstra et al. 2014[11]** A systematic review of pain relief in emergency care in the Netherlands included 4 studies in which paracetamol was used. Pain reduction was seen in all 4 studies, but effective pain relief of more than 20 mm on the VAS or 2 points on the NRS was reported in only 2 of the 4 studies.	IV
	IV, oral	**Charlton et al. 2020[12]** Evaluation of 80 care records, 40 patients had IV paracetamol and 40 had oral paracetamol for reports of abdominal pain, infection and trauma. IV paracetamol provided significant improvements in pain compared with oral paracetamol (NRS reduction 2.02 versus 1.76, p=0.0013). No additional analgesia was required, and AEs were not reported.	III
PARACETAMOL + OPIOIDS			
Paracetamol plus hydrocodone OR codeine OR ibuprofen	Oral	**Bijur et al. 2021[13]** RCT of 600 patients randomised to 5 different regimens with NRS measured at 1 hour. No significant differences between groups were observed. • 400 mg ibuprofen/1 g paracetamol, NRS reduction 3.0 (95% CI 2.6–3.5) • 800 mg ibuprofen/1 g paracetamol, NRS reduction 3.0 (95% CI 2.5–3.5) • 30 mg codeine/300 mg paracetamol, NRS reduction 3.4 (95% CI 2.9–3.9) • 5 mg hydrocodone/300 mg paracetamol, NRS reduction 3.1 (95% CI 2.7–3.5) • 5 mg oxycodone/300 mg paracetamol, NRS reduction 3.3 (95% CI 2.8–3.7) Rescue medication was required more often in those ibuprofen/paracetamol, or hydromorphone/paracetamol compared with codeine/paracetamol or oxycodone/paracetamol. Patients in receipt of opioids were more likely to experience nausea or vomiting.	IA
Paracetamol plus IV hydromorphone	IV	**Bijur et al. 2020[14]** Double blind RCT in 159 patients, receiving 1 mg IV hydromorphone plus placebo or IV paracetamol. At 60 minutes those receiving placebo/hydromorphone had a reduction in NRS of 6.2 units and paracetamol/hydromorphone 5.4 – a difference of only 0.8 (95% CI −0.01,1.8). At 120 minutes NRS pain differences was 0.6. Patients receiving paracetamol/hydromorphone were less likely to request rescue medication at 60–120 minutes post administration (26.9% vs 37.7%) but this was not significant. The incidence of AEs was comparable in both groups, and it was clear that the addition of paracetamol did not provide superior analgesia to hydromorphone alone.	IA

Therapy	Route of administration	Overview of study/data	Level of evidence
Paracetamol plus opioids	IV	**Blok et al. 2021**[15] Additional IV paracetamol to opioids was used to see if additional analgesia could be opioid sparing. Opioid consumption was not different between each group and IV paracetamol was not opioid sparing. There was no difference between groups as to patient being admitted to hospital from the ED and there was no difference in ED LOS. After discharge from the ED those who received paracetamol required lower opioids, but the sample size was small.	IA
Paracetamol plus IV morphine	IV	**Minotti et al. 2022**[16] Multi-centre, double-blind, randomised, placebo-controlled study. Randomised patients (1:1), aged >18 years in the ED with pain score NRS >4 received IV morphine 0.1 mg/kg plus IV paracetamol 1 g or IV morphine 0.1 mg/kg plus IV placebo. Additional IV morphine 0.05 mg/kg was administered every 15 minutes until pain relief. The aim of the study was to understand if IV paracetamol could be opioid sparing, and primary outcomes was mean morphine dose for pain relief. Secondary outcomes were total dose of morphine given, time to pain relief and AEs. Of the 202 patients randomised 177 were allocated to IV morphine plus IV paracetamol and 90 to placebo. Abdominal pain was the most common pain location, and pain score did not differ between groups. Mean morphine dose to achieve initial pain relief was comparable between both groups (paracetamol 0.15 ± 0.07 mg/kg [12 mg ± 5.8 mg]; placebo 0.15 ± 0.07 mg/kg [13 mg ± 6.2 mg]). Total dose of morphine was also comparable between groups (0.19 ± 0.09 mg/kg [15.1 mg] vs 0.19 ± 0.10 mg/kg [15.5 mg]). Similarly, time to pain relief was comparable across both groups at 30 minutes. The rate of AEs was comparable between groups (paracetamol 22.9% vs placebo 32.4%) and not significantly different. Both treatments provide excellent pain relief but are comparable with no evidence of opioid sparing in the ED setting compared with the post-operative setting, which may reflect the use of fixed opioids doses in the ED compared with post-operative dosing. The study is limited by patient heterogeneity due to pain location and potentially high doses of morphine.	IA
NSAIDS			
Diclofenac OR ketorolac	Oral	**Ortiz et al. 2010**[17] Patients with acute pain due to ankle fracture (n=60) were randomised to oral ketorolac, diclofenac, or etoricoxib. Reductions in levels of pain were similar between groups (74.5%, 74.3% and 70.9%, respectively).	IIA
Ketorolac	Oral	**Ghirardo et al. 2023**[18] Multicentre randomised, double-blind comparative study in children with acute pain in the ED aged 8–18 with limb trauma and moderate (NRS 4–6) or severe (NRS 7–10) pain. Patients received ibuprofen 10 mg/kg or ketorolac 0.5 mg/kg or placebo. Primary endpoint was reduction in pain at 60 minutes in patients in severe pain. NRS reduction for ibuprofen at 60 minutes was 2.0 (IQR 1.0–4.0) and 1.0 (IQR 1.0–3.0) for ketorolac (p=NS). At 90 minutes ibuprofen was significantly superior to ketorolac (p=0.008) with more patients having an NRS <4 (p=0.01) or <3 (p=0.01). In those with moderate pain, reduction in NRS at 6 minutes was broadly comparable and not significantly different.	IB

Therapy	Route of administration	Overview of study/data	Level of evidence
Ibuprofen or ketorolac	Oral	**Friedman et al. 2024**[19] All patients (n=307) received paracetamol as run-in therapy and those with inadequate pain relief were randomised to ketorolac or ibuprofen. A second group (n=100) received ibuprofen (n=50) or ketorolac (n=50) with no paracetamol run-in. The primary endpoint was an improvement of ≥1.3 on 0-10 pain scale. Among run-in participants who received an NSAID, 82/99 (83%) achieved the primary outcome versus 84/100 (84%) no run-in participants (p = 0.82). Among all ibuprofen participants, 44/49 (90%) randomised to run-in and 42/50 (84%) randomised to no run-in achieved the primary outcome. Among all ketorolac participants, 38/50 (76%) randomised to run-in and 42/50 (84%) randomised to no run-in achieved the primary outcome. These data indicate that using paracetamol first before NSAIDs does not improve pain outcomes.	IC
Ketorolac	SL	**Neri et al. 2013**[20] In children (4–17 years of age) with fractures or dislocations, SL ketorolac (n=64) was compared with SL tramadol (n=67). Baseline pain score was IQR 8 in both groups. At 100 minutes both groups had significant reductions in pain compared with baseline that were comparable to each other: ketorolac IQR=4, tramadol IQR=5 (p<0.001). Use of rescue medication was significantly higher in tramadol treated patients (12.3%) vs ketorolac treated patients (3.3%) (p=0.098). Rates of adverse events were not significantly different between groups, but adverse events were numerically higher in the tramadol group (4.6%) vs 0% in the ketorolac group and included two children with vomiting and one with vomiting and dry mouth.	IB
Ketorolac	SL	**Plapler et al. 2016**[21] In acute low back pain SL ketorolac over 10 days has proven to be non-inferior to naproxen, but had a faster onset to analgesia at 60 minutes for 24.2% ketorolac treated patients vs 6.5% naproxen treated patients (p=0.049).	IB
Ketorolac	SL	**Cozzi et al. 2019**[22] SL preparations of ketorolac 0.5 mg/kg (n=70), tramadol 2 mg/kg (n=70) and paracetamol 20 mg/kg (n=70) in children with abdominal pain in the ED indicated comparable reductions in pain from baseline at 2 hours. Median IQR pain scores at 2 hours were 2 for ketorolac and 3 for tramadol and paracetamol which was not significantly different. However, children treated with tramadol experienced significantly more adverse events (n=8) compared with paracetamol (n=1) or ketorolac (n=0).	III
Mixed	Oral, topical, IV	**Dijkstra et al. 2014**[11] A systematic review including 5 studies of NSAID use in emergency care reported no clinically meaningful reductions of pain >20 mm on the VAS or 2 points on the NRS.	IV
Mixed	IM, IV	**Pathan et al. 2018**[23] A systematic review and meta-analysis of 36 RCTs including 4,887 patients with acute renal colic reported a marginal benefit of NSAIDs overall over opioids in terms of pain reduction at 30 minutes; fewer rescue treatments were required, and rates of vomiting were lower with NSAIDs than with opioids. Compared with paracetamol, NSAIDs showed no difference in pain reduction at 30 minutes but a reduced requirement for rescue treatments.	IC
Ketorolac	IM	**McReynolds et al. 2005**[24] Patients (n=58) with acute neck pain of <3 weeks duration were randomised to osteopathic manipulation or 30 mg IM ketorolac and pain evaluated one-hour post-dosing on a 5-point Likert scale. Both groups had reductions in pain intensity, but pain relief was significantly superior with manipulation rather than ketorolac (pain reduction 2.8 ± 1.7 vs 1.7 ± 1.6, p=0.02).	IIA

Therapy	Route of administration	Overview of study/data	Level of evidence
Ketorolac	IV	**Hosseininejad et al. 2017[25]** Patients with renal colic (n=300) were randomised to IV morphine and ketorolac (0.1 mg/kg and 30 mg, n=100) or IV ketorolac alone (30 mg, n=100) or IV morphine alone (0.1 mg/kg, n=100) in an RCT. Pain intensity significantly superior with combination therapy compared with IV morphine alone (3.01 ± 0.98 vs 3.66 ± 1.02, p=0.012) and compared with IV ketorolac alone (3.01 ± 0.98 vs 3.68 ± 0.88, p=0.018). Patients receiving combination therapy also required significantly less rescue analgesia than those receiving morphine alone (16% vs 20%, p=0.041) or ketorolac alone (16% vs 24%, p=0.012).	IIA
Ketorolac	IV	**Sotoodehnia et al. 2019[26]** Patients with acute renal colic (n=126) were randomised to IV ketamine 0.6 mg/kg (n=62) or IV ketorolac 30 mg (n=64). Both treatments reduced pain, with the onset of pain relief with ketamine faster than ketorolac (at 5 minutes pain reduction with ketamine superior to ketorolac p<0.001). At all other time points pain reduction was comparable.	IIA
Ketorolac	IV	**Adams et al. 2019[27]** Children with supracondylar humerus fracture received ketorolac as peri-operative analgesia (n=114) vs those who did not (n=228). Mean pain rating 0–29 minutes was significantly lower in patients receiving ketorolac (VAS=0.7) compared with the control group (VAS=1.4) (p=0.017) and remained significantly lower at 30 minutes up to 120 minutes (p=0.036). Patients who received ketorolac required significantly lower doses of oxycodone (1.0 vs 1.2 doses, p=0.003), and postoperative stay in hospital was 50% shorter (13.6 hours vs 20.4 hours, p<0.001). As a result, hospitalisation costs were 40% lower for ketorolac treated patients.	IIA
Ibuprofen	IV	**Friedman et al. 2020[28]** Randomised study of ibuprofen alone compared with ibuprofen in combination with paracetamol in 2 EDs in patients with low back pain (LBP). Pain was measured 1 week after the ED visit. Ibuprofen treated patients had a mean improvement in Roland Morris Disability Questionnaire of 11.9 ± 9.7 and 11.1 ± 10.7 for those on combination treatment, there was no difference between groups (between group difference 0.8, 95% CI −3.0–4.7). At 1 week, moderate-to-severe pain was reported by 28% of those in the ibuprofen group and 28% in the ibuprofen plus paracetamol group. Among ED patients with acute, nontraumatic, non-radicular LBP, adding acetaminophen to ibuprofen does not improve outcomes within 1 week.	IC
Dexketoprofen, ibuprofen	IV	**Dogan et al. 2022[29]** Comparison in LBP of paracetamol (n=71), dexketoprofen (n=70) and ibuprofen (n=69) in the ED and pain was measured using 0–100 mm VAS. At 60 minutes all groups had significantly reduced pain (p<0.05), but there were no significant differences between groups. VAS decrease: • Paracetamol 40 mm • Dexketoprofen 42 mm • Ibuprofen 43 mm	IA

Therapy	Route of administration	Overview of study/data	Level of evidence
Ketorolac	IV vs IM	**Platt et al. 2023[30]** Retrospective chart review in patients aged 65 years or more, presenting to the ED (pain modality was noted). Primary outcome was pain reduction measured by need for rescue medication at 30 minutes after ketorolac administration. Patient groups were: • IV ketorolac 15 mg (n=260) • IV ketorolac 30 mg (n=52) • IM ketorolac 30 mg (n=260) • IM ketorolac 60 mg (n=52) Rescue medication requirement was comparable across groups receiving high dose medication (IV 30 mg or IM 60 mg) 13.5% and low dose medication (IV 15 mg or IM 30 mg) 6.5% (p=0.094). Analgesia in any group was not affected by the presence of concomitant analgesia. The average change in pain scores was also not significantly different across high dose of low dose medication (p=0.154). • IV 15 mg or IM 30mg – pain score reduction NRS 2.9 (±3.1) • IV 30 mg or IM 60 mg – pain score reduction NRS 2.8 (±2.9) Time to pain reduction was also comparable across groups. The occurrence of AEs was low in both groups; oedema was the most commonly reported AE. Pain reduction was not dependant on the dosing of ketorolac	III
Ketorolac	IV	**Forestell et al. 2023[31]** Systematic review of 5 RCTS (n=627 patients) comparing high dose IV ketorolac (≥30 mg) and low dose IV ketorolac (10 mg or 15–20 mg). Pain scores were comparable in patients treated with low dose ketorolac (15–20 mg) and high dose ketorolac (mean treatment difference on VAS 0–100 mm was 0.05 [95% CI 4.91, 5.01]). Even at doses of 10 mg ketorolac no difference in pain score compared with high doses was noted (mean treatment difference on VAS 0–100 mm was 1.58 mm [95% CI -8.86 to 5.71]). Patients treated with low doses of ketorolac may have an increased need for rescue medication than those treated with high doses (RR 1.27 95% CI 0.86, 1.87) in some studies. Low doses of ketorolac had no impact on observed AEs such as nausea, flushing and dizziness, and no episodes of GI bleeding or renal dysfunction were reported.	IB
Diclofenac	Topical – patch	**Kuehl et al. 2010[32]** A systematic review of 8 studies of the diclofenac patch reported reductions in VAS pain scores ranging from 26% to 88% on Day 7 and 56% to 61% on Day 14. Median time to pain resolution was 3 days less than with placebo.	IV
Diclofenac	Topical – patch	**Mueller et al. 2010[33]** Post-hoc analysis of an RCT comparing the diclofenac patch (n=60) with placebo (n=60) in pain due to acute traumatic stress injury revealed that diclofenac patch was consistently superior to placebo in providing relief from pain on movement, with mean differences in VAS score versus placebo greatest on Day 2 and Day 3 of the 7-day study (both p<0.0001).	III

Therapy	Route of administration	Overview of study/data	Level of evidence
Diclofenac	Topical – patch	**Lionberger et al. 2011**[34] Multicentre, randomised, placebo-controlled study in 134 adults with acute ankle pain due to sprain. Patients with acute ankle pain caused by a minor sprain were randomised to the diclofenac patch (n=68) or placebo (n=66) daily for 7 days and pain intensity was evaluated on treatment days 1, 2, 3 and 7. Patients treated with the diclofenac patch experienced a significantly greater reduction in pain (VAS 66.9 to 10.5 on Day 7) compared with placebo (VAS 70 to 18.4 on Day 7 p=0.0008), beginning 4 hours into treatment (p=0.02). Diclofenac patch was well tolerated.	IB
Diclofenac	Topical – patch	**Costantino et al. 2011**[35] Patients with acute ankle sprain in the ED were randomised to a diclofenac/heparin (n=142), diclofenac (n=146) or placebo (n=142) plaster. The diclofenac/heparin plaster was associated with a significantly greater mean reduction in pain on movement after 3 days than the diclofenac only plaster, and both active treatments provided significantly greater pain relief than placebo.	IB
Diclofenac	Topical – patch	**Kuehl et al. 2011**[36] In patients with acute pain due to clinically significant minor soft tissue injury randomised to diclofenac (n=207) or placebo (n=211) patch, patients treated with the diclofenac patch had an 18% greater reduction in mean pain score versus placebo, and median time to pain resolution was 2 days shorter in the diclofenac patch group.	III
Diclofenac	Topical – patch	**Lionberger et al. 2011**[34] Patients with acute ankle pain caused by a minor sprain were randomised to the diclofenac patch (n=68) or placebo (n=66) daily for 7 days. Patients treated with the diclofenac patch experienced a significantly greater reduction in pain compared with placebo, beginning 4 hours into treatment (p=0.02).	IB
Diclofenac	Topical – patch	**Li et al. 2013**[37] Patients with minor soft tissue injury occurring within 72 hours of study entry were randomised to diclofenac (n=192) or placebo (n=192) patch. Reduction in pain on movement after 7 days was significantly greater in the diclofenac plaster group than with placebo, with the difference in efficacy evident after 1 day.	IB
Diclofenac	Topical – spray	**Predel et al. 2013**[38] An RCT comparing diclofenac spray gel (n=118) with placebo (n=114) in the treatment of acute uncomplicated ankle sprain found a significantly greater proportion of patients achieved at least a 50% decrease in ankle swelling in the diclofenac arm. Spontaneous pain VAS scores were significantly lower in the diclofenac group than the placebo group at all time points.	IB
Diclofenac	Topical – gel	**Predel et al. 2012**[39] Patients with acute ankle sprain were treated with diclofenac gel (2.32% diclofenac) twice (n=80) or three times per day (n=80), or with placebo (n=82). At Day 5, the reduction in pain on movement on the VAS in both diclofenac groups was almost double that with placebo (p<0.0001). By study end (Day 8), ankle swelling in patients treated with diclofenac gel (0.3 cm) was one-third that in those treated with placebo (0.9 cm) (p<0.0001). Patients treated with diclofenac gel had significantly greater functional movement that was not seen with placebo (p<0.0001). At Day 5, treatment satisfaction was “good” to “excellent” in almost 90% of patients treated with diclofenac gel but only “good” or “very good” in 23% of placebo patients (p<0.0001).	IIA
Ketoprofen	Topical – gel	**Serinken et al. 2016**[40] An RCT comparing ketoprofen gel (n=50) with placebo (n=50) in the treatment of pain due to ankle sprain reported greater reduction in VAS score in the ketoprofen arm at 15 and 30 minutes.	IIA

Therapy	Route of administration	Overview of study/data	Level of evidence
Mixed	Topical – mixed	**Lionberger et al. 2010**[41] A review of published data on the use of topical NSAIDs in the treatment of acute soft tissue injuries reported that topical NSAIDs are significantly more effective than placebo in relieving acute pain. Topical NSAIDs provided comparable pain relief to oral NSAIDs, but with fewer AEs.	IV
Mixed	Topical – mixed	**Massey et al. 2010**[42] A Cochrane review of the use of topical NSAIDs in acute pain in 47 studies and 3,455 participants reported a number needed to treat to achieve 50% pain relief versus placebo was 4.5 for 6 to 14 days.	IA
DIPYRONE (metamizole)			
	IV	**Sanchez-Carpena et al. 2007**[43] A randomised, double-blind study compared IV dipyrone (n=103) with IV dexketoprofen 25 mg (n=101) or 50 mg (n=104) in patients with moderate-to-severe pain due to renal colic. Reductions in VAS score were comparable between dipyrone and dexketoprofen 50 mg groups, though the onset of analgesia was slower, with greater reductions in pain in the first 30 minutes in the dexketoprofen groups.	III
	IV	**Peiro et al. 2008**[44] In patients with acute pancreatitis pain randomised to receive morphine (n=8) or IV dipyrone (n=8), 75% of dipyrone-treated patients achieved pain relief within 24 hours compared with 37.5% of morphine-treated patients, with a faster onset of pain relief (10 hours versus 17 hours).	III
OPIOIDS			
Oxycodone	Oral	**Fathi et al. 2015**[45] Patients in the ED with soft tissue injuries were randomised to a single dose of either oral oxycodone (n=75) or oral naproxen (n=75). Pain scores were similar between groups at all time points assessed, although more patients given oxycodone than naproxen required additional analgesia in the first 24 hours after discharge (16.0% versus 6.6%).	IB
Fentanyl	Buccal	**Shear et al. 2010**[46] Patients receiving buccal fentanyl for orthopaedic extremity pain in the ED (n=30) had a faster onset of pain relief than those who received oxycodone/paracetamol (n=30) (median 10 versus 35 minutes). Patients in the fentanyl arm also achieved a greater magnitude of pain relief and lower rescue medication rate.	IIB
Oxycodone	Buccal	**Arthur et al. 2015**[47] In an RCT in ED patients with simple MSK injury with no complicating factors, there were no significant differences in terms of respect to time-to analgesia, analgesic efficacy, side effects, and patient satisfaction between buccal oxycodone with paracetamol (n=34) and buccal fentanyl (n=38).	IIA
Fentanyl	OM	**Pietsch et al. 2023**[48] An observational study in 177 patients treated with OM fentanyl in prehospital trauma in ski and bike resorts. OM fentanyl significantly reduced pain from baseline by a median of NRS 3 (IQR 2 to 4) $p<0.0001$. Regression analysis indicated that the absolute reduction in pain but there was no difference observed because of age or gender, and no major adverse events were observed.	III

Therapy	Route of administration	Overview of study/data	Level of evidence
Sufentanil	SL	**Melson et al. 2014**[49] (*)Patients undergoing major elective surgery were randomised to a hand-held PCA device dispensing sufentanil SL tablets with a 20-minute lockout (n=177) or IV PCA morphine with a 6-minute lockout (n=180) for the treatment of acute postoperative pain. Successful analgesia (according to Patient Global Assessment) was achieved in 78.5% of patients receiving sufentanil and 65.6% of those receiving morphine.	IIB
Sufentanil	SL	**Meijer et al. 2018**[50] (*)A hand-held PCA device dispensing sufentanil SL tablets (with a lockout period of 20 minutes) was used for postoperative pain relief in 280 patients undergoing major surgery. SL sufentanil use provided effective analgesia in 90% of patients, with NRS scores <4 in 75% of patients. Over 70% of patients were highly satisfied with the system.	III
Sufentanil	SL	**Miner et al. 2018**[51] Patients presenting at the ED with pain ≥4 on the NRS due to trauma or injury received either a single (n=40) or multiple (n=36) doses (up to 3 additional doses at least 60 minutes apart) of SL sufentanil 30 µg. In both groups, reduction in pain was clinically meaningful within 30 minutes, and pain levels had dropped by 36% at 60 minutes. 75% of patients in the multiple dose cohort required only one dose of sufentanil in total.	III
Sufentanil	SL	**Miner et al. 2019**[52] Pooled safety study for Phase 3 studies of SL sufentanil for short-term treatment of moderate-to-severe acute pain in 804 patients. AEs were experienced by 60.5% (SL sufentanil) and 61.4% (placebo) and treatment-related AEs were experienced by 43.8% (SL sufentanil) and 33.5% (placebo) (10.3% difference; 95% CI: 2.0–18.6) of patients. Differences were significant for treatment-related AEs but not for AEs overall. Across all studies, nausea, which occurred in 34.1% of patients receiving SL sufentanil, was the only moderate AE that occurred in >5% of patients. Findings from the pooled analysis support that SL sufentanil is well tolerated, with most AEs considered mild or moderate in severity, for the treatment of moderate-to-severe acute pain in medically supervised settings.	III
Sufentanil	SL	**McWilliams et al. 2024**[53] Retrospective case analysis from the pre-hospital setting in search and rescue scenarios. Sixty-four cases were included in the analysis and demonstrated that mean pain score reduced from 8.0 ± 1.9 before sufentanil administration to 5.5 ± 2.5 after, reflecting a statistically significant difference of 2.6 ± 2.1 ($p < 0.001$). The results also revealed statistically significant reductions in HR and SBP following SL sufentanil administration (mean HR dropped by 4.2 ± 9.1 beats/min, p=0.004, and mean SBP dropped by 11.1 ± 21.8 mmHg, p=0.01). Changes in vital signs, although statistically significant, were not clinically significant and did not necessitate additional monitoring or intervention in any patients. This study suggests that SL sufentanil can provide significant reductions in pain with a favourable effect on vital signs.	III
Fentanyl	IN	**Borland et al. 2011**[54] An RCT performed in a children's hospital ED randomised paediatric patients aged 3 to 15 years with fractures to standard (n=98) or high concentration (n=91) IN fentanyl. There was no statistically significant difference in median pain score between the 2 groups at any of the study time points. Within groups, patients in the standard concentration group with weight <50 kg had a significantly greater reduction in pain score than those weighing ≥50 kg. There was no significant difference by weight group within the high concentration arm.	IIA

Therapy	Route of administration	Overview of study/data	Level of evidence
Sufentanil	IN	**Stephen et al. 2012[55]** IN sufentanil was given to 15 ED patients with acute extremity injuries. Over 30 minutes, mean pain score decreased by 4.3 points and 8 patients achieved a final pain score of ≤3. Average patient satisfaction was 4.5 out of 5.	III
Sufentanil	IN	**Steenblik et al. 2012[56]** Patients presenting with acute extremity injuries (most commonly upper extremity dislocations) to a ski resort clinic (n=40) were given IN sufentanil. Mean reduction in pain score was 4.7 at 10 minutes and 5.7 at 30 minutes. Five patients (12.5%) required more than 1 dose of sufentanil, and 78% of patients were very satisfied with their treatment.	III
Fentanyl	IN vs. SC	**Tanguay et al. 2020[57]** Retrospective chart analysis of IN fentanyl compared with SC fentanyl in patients (aged ≥14 years) with acute severe pain in the pre-hospital setting, and a subgroup analysis of patients aged ≤70 years and ≥70 years performed. 82.7% of patients had complete data (IN fentanyl 84.0%, SC fentanyl 81.2%). No difference was observed in time to administration or in the effectiveness of IN fentanyl and SC fentanyl, and neither route of administration resulted in major adverse events that required intervention. Subgroup analysis of IN fentanyl patients demonstrated that patients aged ≥70 years were more likely to experience pain relief compared to those <70 years. IN fentanyl was shown to be effective in all patients and potentially more effective in older patients.	III
Sufentanil	IN	**Kreps et al. 2021[58]** Observational, open-label sequential study in the ED in severe non-visceral pain. Control patients received SoC opioids and the intervention group received IN sufentanil. Pain at baseline was not comparable between groups (IN sufentanil AVPS score 8.5 [IQR 8.0–10.0] vs SoC 7.9 [IQR 7.0–9.4], p=0.026), but pain reduction was larger for those receiving sufentanil after 15 minutes: 2.5 vs 1.6 p=0.005 and remained significant at 30 minutes (AVPS 4 vs 3.1, p=0.02). After 30 minutes no difference in pain score was noted. No side effects were recorded with SoC but were reported by 62 sufentanil patients (68.1%). The most common AEs were vertigo (60.4%), nausea (30.0%) and vomiting (20.0%). Significantly fewer patients on SoC received rescue analgesia (4.3%) versus those on sufentanil (10.1%) (p=0.018).	IIA
Fentanyl	IN	**Anderson et al. 2022[59]** Single centre, retrospective chart review of initial dose 30 µg IN fentanyl rising to 102–265 µg based on pain (n=3,205). Fentanyl provided effective analgesia and was well tolerated even at doses >100 µg.	IIB
Sufentanil	IN	**Hutchings et al. 2023[60]** Systematic review of 4 studies, three in the ED and one in the pre-hospital setting of 467 patients were included. Primary outcome was pain reduction and secondary endpoints were AEs, rescue analgesia, and patient and provider satisfaction. Efficacy was determined by the percentage of patients achieving a reduction in pain to NRS ≤3/10. In a placebo-controlled study, IN sufentanil was superior to placebo for pain reduction at 30 minutes with 20.8% of patients achieving NRS <3 (95% CI 4.0–36.2%, p=0.01). In two studies IN sufentanil was comparable with IV morphine (0.1 mg/kg) and in the pre-hospital study a loading dose of IV sufentanil followed by smaller rescue doses was comparable with IV morphine. Mild AEs were common in all studies but sedation was noted more often with sufentanil.	IC

Therapy	Route of administration	Overview of study/data	Level of evidence
Sufentanil	IN	**Malinverni et al. 2024[61]** Single-centre, open-label, randomised, controlled, parallel-group study of trauma patients the ED with trauma pain ≥7 in receipt of IN sufentanil plus oral/IV paracetamol or IV opioids plus oral/IV paracetamol. Primary endpoint was change in VAS from baseline at 15–20 minutes. Secondary outcomes included between-group differences in mean VAS scores at 60 minutes and the proportion of patients experiencing side effects. The minimum clinically important difference was defined, as a change of 1 on the VAS. Additional outcomes include the use of rescue analgesia. Pain reduced over time in both groups but was significantly greater in the IN sufentanil group (VAS reduction 3.0, [IQR 1.7–5.0] vs 1.5 [IQR 0.9–3.0]; p<0.001). VAS pain score was statistically significantly lower in the sufentanil group (5.0 [IQR 3.0–7.0] vs 6.6 [IQR 5.0–73]; p=0.002). Onset to pain relief was faster for sufentanil. Statistically lower pain scores remained at 60 minutes (p<0.001). There was no change in the use of oral/IV paracetamol in either group, and the rate of rescue analgesia was similar (sufentanil 24.1% vs 23.0%; p=NS). Adverse events were more common in the sufentanil group (71.1% vs 23.0%; p<0.001), similarly the rate of SAEs in the sufentanil group were higher but this was not significant.	IIA
Fentanyl	IN	**Serra et al. 2023[62]** Systematic review of IN fentanyl in children (n=18 studies), adults (n=5), older people (n=1) in both ED and pre-hospital settings. In children IN fentanyl was equally effective to comparators, delayed the time to IV opioids, reduced ED length of stay and hospital admission rates. Patient satisfaction was generally comparable in all studies, but in one was suggested to be higher than IM morphine. In adults, IN fentanyl was comparable with SC fentanyl and IV morphine, but one study suggested IN fentanyl was less effective than IV fentanyl. Time to onset of analgesia was comparable between IN fentanyl and IV morphine but a higher dose of IN fentanyl was required. Patient satisfaction results indicated in one study no difference between IN or IV fentanyl in patients rating of satisfaction, however when compared with IN ketamine, IN fentanyl was judged to provide more satisfactory analgesia. AEs including hypoxia, sedation, bradycardia were reported with IN fentanyl but these were considered transient and minor.	IC
Sufentanil	IV	**Bounes et al. 2010[63]** Patients with acute severe trauma pain were randomised to IV sufentanil (n=54) or IV morphine (n=54). At 15 minutes, 74% of patients in the sufentanil group achieved pain relief (defined as NRS ≤3) versus 70% of those in the morphine group. Duration of analgesia was longer in the morphine group.	IIB
Morphine	IV	**Birnbaum et al. 2012[64]** In an RCT, patients in the ED with acute abdominal pain received an initial dose of IV morphine followed by physician-managed analgesia as needed. Patients randomised to PCA dosing also received either 1 mg (n=69) or 1.5 mg (n=72) morphine on demand with a 6 minute lockout between doses, while the non-PCA arm (n=70) did not. All 3 groups had similar, significant reductions in NRS scores to 30 minutes, after which NRS scores in the PCA groups continued to decline (to 120 minutes) while those in the non-PCA group did not (p=0.004).	IIA
Morphine	IV	**Rahman et al. 2012[65]** Patients with acute pain presenting to two EDs were randomised to morphine given either via PCA (n=24) or as titrated boluses (n=23). Patients in the PCA group had a significantly greater reduction in pain on the VAS than the bolus group (p<0.001), with similar consumption of morphine.	IIA

Therapy	Route of administration	Overview of study/data	Level of evidence
Morphine	IV	**Rahman et al. 2012**[66] In an RCT, patients with acute traumatic pain of VAS score ≥7 presenting to the ED were randomised to morphine given either via PCA (n=47) or as titrated boluses (n=49). Patients in the PCA group had lower mean VAS scores than the bolus group at all time points, and were more satisfied with their care.	IIA
Morphine	IV	**Farsi et al. 2013**[67] In an RCT in patients with limb trauma in the ED, IV morphine (n=100) or placebo (n=100) was given 30 minutes after an initial dose of IV morphine. Patients in the morphine arm had significantly reduced pain at 1 hour compared with placebo (p<0.05), with no significant difference in the rate of AEs.	IIA
Fentanyl	IV	**Wenderoth et al. 2013**[68] In a retrospective cohort study of IV fentanyl versus IV morphine, 168 patients with trauma pain in the ED achieved similar analgesia regardless of receipt of fentanyl or morphine (a reduction of NRS 2, [p=NS]). Baseline pain score in the IV fentanyl group was higher (NRS 10, IQR 8–10)) than IV morphine treated patients (NRS 8, IQR 4–10). Time to lowest pain score was faster with IV fentanyl (22 vs 47 minutes; p<0.001). Adverse event profiles in both groups were comparable, although the use of prophylactic anti-emetics was significantly higher in morphine treated patients (21.4% vs 0%; p<0.001).	III
Fentanyl	IV	**Farahmand et al. 2014**[69] In an RCT comparing nebulised fentanyl (n=47) with IV morphine (n=43) in ED patients with moderate-to-severe acute limb pain, fentanyl and morphine provided similar reductions in pain of >3 points on the NRS. Patient satisfaction in both groups was similar and no adverse effects were reported in the fentanyl group.	IIA
Fentanyl	IV	**Friesgaard et al. 2016**[70] Of 2,348 patients treated with IV fentanyl in a pre-hospital setting, 79.3% achieved pain reductions of NRS >2, but moderate-to-severe pain was still reported by 60% of patients on arrival at hospital.	III
Mixed opioids	IV	**Dalton et al. 2022**[71] Using a database 267,281 of 3,831 patients, 7% (n=768) were treated with opioids in the pre-hospital setting. Fentanyl was the most used opioid (88.2%) and median dose was 10 morphine equivalents. Patients who received opioids had higher baseline pain than those not receiving opioids (9 versus 4, p<0.001) and experienced a median reduction in pain score of 3 points. AEs were rare and included altered mental status and respiratory compromise.	III
Morphine	IV	**Oon et al. 2024**[72] SLR and meta-analysis of 8 trials (n=1490) comparing PCA and IV morphine. Pain was comparably reduced by both approaches (treatment difference −0.2, p=0.25), and there were no differences in dosages used to reduce pain. Overall, more patients were satisfied with PCA than IV (p<0.001) and fewer patients on PCA required rescue analgesia (p<0.001). Reporting of AEs in the studies included was too limited to draw firm conclusions.	IA
Fentanyl, morphine and alfentanil	IV, oral, intraosseous	**Colding-Jørgensen et al. 2025**[73] Registry based study in Denmark exploring the use of strong opioids (morphine, fentanyl and alfentanil) in children in the pre-hospital setting. Fentanyl was the most administered opioid (96.4% of 1,700 patients). The IV route was used in 63.4% of cases and 97% of all doses provided to patients were within recommended dosing ranges. Only 5.7% of all children aged <15 years received opioids and 75% of these were aged >10 years and only 8.5% of patients were aged <5 years. These data suggest a potential for under-treatment of pain in children.	III

Therapy	Route of administration	Overview of study/data	Level of evidence
KETAMINE			
	Oral	**Gerges et al. 2022**[74] Prospective, randomised, open-label trial in 60 patients aged >18 years with acute moderate-to-severe MSK pain and initial NRS score of ≥5. Patients received either aspirin 324 mg or 0.5 mg/kg oral ketamine. Pain was measured at 30, 60, 90 and 120 minutes. Primary endpoint was change in pain at 60 minutes. At 60 minutes mean change in pain score (measured by NRS) for aspirin was 2.1 (8.4 to 6.3, 95% CI 1.35–3.00) and oral ketamine 4.1 (7.8 to 3.7, 95% CI 3.25–4.90). No serious AEs occurred in either group, or clinically relevant change in vital signs observed. No patients required rescue medication at 60 minutes. The most common AEs reported were dizziness and fatigue.	III
	IN	**Shimonovichh et al 2016**[75] Patients in the ED with moderate-to-severe acute traumatic pain were randomised to IN ketamine (n=34), IV morphine (n=26) or IM morphine (n=30). Pain relief 1 hour after treatment was significant and comparable between groups. IN ketamine was clinically comparable to IV morphine in terms of time to onset (14.3 versus 8.9 minutes) and time to maximum pain reduction (40.4 versus 33.4 minutes).	IIA
	IN vs IV	**Parvizrad et al. 2017**[76] In an RCT comparing IN ketamine (n=77) with IV ketamine (n=77) in patients with orthopaedic trauma, IN ketamine was found to be as effective as IV ketamine in reducing pain at 30 minutes. Rescue analgesia was required in 20% of patients (with no difference between groups). Adverse events were mild and transient in both groups.	IB
	IN	**Farnia et al. 2017**[77] Patients with renal colic (n=40) received IV morphine (n=20) or IN ketamine (n=20) in a double-blind RCT. At baseline pain scores were higher in the morphine group vs that in the ketamine group (VAS: morphine 7.40 ± 1.18; ketamine 8.35 ± 1.30) (p=0.021). At 5 minutes post-administration, pain relief with morphine was superior to ketamine, VAS scores were 6.07 ± 0.47 for morphine and 6.87 ± 0.47 for ketamine (p=0.025). At 15 minutes and 30 minutes, pain scores for both groups were comparable. At 15 minutes: morphine 5.24 ± 0.49 morphine, ketamine 5.60 ± 0.49, mean difference –0.36; at 30 minutes: morphine 4.02 ± 0.59, ketamine 4.17 ± 0.59, mean difference –0.15.	IB
	IN	**Reynolds et al. 2017**[78] Children aged 4 to 17 years with suspected extremity fractures were randomised to IN ketamine (n=43) or IN fentanyl (n=44). Similar pain relief was observed at 20 minutes between groups, with both groups requiring a similar level of opioid rescue therapy (16% versus 18%).	IB
	IN	**Frey et al. 2018**[79] Children aged 8 to 17 years presenting to the ED with moderate-to-severe pain due to traumatic limb injuries were randomised to either IN ketamine (n=45) or IN fentanyl (n=45). After 30 minutes pain reduction was comparable between groups (−30.6 and −31.9 mm on 100 mm VAS). The need for rescue analgesia was similar between groups.	IB

Therapy	Route of administration	Overview of study/data	Level of evidence
	IN	**Li et al. 2021[80]** SLR of seven studies of IN ketamine versus opioids for acute pain management in ED at 15, 30 and 60 minutes. Comparisons included: • IN ketamine vs placebo (3 studies) • IN ketamine vs opioids (4 studies) Meta-analysis of the included studies demonstrated a tendency towards better pain relief with IN ketamine compared with placebo at 15 minutes (mean difference −0.90 95% CI: −2.34, 0.54 I^2=94% p=0.22) and 60 minutes (mean difference: −1.47 95% CI: −3.04, 0.10 I^2=71% p=0.07). The need for rescue medication was significantly lower for IN ketamine than placebo (OR: 0.36 95% CI: 0.16, 0.80 I^2=66% p=0.01). Meta-analysis of the included studies demonstrated a tendency towards better pain relief with IN ketamine compared with placebo (mean difference −0.90 95% CI: −2.34, 0.54 I^2=94% p=0.22) and 60 minutes (mean difference: −1.47 95% CI: −3.04, 0.10 I^2=71% p=0.07). The need for rescue medication was significantly lower for IN ketamine than placebo (OR: 0.36 95% CI: 0.16, 0.80 I^2=66% p=0.01). Compared with opioids, IN ketamine had comparable AEs, but significantly more AEs i.e. dizziness than those reported by placebo-treated patients (OR: 1.84 95% CI: 1.35, 2.51 I^2=0% p=0.001). Compared with opioids there was no significant difference in pain relief at 154 minutes, but IN ketamine provided better pain reduction at 30 minutes (p=0.04). One study reported pain scores at 60 minutes with no difference in efficacy. Meta-analysis of studies of IN ketamine versus opioids showed that IN ketamine significantly reduced pain (mean difference: −0.82 95% CI: −1.43, −0.20 I^2=64% p=0.009). The need for rescue medication was higher for IN ketamine than opioids (OR: 4.69 95% CI: 1.75, 12.60 I^2=not applicable p=0.02). AEs with IN ketamine were similar to that with opioids with no difference in the incidence of dizziness (OR: 1.78 95% CI: 0.54, 5.93 I^2=43% p=0.34) and nausea/vomiting (OR: 1.47 95% CI: 0.67, 3.20 I^2=0% p=0.33). IN ketamine had comparable AEs, but with significantly increased incidence of dizziness, than those reported by placebo-treated patients (OR: 1.84 95% CI: 1.35, 2.51 I^2=0% p=0.001). Emergent AEs were significantly increased with IN ketamine as compared to opioids and placebo.	IC
	IN	**Seak et al. 2021[81]** SLR and meta-analysis of 7 studies (of high or moderate quality) including 1,760 patients in receipt of IN ketamine with IV analgesics or placebo. Pain scores were comparable between patients receiving IN ketamine or IV analgesics (morphine or fentanyl) with no significant difference in pain score at any time points 5 minutes (mean difference 0.94, p=NS), 15 minutes (mean difference 0.15, p=NS), 25 minutes (mean difference 0.24, p=NS), 30 and 60 minutes (mean difference at 30 minutes −0.05, p=NS; 60 minutes mean difference −0.42, p=NS). There was no significant differences in the need for rescue analgesia between ketamine and opioids. Only mild AEs were observed in those who received IN ketamine, but patients experienced an increased risk of dizziness (OR 1.9 95% CI 1.4–2.5; p<0.0001) difficulty concentrating (OR 5.3 95% CI 1.5–19.0; p=0.01), confusion (OR 7.0 95% CI 1.6–29.9; p=0.009) or disorientation (OR 9.2 95% CI 3.6-23.4; p<0.00001) compared with control groups. IN ketamine was non-inferior to IV analgesics.	IA

Therapy	Route of administration	Overview of study/data	Level of evidence
	IN	**Tongbua et al. 2022[82]** Double-blind, randomised controlled trial of patients aged >65 years in the ED with acute moderate-to-severe MSK pain (NRS ≥5) randomised to IN ketamine or IV morphine. Mean (±SD) baseline pain scores were similar in IN ketamine and IV morphine groups (8.16 ± 1.68 versus 7.62 ± 1.85, p>0.05). After 30 minutes, mean (±SD) pain scores were reduced in both groups to 6.03 ± 1.68 and 5.81 ± 2.76, respectively. The mean difference at 30 minutes was not significant (0.22, 95% CI: −1.04 to 1.48). Patients randomised to IN ketamine (n=37) or IV morphine (n=37) achieved comparable pain relief at 30 minutes (NRS 6.03 vs 5.81), and NRS change from baseline was −2.14 (95% CI −2.79 to −1.48) for IN ketamine and −0.81 (95% CI −3.26 to −1.26) for IV morphine and the mean difference (−0.32, 95% CI: −1.17 to 0.52) did not exceed the margin for non-inferiority (upper limit of 95% CI <1.3). There was no difference in rescue analgesia requirements between IN ketamine and IV morphine groups, and no difference in dizziness or vomiting.	IIB
	Nebulised	**Drapkin et al. 2020[83]** Case series in 5 adults of nebulised ketamine in the ED. Three patients received 1.5 mg/kg, one received 1 mg/kg and one received 0.75 mg/kg. All patients experienced a decrease in pain up to 120 minutes and no AEs were reported.	IV
	Nebulised	**Rhodes et al. 2021[84]** Case series of nebulised ketamine in children aged 10–16 years (n=5) with a mix of MSK pain including fracture and joint effusion. All patients experienced a reduction in pain from 15 minutes, which was maintained up to 60 minutes. No change in baseline vitals was observed and four of the five patients experienced dizziness that resolved by 60 minutes.	III
	Nebulised	**Dove et al. 2021[85]** Prospective, randomised, double-blind trial. Patients (n=120) in the ED were randomised to 3 doses of nebulised ketamine (0.75 mg/kg, 1 mg/kg and 1.5 mg/kg) and NRS pain score measured at 30 minutes. At 30 minutes the reduction in pain score was comparable across all groups with all experiencing a reduction in pain score >1.3. Reductions in pain score were: • 0.75 mg/kg: 8.7 at baseline to 4.7 at 30 minutes and 3.7 at 120 minutes • 1 mg/kg: 8.6 at baseline to 4.4 at 30 minutes and 3.4 at 120 minutes • 1.5 mg/kg: 8.7 at baseline to 4.6 at 30 minutes and 3.6 at 120 minutes. Ketamine was effective at all doses tested, up to 120 minutes.	IIB

Therapy	Route of administration	Overview of study/data	Level of evidence
	Nebulised vs IV	**Nguyen et al. 2024**[86] Prospective, randomised, double-blind, double-dummy in one ED of IV ketamine in adult patients (aged ≥18 years) with a NRS score of ≥5. Patients received single dose of nebulised ketamine 0.75 mg/kg or IV ketamine 0.3 mg/kg. Primary study outcome was differences in NRS at 30 minutes. Secondary outcomes were rescue analgesia, AEs, and pain scores at 15, 30, 60, 90 and 120 minutes. Minimum clinically important difference was designated as 1.3 points. Baseline pain scores in the nebulised (n=75) or IV ketamine group (n=75) were comparable. Pain reduction from 8.2 to 3.6 for those receiving nebulised ketamine and 8.2 to 3.8 for IV ketamine was observed (mean treatment difference 0.23 [95% CI −1.32–0.86]). No significant differences in pain reduction between the two groups was observed at any other timepoint. No clinical concerning changes in vital signs were observed in any patients, and no SAEs were noted. But more subjects in the IV group experienced sedation, restlessness, dizziness and feelings of unreality. There was no difference in rescue analgesia requirements.	IIA
	Nebulised	**Cetin et al. 2025**[87] SLR and meta-analysis of nebulised ketamine in the ED. Thirteen studies met the criteria for inclusion. In 8 studies nebulised ketamine was comparable with active controls, and in 4 studies ketamine was comparable with IV morphine at 30 minutes with similar rates of rescue analgesia required 16.9% versus 17.4%. Most studies (11/13) reported no difference in AEs (39.1% versus 37.8%) and no reports of serious AEs. Nebulised ketamine is comparable to morphine, but the level of confidence in the meta-analysis was low.	IA
	IV	**Jennings et al. 2012**[88] Patients with pain due to trauma in the pre-hospital setting were randomised in an open-label study to morphine or morphine plus ketamine. All patients received IV morphine 5 mg, and were then randomised to ketamine (mean total dose 40.6 ± 25 mg) or morphine (mean total dose 14.4 ± 9.4 mg). Mean change in pain score from baseline was –5.6 (95% CI –6.2 to –5.0) for ketamine and –2.4 (95% CI –3.7 to –2.7) for morphine. AEs were more commonly reported in patients treated with ketamine (n=27/70, 39%), the most common of which was disorientation, vs morphine (n=9/65, 14%), the most common of which was nausea.	IIA
	IV	**Majidinejad et al. 2014**[89] Patients with long bone fractures were randomised to IV morphine (n=63) or low-dose IV ketamine (n=63). Pain scores decreased significantly in both groups at 10 minutes, with no significant differences between groups.	IIB
	IV	**Miller et al 2015**[90] An RCT of patients with acute pain in the ED compared low-dose IV ketamine (n=24) with IV morphine (n=21). There were no significant differences in NRS reduction between groups at any time point. Time to achieve maximum NRS reduction was 5 minutes for ketamine and 100 minutes for morphine.	IB

Therapy	Route of administration	Overview of study/data	Level of evidence
	IV and IN	**Sandberg et al. 2020**[91] Systematic review exploring ketamine (range of administration routes) versus opioids when given alone and when administered in combination with nitrous oxide. Studies covered 5 comparisons • IV ketamine vs IV opioids (three studies) • IV ketamine plus IV morphine vs IV morphine (three studies) • IV ketamine as an infusion vs IV ketamine single dose (one study) • IN ketamine plus nitrous oxide vs nitrous oxide alone (one study) • IV ketamine vs no analgesia. Most studies (n=5/8) were noted to contain high levels of bias. In studies of ketamine versus opioids, ketamine provided a greater reduction in pain score than morphine or fentanyl but was comparable with pentazocine. In these studies, fewer patients treated with ketamine experienced AEs of nausea and vomiting, and fewer patients treated with opioids experienced agitation. Ketamine plus morphine versus morphine only showed lower pain scores in the combination group versus morphine alone, but a meta-analysis done by these authors indicated the difference was not significant. AEs were broadly comparable, but there was a trend towards fewer AEs with morphine alone. Continuous IV ketamine infusions compared with a single bolus dose of ketamine in patients also receiving morphine demonstrated comparable pain relief. IN ketamine plus nitrous oxide versus nitrous oxide alone showed superior pain relief in the combination group with a NRS pain reduction of 2 or more, with no serious AEs reported. Compared with no analgesia in a warzone, ketamine was superior to no analgesia but this was not significant. There was inconsistent reporting across studies, with imprecision in results and lack of randomisation, but it was considered that IV ketamine was at least as effective as opioids.	IC
	IV	**Lovett et al. 2021**[92] Randomised, prospective, double-blind non-inferiority study in patients aged 18–59 years with acute moderate-to-severe pain in the ED treated with IV ketamine 0.15 mg/kg or 0.3 mg/kg. The primary endpoint was the 11-point NRS pain score between groups at 30 minutes. Secondary endpoints included NRS pain scores at 15 and 60 minutes; change in NRS at 15, 30, and 60 minutes; rescue analgesia; and adverse effects. Forty-nine patients were randomised to 0.15 mg/kg and 0.3 mg/kg respectively. Mean baseline NRS score at 30 minutes post-intervention for ketamine 0.15 mg/kg was 4.7 (95% CI 3.8–5.5) and 5.0 in the 0.3 mg/kg group (95% CI = 4.2–5.8); (mean difference = 0.4, 95% CI = −0.8 to 1.5). Data indicate that ketamine 0.15 mg/kg was non-inferior to 0.3 mg/kg (lower limit of 95% CI = −0.8 to ≥1.3). Adverse effects were similar at 30 minutes. At 15 minutes, the 0.3 mg/kg group experienced greater change in NRS; however, more adverse effects occurred.	IB
	IV	**Balzer et al. 2021**[93] SLR and meta-analysis of 8 RCTs in 1,191 patients explored low-dose IV ketamine against IV morphine. At 60 minutes there was no difference in mean pain score, but there was a trend favouring morphine between 60 minutes and 120 minutes. The requirement for rescue medication was comparable in both groups (RR 0.97; 95% CI 0.5 to 3.16) and the rate of AEs was comparable between both groups.	IA

Therapy	Route of administration	Overview of study/data	Level of evidence
	IV	**Esfahani et al. 2021**[94] Seventy three patients were enrolled and 36 allocated to ketamine and 37 allocated to morphine – baseline characteristics were comparable in both groups. Mean pain score changed −6.2 (95% CI −5.72 to −6.69) for those receiving ketamine versus −5.8 (95% CI −5.15 to −6.48) for morphine. At all timepoints mean pain score was lower in those receiving ketamine versus morphine ($p<0.05$), and the mean total pain reduction was greater with ketamine than morphine ($p=0.002$). This study suggested that low doses of ketamine are as effective in managing pain than morphine for those with lower limb trauma.	IA
	IV	**Moradi et al. 2022**[95] Single-centre randomised ED clinical trial in 200 patients with acute pain who received ketamine plus haloperidol or fentanyl as analgesia. Primary endpoint was pain score at baseline and post-administration and safety. There was no significant difference between the mean scores of initial pain in the two groups, but at all intervals of 5, 10, 15 and 30 minutes after injection, the mean of pain scores of patients in the group receiving ketamine plus haloperidol were lower. The need for injection of rescue analgesic was 9% in the ketamine plus haloperidol group and 34% in the fentanyl group. The mean agitation score did not differ between the two groups except at 10 minutes when agitation was higher in those receiving ketamine.	IIB
	IV	**Beaudrie-Nunn et al. 2023**[96] Doses of ketamine <0.3 mg/kg and >0.3 mg/kg were compared in a multi-centre, retrospective cohort study in 21 EDs in 3,796 patients. Median baseline pain score in the low dose group (n=258) was NRS 8.2 and NRS 7.8 in the high-dose group (n=126). Both groups had significant reductions in pain score within 60 minutes of administration but there was no significant difference between the two groups. AEs were comparable between groups with the most common AEs being agitation (7.3%) and nausea (7.0%).	IA
	IV and IN	**Shi et al. 2024**[97] Twenty-six studies were included in a meta-analysis to evaluate IV or IN ketamine with pain reduction evaluated at 15, 30, 45 and 60 minutes. At early timepoints (15 and 30 minutes) ketamine provided more effective pain relief than comparators (morphine and fentanyl) but this was not significant. At 60 minutes there was no difference in pain relief between ketamine and comparators. The most common dosage of ketamine was 0.3 mg/kg. There was no significant difference in the requirement for rescue analgesia in any treatment group and AEs were broadly comparable across groups. The authors noted that many studies had a high risk of bias, but pain relief within 30 minutes was clinically meaningful with an optimal dose of 0.3 mg/kg. Beyond 30 minutes the analgesia provided by ketamine was comparable to other analgesics.	IC
	IV/IN	**Guo et al. 2024**[98] This meta-analysis of 15 RCTs involving 1,768 patients compared IV/IN ketamine with IV morphine. Primary outcome measures were pain scores (NRS and VAS) with secondary endpoints of complete resolution of pain, reduction in pain of NRS ≥3 points or reductions in NRS of ≥50 or 60%, change in NRS score, change in VAS score, rescue medication, adverse events and patient satisfaction. At 30 minutes, patients treated with ketamine had lower NRS pain scores than those treated with morphine ($p<0.00001$) but morphine was superior at 120 minutes ($p=0.0003$). Complete resolution of pain was observed in three times more patients in the ketamine group at 15 minutes than morphine (RR 3.18 95% CI 1.75–5.78, $p=0.0001$). Ketamine treatment was associated with fewer AEs than morphine (RR 0.34 95% CI 0.18–0.66, $p=0.001$).	IA

Therapy	Route of administration	Overview of study/data	Level of evidence
	IV	**Azizkhani et al. 2025[99]** Double-blind, randomised study in two ED settings, in patients aged >18 with acute onset, moderate pain randomised to receive IV ketamine at two doses in 80 patients. Patients received either 0.3 mg/kg ketamine over 1 minute followed by an infusion of placebo over 30 minutes or ketamine bolus 0.15 mg/kg followed by ketamine infusion 0.15 mg/kg over 30 minutes. Primary outcome measures was median decrease in NRS, levels of sedation, changes in vital signs and AEs. All groups experienced a significant reduction in pain at 30 minutes ($p<0.001$), with pain scores lower in the ketamine bolus plus infusion groups (p=NS). Vital signs and AEs were comparable in both groups. No impact on vital signs was observed in both groups, apart from a comparable increase in blood pressure. Patients in the infusion group required less rescue analgesia but this was not significantly different between groups. The most common side effects were feelings of unreality, hallucination, agitation, and nausea. No statistically significant difference was observed between study groups in any side effect including the mean agitation or sedation as measured by the RASS scale.	IB
	IV	**Moradi et al. 2025[100]** A single-centre, randomised controlled trial of 258 adult patients in the ED with acute limb trauma pain. One group received IV ketamine (0.3 mg/kg) plus dexmedetomidine (0.5 mcg/kg), and the other group IV morphine (0.1 mg/kg). Pain, agitation scores and side effects were compared between the two groups. Primary outcome was pain reduction at 30 minutes. At baseline mean pain score was 8.51 (ketamine plus dexmedetomidine 8.5 ± 1.4; morphine 8.4 ± 1.4). After 30 minutes post-administration mean pain score of patients in the ketamine-dexmedetomidine group was lower than the morphine group (ketamine plus dexmedetomidine: 1.4 ± 2.3 vs morphine: 3.3 ± 2.3, $p<0.001$). The need for rescue analgesic was 8.3% in the ketamine-dexmedetomidine group and 24% in the morphine group. The mean agitation score in the ketamine group was higher during the first 10 minutes post-injection (ketamine-dexmedetomidine 0.1 ± 0.6, p=0.052 vs morphine 0.0 ± 0.2, p=0.002) but this was resolved by 30 minutes (ketamine-dexmedetomidine 0.0 ± 0.3, p=0.007 vs morphine 0.0 ± 0.2, p=0.006).	IB
	Mixed (IV, IN, nebulised)	**Alanazi et al. 2022[101]** SLR of four RCTS of ketamine versus opioids (morphine and fentanyl) for severe pain in children. Ketamine was non-inferior to opioids determined by patient self-report pain assessment.	IC
	Mixed	**Fjendbo Galili et al. 2023[102]** Evaluation of sub-dissociative single-dose ketamine (routes of administration vary) trials (n=8) evaluated in SLR and meta-analysis included (n=903). Studies were judged to be at moderate to high risk of bias. Mean pain intensity scores were significantly lower 60 minutes after study drug administration favouring adjuvant ketamine (mean difference −0.76; 95% CI −1.19 to −0.33), compared with opioids alone. There was no evidence of differences in mean pain intensity scores at any other time point. Patients who received adjuvant ketamine were less likely to require rescue analgesia, no more likely to experience serious side effects and had higher satisfaction scores, compared with opioids alone. Thes data indicate effective pain reduction with ketamine that is comparable with opioids.	IA

Therapy	Route of administration	Overview of study/data	Level of evidence
METHOXYFLURANE			
	Inhaled	**Bendall et al. 2011**[103] In paediatric patients with moderate-to-severe acute pain in a pre-hospital setting, effective analgesia (defined as a reduction in NRS pain score of at least 30%) was achieved in 78.3%, 87.5% and 89.5% of patients given methoxyflurane, morphine and fentanyl, respectively.	III
	Inhaled	**Johnston et al. 2011**[104] In a retrospective observational study of 1,024 patients with visceral pain who received methoxyflurane (n=465), IN fentanyl (n=397) or both (n=162) in the pre-hospital setting, methoxyflurane provided more rapid onset of action than IN fentanyl (VAS 2.0 versus 1.6 at 5 minutes), although fentanyl provided greater pain reduction by arrival at hospital (3.2 versus 2.5).	III
	Inhaled	**Coffey et al. 2014**[105] In a Phase 3 study of patients presenting to the ED with minor trauma (including 90 individuals aged 12 to 17 years), those randomised to methoxyflurane (n=150) reported significantly greater reductions in pain severity at all time points tested than those randomised to placebo (n=150) (p<0.0001). Onset of pain relief occurred within 6 to 10 inhalations and the greatest treatment effect with methoxyflurane (of −18.5 mm) was seen at 15 minutes.	III
	Inhaled	**Coffey et al. 2016**[106] In the adult subgroup of the above Phase 3 study, mean change from baseline was greater for methoxyflurane than placebo at all time points (−34.8 versus −15.2 mm on 100 mm VAS at 20 minutes). Median time to first pain relief was 5 minutes, versus 20 minutes with placebo, and 79.4% of patients in the methoxyflurane arm experienced pain relief within 1 to 10 inhalations.	IIA
	Inhaled	**Mercadante et al. 2019**[107] Adult trauma patients treated with methoxyflurane (n=135) or SoC analgesia (n=135; NRS ≥4–6 IV paracetamol/IV ketoprofen; NRS ≥7 IV morphine) had a greater reductions in VAS over 10 minutes than SoC (ΔVAS −5.94 mm; 95% CI: −8.83 mm, −3.06 mm p<0.001). Over 10 minutes comparable results were observed in patients with moderate baseline pain (ΔVAS −5.97 mm; 95% CI: −9.55 mm, −2.39 mm p=0.001) where SoC was IV paracetamol or IV ketoprofen and severe baseline pain where patients received IV morphine (ΔVAS −5.54 mm; 95% CI: −10.49 mm, −0.59 mm p=0.029). Median time to onset of first pain relief was 9 minutes (95% CI, 7.2 minutes, 10.28 minutes) with methoxyflurane compared with 15 minutes (95% CI, 14.17 minutes, 15.83 minutes) for SoC.	IIA
	Inhaled	**Borobia et al. 2020**[108] In adult trauma patients treated with methoxyflurane (n=156) or SoC (n=149), change from baseline pain was greater over 20 minutes for methoxyflurane than SoC 2.5 points vs 1.4 points (p<0.001). Significant reductions in pain were demonstrated for methoxyflurane regardless of baseline pain, and pain reduction with methoxyflurane was greater than SoC even if SoC contained opioids. Onset to pain reduction was 3 minutes for methoxyflurane compared with 10 minutes for SoC (p<0.001).	IIA

Therapy	Route of administration	Overview of study/data	Level of evidence
	Inhaled	**Brichko et al. 2020[109]** Patients were randomised to SoC analgesia or methoxyflurane (n=120), primary outcome was 50% reduction in pain score by 30 minutes and secondary endpoints at multiple timepoints. At 30 minutes 6 patients (10%) in the methoxyflurane group and 3 (5%) in the SoC group achieved a 50% reduction in pain score (p=NS). Reduction in pain (NRS reduced by 2 points) was significant at all timepoints for those receiving methoxyflurane (p<0.001). Time to requirement for rescue analgesia was longer for methoxyflurane 66 minutes versus SoC 46 minutes (p=0.024). No serious AEs were recorded.	IA
	Inhaled	**Ricard-Hibon et al. 2020[110]** Randomised, prospective, double-blind, placebo-controlled, trial in eight EDs in adults with pain score NRS ≥4. Patients received either methoxyflurane plus SoC analgesia or SoC plus placebo. Primary outcome measure was time until pain relief ≤30 mm, assessed on the 100 mm VAS. A total of 351 patients were analysed (methoxyflurane plus SoC n=178; SoC plus placebo n=173). Median pain prior to first inhalation was 66 mm, 75% of patients had severe pain (NRS 6–10). Median time to pain relief was 35 minutes [95% confidence interval (CI), 28–62] for methoxyflurane plus SoC versus pain relief not reached in SoC plus placebo (> 92 minutes – last timepoint for evaluation) (HR, 1.93 [95% CI 1.43–2.60]; p < 0.001]. Pain relief was most pronounced in the severe pain subgroup with an NRS ≥6 (HR 2.5 [95% CI 1.7–3.7]). Patients received the following as SoC • No analgesia: 38% of methoxyflurane plus SoC patients versus 29% of SoC-treated patients (p=0.07) • Weak opioids: 6% of methoxyflurane plus SoC patients versus 8% of SoC-treated patients • Strong opioids: 1% of methoxyflurane plus SoC patients and 1% of SoC-treated patients • Escalation to weak or strong opioids: 8% of methoxyflurane plus SoC patients versus 17% of SoC-treated patients (p = 0.02). Most adverse events were of mild intensity (111/147 events). The most common AEs were dizziness, somnolence, cough and nausea. Methoxyflurane used as part of a multimodal analgesic approach was effective in providing pain relief for adult trauma patients, particularly in those with severe pain.	IA
	Inhaled	**Serra et al. 2020[111]** Sub-group post-hoc analysis of the MEDITA study methoxyflurane by Mercadante et al. 2019 in patients aged ≥65 years. All patients had NRS ≥4 and received methoxyflurane or SoC (IV paracetamol 1 g, or ketoprofen 100 mg [moderate pain NRS 4–6] or IV morphine 0.1 mg/kg [severe pain NRS ≥7]). Primary endpoint was overall change in VAS at 3, 5 and 10 minutes. Secondary endpoints were time to onset of pain relief, efficacy up to 30 minutes and safety. Pain reductions were similar regardless of treatment, but time to onset of pain relief was shorter with methoxyflurane (9 minutes vs 15 minutes for SoC). Patients were 5.7 times more likely to express satisfaction with methoxyflurane than SoC and satisfaction was 3.4 times more likely for clinicians. AEs were similar in all patients, all of which were non-serious and there were no changes in vital signs.	III

Therapy	Route of administration	Overview of study/data	Level of evidence
	Inhaled	**Young et al. 2020**[112] Service evaluation of methoxyflurane (n=79) versus those in receipt of SoC analgesia (n=80) evaluating length of stay in the ED. Mean time spent in the ED was reduced by 71 minutes for those treated with methoxyflurane compared with SoC (276 minutes vs 347 minutes) which was statistically significant (p=0.038). Results were maintained by injury type. For shoulder dislocation methoxyflurane significantly reduced length of stay in the ED (167 minutes vs 350 minutes p=0.009) and was lower than SoC for upper limb injury (273 minutes versus 345 minutes) but this was not statistically significant. There were no reported significant adverse events associated with methoxyflurane treatment and it was generally well tolerated.	III
	Inhaled	**Fabbri et al. 2021**[113] A meta-analysis using pooled data from RCTs demonstrated that pain intensity difference was significantly superior for methoxyflurane to SoC analgesia (treatment effect 11.88, 95% CI 9.75–14.00, p<0.0001). Onset to analgesic effect was rapid with superiority of analgesic effect observed at 5 minutes and this was maintained at all timepoints. Comparable results were also noted in elderly patients.	IA
	Inhaled	**Johansson et al. 2021**[114] Pre-hospital evaluation of 32 patients (16 male; 16 female) with on-scene NRS median pain score of 8 (IQR 7.25–10.0) reduced to NRS 5 (IQR 4.0–7.0 p=0.001) by arrival at hospital. Women had lower median pain scores than men (4.0 [IQR 3.76–6.0] vs 6.0 [IQR 5.0–7.25], p=0.036). On average patients required 2 inhalers and the average number of inhaled breaths to achieve pain relief was 17 ± 9. The authors indicate significantly lower pain scores for patients treated with methoxyflurane, but the study was limited by the diversity of patient population and aetiology of pain and its observational design.	III
	Inhaled	**Lim et al. 2021**[115] Randomised, crossover study (paramedic administration) of methoxyflurane and IM tramadol in patients aged ≥16 years with MSK trauma. Primary endpoint was reduction in NRS ≥3 within 20 minutes. At 5 minutes pain relief was greater with methoxyflurane compared with tramadol (NRS reduction 2.0 vs 1.0, p=0.001) which remained significant at 10 and 15 minutes (10 minutes: NRS reduction 3.0 vs 1.0, p=0.001; 15 minutes: 4.0 vs 1.0, p=0.001) and remained significant by 20 minutes (NRS reduction 4.0 vs 1.0, p=0.028). More patients treated with IM tramadol had a NRS reduction ≥3 (71.6%) versus methoxyflurane-treated patients (46.7%). Administration time was faster for methoxyflurane than IM tramadol (9 minutes vs 11 minutes p<0.001). AEs were more common with methoxyflurane 44.3% vs 6.3% (p<0.001) but were mostly mild. Patients treated with methoxyflurane had higher paramedic and patient satisfaction scores.	IIA

Therapy	Route of administration	Overview of study/data	Level of evidence
	Inhaled	**Siriwardena et al. 2021**[116] A non-randomised pre-hospital study in 483 patients. Verbal numerical pain scores (VNPS) were collected from all patients and compared with retrospective pain scores from a database in comparable patients. Methoxyflurane's time to achieve maximum pain relief was significantly faster (all p-values <0.001): 25.7 mins (95% CI 24.4–27.0) versus nitrous oxide 44.4 (39.5–49.3); 25.8 (24.5–27.1) versus IV paracetamol 40.7 (34.6–46.9); 25.7 (24.4–27.0) versus IV morphine 41.9 (38.9–44.8). Scenario analyses of time spent in severe pain (VNPS on administration scoring 10 reducing to a score of 7) were significantly less for methoxyflurane (all difference p-values <0.001): 7.6 mins (95% CI 6.5–8.7) versus nitrous oxide 24.6 (20.1–29.0); 6.7 (5.6–7.7) versus IV paracetamol 23.0 (17.9–28.0); 6.9 (5.9–7.9) versus IV morphine 14.9 (13.3–16.6). Modelling results included demonstration of statistically significant clinical effectiveness of methoxyflurane over each comparator (all p-values <0.001). Thirty-two patients reported side effects, 19 of whom discontinued early. Thirteen patients, 10 aged over 75 years, were non-adherent to instructions given on inhaler use.	III
	Inhaled	**Trimmel et al. 2022**[117] Observational study in adult trauma patients (e.g. dislocations, fracture or low back pain following minor trauma) with moderate-to-severe pain (NRS ≥4) receiving methoxyflurane for up to 30 minutes. Median numeric pain rating was 8.0 (7.0–8.0) in 109 patients. Sufficient analgesia (reduction of NRS ≥3) was achieved by inhaled methoxyflurane alone in 67 patients (61%). The analgesic effect was progressively better with increasing age. Side effects were frequent (n=58, 53%) but mild. User satisfaction was scored as very good when pain relief was sufficient, but fair in patients without benefit. Technical problems were observed in 16 cases (14.7%), mainly related to filling of the inhaler. In every fifth use, the fruity smell of methoxyflurane was experienced as unpleasant. No negative effects on vital signs were observed. This study indicates that methoxyflurane is appropriate and beneficial for pain relief when transporting patients to hospital.	III
	Inhaled	**Hyldmo et al. 2024**[118] Systematic review of inhaled analgesics including methoxyflurane or nitrous oxide. Seven studies (n=56,535 patients) compared methoxyflurane or nitrous oxide to placebo or other drugs. All evidence was judged to be of poor quality, many with a high risk of bias. Only one study involved nitrous oxide and pain reduction was moderate, but clinically important, compared with placebo. No significant difference was observed in AEs between nitrous oxide and placebo. For methoxyflurane, it was anticipated that onset to analgesia would be faster than IV analgesics because of the extended set-up time for IV administration. However, it was suggested that IV analgesics will have a longer duration of action. Reduction of pain judged as a reduction in NRS ≥3 was not apparent at 20 minutes with methoxyflurane. However, at timepoints longer than 20 minutes, the potential to reduce NRS by ≥3 was improved with 47% of patients reporting this reduction. The authors note however, that this reduction with longer duration of use, may reflect the use of a second methoxyflurane inhaler. Methoxyflurane was generally associated with a low rate of AEs, but it is unclear if these differ for pre-hospital or ED patients due to transport and evacuation. Methoxyflurane also appears to have an acceptable level of environmental contamination, but the authors noted many countries do not have set occupational limits.	IC

Therapy	Route of administration	Overview of study/data	Level of evidence
	Inhaled	**Kelty et al. 2024**[119] Retrospective cohort safety study in the pre-hospital setting using probabilistic data of 37,211 children. The cohort included 9,472 treated with methoxyflurane alone (25.5%), 1,235 (3.3%) treated with opioids alone and 23,740 (63.8%) treated with combined methoxyflurane and opioids. Death in children and adolescents was uncommon, with less than five deaths (<0.1%) observed in the 12 months following treatment with methoxyflurane and no deaths in those treated with both methoxyflurane and an opioid analgesic. Adverse drug reaction was rare (<0.1%) in patients treated with methoxyflurane, as was liver and kidney toxicity with no case observed. At 90-days follow-up, there was no significant difference in hospitalisation in patients treated with methoxyflurane and those treated with methoxyflurane and an opioid analgesic (aOR:1.01, 95% CI:0.85–1.21). Compared with methoxyflurane treated patients, patients treated with an opioid analgesic were more likely to be hospitalised (aOR:1.23, 95% CI:1.09–1.39).	III
	Inhaled	**Lam et al. 2025**[120] SLR of methoxyflurane studies (n=6 studies). All studies were considered of high to moderate quality. Baseline pain scores were comparable across all studies ranging from VAS 63–66 mm or an NRS of 4–7 with one study including patients with severe pain (NRS >8). Pain reduction was evident within 5 minutes of methoxyflurane initiation, pain reduction was up to VAS 30–39 mm and NRS (0–10 scale) −5.75, with pain reduction maintained up to 30 minutes post-initiation. However, comparator drugs like fentanyl and morphine were associated with a more durable analgesia over time. Compared with placebo, methoxyflurane-treated patients required fewer breaths of the inhaler to achieve pain relief and required less rescue analgesia. AEs were comparable between all treatment groups. Patient satisfaction with methoxyflurane was very good or excellent as measured on a 5-point Likert scale and ~95% reported high satisfaction compared with 64–68% of placebo-treated patients.	IA
	Inhaled	**Smyth et al. 2025**[121] PACKMaN was a double-blind, controlled, superiority randomised trial in the prehospital setting in ambulances. Patients aged >16 years were randomised to receive methoxyflurane and morphine (n=230 [51%]) or methoxyflurane and ketamine (219 [49%]). Primary endpoint was sum of pain intensity difference (SPID), which was comparable across all patients with no significant difference (SPID methoxyflurane plus morphine 3.4 versus 3.5 for methoxyflurane plus ketamine). Onset to pain relief was faster for ketamine treated patients whilst the duration of pain relief was longer for morphine treated patients. There was no difference in ED LOS or changes in vital signs. Both groups had comparable numbers of AEs but the most common AEs in the morphine group was hypotension and behavioural in the ketamine group.	IIB
	Inhaled	**Simensen et al. 2025**[146] PACKMaN was a double-blind, controlled, superiority randomised trial in the prehospital setting in ambulances. Patients aged >16 years were randomised to receive methoxyflurane and morphine (n=230 [51%]) or methoxyflurane and ketamine (219 [49%]). Primary endpoint was sum of pain intensity difference (SPID), which was comparable across all patients with no significant difference (SPID methoxyflurane plus morphine 3.4 versus 3.5 for methoxyflurane plus ketamine). Onset to pain relief was faster for ketamine treated patients whilst the duration of pain relief was longer for morphine treated patients. There was no difference in ED LOS or changes in vital signs. Both groups had comparable numbers of AEs but the most common AEs in the morphine group was hypotension and behavioural in the ketamine group.	IB

Therapy	Route of administration	Overview of study/data	Level of evidence
NERVE BLOCK			
Bupivacaine, plus other anaesthetics not identified	Mixed nerve block, spinal block	**Abou-Setta et al. 2011**[122] A systematic review of pain management in hip fracture included 32 studies on nerve blockade and concluded that nerve blockades are effective for relieving acute pain and reducing delirium.	IV
Drugs not identified	Femoral nerve block	**Riddell et al. 2016**[123] A review of 7 studies of femoral nerve block in hip fracture reported decreased rescue analgesia requirements in 6 studies and no AEs.	IV
Bupivacaine	Femoral nerve block	**Morrison et al. 2016**[124] In an RCT including individuals with hip fracture in the ED, patients were randomised to receive femoral nerve block at admission followed by continuous fascia iliac block within 24 hours (n=79) or conventional analgesics (n=82). Pain scores 2 hours after presentation at the ED favoured the nerve block group over the control group (3.5 versus 5.3, p=0.002). At 6 weeks, participants who received nerve block reported better walking and stair climbing ability (mean Functional Independence Measure locomotion score of 10.3 versus 9.1, p=0.04).	III
Drugs not identified	Fascia iliac block	**Miller et al. 2016**[125] A national observational study in the UK received responses from 77% of all acute medical trusts in the UK. Of these, 62% of routinely provide fascia iliac compartment block for the management of pain caused by proximal femoral fracture.	III
Bupivacaine plus lidocaine	Brachial plexus block	**Galos et al. 2016**[126] Patients undergoing surgery for fixation of acute closed distal radius fractures were randomised to brachial plexus blockade (n=18) or general anaesthesia (n=18). Patients who received nerve block had lower pain scores at 2 hours after surgery (1.4 versus 6.7), but higher scores at 12 hours (6.0 versus 3.8) and 24 hours (5.3 versus 3.8).	III
Bupivacaine	Ultrasound guided fascia iliaca nerve block	**Kolodychuk et al. 2022**[127] A prospective cohort study in 65 patients in the ED with isolated femoral neck, intertrochanteric, and subtrochanteric femur fractures of whom 39 patients (60%) received nerve block with 40 ml 0.25% bupivacaine. In patients receiving nerve block opioid consumption preoperatively compared with those without nerve block (n=26), 17.4 vs 32.0 morphine milliequivalents, and a lower mean opioid consumption during their hospital each day (13.3 vs 24.0 morphine milliequivalents) and overall, during their hospital stay (54.5 vs 117.5 morphine milliequivalents). Patients treated with nerve block had a shorter length of post-ED hospital stay (4.3 vs 5.2 days). There was no significant difference in discharge disposition destination between groups and no patients reported complications.	III

Therapy	Route of administration	Overview of study/data	Level of evidence
Ketamine	Ultrasound guided peripheral nerve block	**Mohanty et al. 2023**[128] Prospective, open-label randomised study of 111 patients with isolated traumatic extremity injuries undergoing ultrasound-guided peripheral nerve block with ketamine. The primary endpoint was reduction in NRS by at least 3 points without rescue analgesia, and secondary outcomes were the need for rescue analgesia, adverse events and patient satisfaction. NRS was significantly lower in the nerve block group than IV ketamine dosing at all time points (30, 60, 120, 180 and 240 minutes post-dosing; p<0.001). More patients treated with nerve block reached the endpoint of NRS reduction ≥3 (100% vs 65% (−1.02 95% CI 1.42, 0.62). No patients in the nerve block group required rescue analgesia compared with 18% in the IV sub-dissociative ketamine dose group. NRS reduction from baseline was higher at 30 minutes for the nerve block group than IV ketamine group (treatment difference −2.17 [95% CI −2.64–1.69]). No patients experienced complications and patient satisfaction was higher in patients treated with nerve block than IV ketamine.	IC
Bupivacaine, ropivacaine	Ultrasound guided nerve block	**Bhattaram et al. 2024**[129] Retrospective analysis of ultrasound guided nerve block (femoral, fascia iliaca, serratus anterior) in 274 patients. Significant reductions in pain score post-block were observed with average NRS decrease of 2.9 ± 1.09 at 15 minutes and 5.8 ± 1.39 at 30 minutes. Complications were only recorded in 2 patients.	III

Therapy	Route of administration	Overview of study/data	Level of evidence
Bupivacaine	Peripheral nerve block	**Shinde et al. 2024**[130] Prospective, observational study in a single ED exploring the role of regional anaesthesia (variety of techniques including, adductor canal blocks (3.1%), fascia iliac blocks (12.6%), femoral blocks (7.4%), and axillary brachial plexus blocks (6.3%), among others. Mean VAS reduced from 8.8 to 1.9 ($p<0.001$) after bupivacaine administration, with 66.3% patients reporting pain relief within 5 minutes. Duration of pain relief varied: 41.1% had relief for ≤3 hours and 58.9% had relief lasting ≥3 hours. Most patients did not require rescue analgesia (89.5%). Adverse events were not reported, but authors indicate a place for peripheral nerve block in the ED but recognise the limitations of the study including its single centre design.	IIB
Ropivacaine plus dexamethasone	Ultrasound guided nerve block	**Pradhan et al. 2025**[131] Observational, descriptive, longitudinal study of peripheral nerve block for patients with upper limb fractures from distal humerus to distal phalynx. Primary objective was to evaluate onset and duration of ultrasound-guided peripheral nerve block with 0.2% ropivacaine plus 8 mg dexamethasone with 0.2% ropivacaine alone. Ropivacaine alone had a faster time to onset of pain relief (7.23 ± 0.83 minutes vs 10.31 ± 2.01 minutes) but duration of analgesia was significantly better for ropivacaine plus dexamethasone (duration 489.18 ± 78.34 minutes versus 591.29 ± 101.21 minutes; $p<0.0001$) as was reduction in pain score (mean VAS score 3.35 ± 0.12 vs 5.26 ± 0.23; $p<0.0001$). AEs were comparable in both groups, including hypotension, bradycardia and nausea with no significant difference between groups.	III
Bupivacaine OR ropivacaine	Ultrasound guided nerve block	**Abu-Halimah et al. 2025**[132] SLR of 9 randomised controlled trials of ultrasound guided nerve block for acute pain in the ED – no meta-analysis was possible. A range of nerve blocks were included although femoral nerve block for femoral neck and intertrochanteric fractures was most common. In all studies, pain reduction was effective with minimal side effects, but hypotension was observed in up to 8% of patients which was managed most typically with no intervention. Ultrasound guided nerve blocks were also linked to shorter ED stays, higher levels of patient satisfaction, and a low rate of complications when carried out by trained providers. It was concluded that included studies had low bias.	IC
Bupivacaine OR ropivacaine	Ultrasound guided nerve block	**Gawel et al. 2025**[133] SLR of SAPB in patients in the ED for a range of indications including rib fracture, tube thoracostomy, acute herpes zoster, chest wall burns, and unspecified chest wall injury either in the ED or in two cases to facilitate transportation to hospital. All blocks (n=82) were performed with bupivacaine or ropivacaine and in some adjuvants were also used including lidocaine, adrenaline, dexamethasone or methylprednisolone. Across all indications and studies pain reduction was noted with nerve block. Two studies in rib fracture showed pain reduction of up to NRS 3 or more. Similarly, in tube thoracotomy case studies indicated effective pain relief and patient preference for nerve block over procedural sedation. In many cases, onward requirement for opioids was reduced as was the need for other analgesics.	III

Therapy	Route of administration	Overview of study/data	Level of evidence
Bupivacaine plus dexamethasone	Ultrasound guided nerve block	**Goldsmith et al. 2025**[134] Prospective, multicentre, observational study in a convenience sample of sciatic nerve block in patients with acute sciatica to observe outcomes of ultrasound-guided transgluteal sciatic nerve block with bupivacaine (plus dexamethasone to improve duration of analgesia) with pain scores measured at 24 and 48 hours post-intervention. Sixty-three patients were enrolled and median pain scores reduced from 9 (IQR 8–10) pre-nerve block to 5 (IQR 3–7, p<0.001) at 24 hours and 4 (IQR 2–6.5, p<0.001) at 48 hours. Ambulation improved post-block with 27% unable to walk pre-block and reducing to 11% post-block. The ability of patients to 'get up and go' increased from 1.6% pre-block to 33% post-block (p=0.003).	III
Ropivacaine	Ultrasound-guided peripheral nerve block vs Bier block	**Tsao et al. 2025**[135] Open-label non-inferiority randomised controlled trial in adults aged ≥18 years with distal radius or ulnar fractures requiring reduction. Patients were randomised to ultrasound-guided supraclavicular block versus Bier block. Ultrasound-guided nerve block was non-inferior to Bier block (p<0.001). At 1-hour post-dosing pain was significantly lower in ultrasound-guided nerve block than Bier block (treatment difference -1.8 VAS). There were no differences in AEs between treatment groups. Ultrasound-guided nerve block was non-inferior to Bier block during closed reduction with prolonged analgesia.	III
LIDOCAINE			
	IA	**Cheok et al. 2011**[136] IA lidocaine (n=32) was compared with IV pethidine and diazepam (n=31) for the relief of pain during reduction of acute anterior shoulder dislocations. There was no significant difference between groups in terms of pain relief or patient satisfaction, and patients in the lidocaine group had a shorter duration of hospitalisation and fewer complications.	IB
	IA	**Wakai et al. 2011**[137] A Cochrane review of 5 studies (n=211) comparing IA lidocaine with IV analgesia with or without sedation for manual reduction of acute anterior shoulder dislocation in adults reported no significant difference between lidocaine and analgesia/sedation regarding pain during the procedure and post-reduction pain relief. Lidocaine may be associated with fewer adverse effects and a shorter recovery time.	IA
	IA	**Jiang et al. 2014**[138] A meta-analysis of 9 RCTs including 438 patients compared IA lidocaine with IV analgesia and sedation. IA lidocaine was not significantly different compared with IV analgesia and/or sedation for reduction of acute shoulder dislocation in the ED in terms of pain relief or patient satisfaction but did have a shorter duration of hospitalisation (p=0.03) and lower risk of complications (p<0.00001).	IA
	IV	**Soleimanpour et al. 2012**[139] Patients referred to the ED due to renal colic were randomised to IV lidocaine (n=120) or IV morphine (n=120). Patients in the lidocaine group had significantly greater pain relief than those in the morphine group at 30 minutes (p=0.0001).	III
	IV	**Firouzian et al. 2016**[140] Patients presenting to the ED with renal colic (n=110) were randomised to IV morphine plus IV lidocaine or IV morphine alone. Patients in the combination group had a reduced length of time to becoming pain free (87 versus 100 minutes) and nausea free (27 versus 58 minutes).	IIB

Therapy	Route of administration	Overview of study/data	Level of evidence
	IV	**Farahmand et al. 2018**[141] In a randomised study, patients with acute traumatic extremity pain were given either IV lidocaine (n=25) or IV morphine (n=25). Pain scores decreased significantly in both groups over 1 hour, with no significant differences between groups.	IIB
	IV	**Akhgar et al. 2021**[142] RCT of IV lidocaine versus IV morphine in 104 patients with mean pain score 8.23. Mean pain score was comparable in both groups except for 30 minutes post administration where IV lidocaine had a lower pain score 5.05 versus 6.39 (p=0.01).	IA
	IV	**Zhong et al. 2021**[143] Systematic review and meta-analysis of 12 randomised clinical trials in 1,351 patients with a range of pain conditions in the ED (abdominal pain, renal or biliary colic, traumatic pain, radicular low back pain, critical limb ischemia, migraine, tension-type headache, and pain of unknown origin) evaluated efficacy of IV lidocaine versus comparators (morphine n=6; ketorolac n=2; dexketoprofen n=2; hydromorphone n=1; fentanyl n=1). Pooled analysis indicated that IV lidocaine was as effective as comparator analgesia at all time points (15, 30, 45 and 60 minutes). No significant differences were observed in rescue analgesia requirements, but subgroup analysis indicated that rescue analgesia was required for patients in receipt of IV lidocaine with abdominal pain but not for MSK pain. Meta-analysis indicated no differences in the incidence of side effects between any study groups (OR: 1.09 95% CI: 0.59, 2.02 I^2= 48% p=0.78).	IC
	Patch	**Zink et al. 2011**[144] A retrospective analysis compared patients with rib fracture treated with lidocaine patch (n=29) with a matched control cohort (n=29). In the 24 hours after receiving lidocaine, patients in the active treatment group had a greater decrease in pain scores than controls (p=0.01). At 60 days, patients in the lidocaine group had a lower McGill Pain Questionnaire score, even though only 1 patient was still using a patch at this time point.	
	Patch	**Felemban et al. 2024**[145] Systematic review and meta-analysis of 10 randomised clinical trials in 523 patients indicated that lidocaine patches are more effective than placebo in controlling MSK and neuropathic pain in the ED, but efficacy data could not be pooled due to high levels of heterogeneity. Efficacy of lidocaine patches was comparable with NSAIDs in two studies, with no statistically significant difference in efficacy. The risk of adverse events was similar for lidocaine patches and comparators (risk ratio: 0.90; 95% CI: 0.48–1.67) but evidence was of moderate quality.	IC

(*) Study undertaken in patients with post-operative pain.
AEs, adverse events; aOR, adjusted odds ratio; AVPS, analogue visual pain score; CI, confidence interval; ED, emergency department; HR, heart rate; IA, intra-articular; IM, intramuscular; IN, intranasal; IQR, inter quartile range; IV, intravenous; LBP, low back pain; LOS, length of stay; MSK, musculoskeletal; NRS, numeric rating scale; NS, not significant; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio; OM, oromucosal; PCA, patient controlled analgesia; RASS, Richmond Agitation Sedation Score; RCT, randomised controlled trial; SAEs, serious adverse events; SAPB, serratus anterior plane block; SBP, systolic blood pressure; SC, subcutaneous; SL, sublingual; SLR, systematic literature review; SoC, standard of care; VAS, visual analogue scale; VNPS, verbal numeric pain scale.

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