Pharmacological management of acute nociceptive pain

Tratamento farmacológico da dor aguda nociceptiva

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Abstract

Acute nociceptive pain is one of the main causes of seeking medical care, and its inadequate management may lead to chronicity and negatively impact functional recovery. This update provides a critical, evidence-based review of the pharmacological treatment of acute pain, focusing on a multimodal, individualized approach. Paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) remain the cornerstone of therapy for mild to moderate pain, and the choice between non-selective NSAIDs and selective cyclooxygenase (COX)-2 inhibitors is guided by the patient's gastrointestinal and cardiovascular risk profile. Topical NSAIDs represent an effective and safe alternative for localized musculoskeletal pain. Short-acting opioids are reserved as rescue therapy for severe and refractory pain and should be prescribed at the lowest effective dosage and for the shortest possible duration, with a clear tapering strategy. The application of these drugs is discussed in common settings, such as orthopedic trauma and postoperative pain, and in specific populations, including older individuals, pregnant women, and patients with renal or hepatic comorbidities, who require individualized dosage adjustments to ensure safety. The implementation of rational analgesic use is fundamental to maximizing pain relief, minimizing adverse effects, and preventing medication misuse, thereby effectively relieving suffering and optimizing clinical outcomes.

Keywords: Anti-inflammatory drugs, non-steroidal; Postoperative pain; Analgesics; Acute pain.

Resumo

A dor aguda nociceptiva é uma das principais causas de procura por atendimento médico, e seu manejo inadequado pode levar à cronificação e impactar negativamente a recuperação funcional. Esta atualização apresenta uma revisão crítica e baseada em evidências sobre o tratamento farmacológico da dor aguda, com foco em uma abordagem multimodal e individualizada. O paracetamol e os anti-inflamatórios não esteroides (AINEs) constituem a base da terapia para dor de intensidade leve a moderada, sendo a escolha entre AINEs não seletivos e inibidores seletivos da COX-2 guiada pelo perfil de risco gastrointestinal e cardiovascular do paciente. AINEs tópicos representam uma alternativa eficaz e segura para dor musculoesquelética localizada. Opioides de curta duração são reservados como terapia de resgate para dor intensa e refratária, devendo ser prescritos na menor dose eficaz e pelo menor tempo possível, com um plano de descalonamento claro. A aplicação destes fármacos é discutida em cenários clínicos prevalentes, como trauma ortopédico e dor pós-operatória, e em populações especiais, incluindo idosos, gestantes e pacientes com comorbidades renais ou hepáticas, que exigem ajustes específicos para garantir a segurança. A implementação de princípios de uso racional de analgésicos é fundamental para maximizar a analgesia, minimizar os efeitos adversos e prevenir o uso indevido de medicamentos, visando o alívio eficaz do sofrimento e a otimização dos desfechos clínicos.

Palavras-chave: Anti-inflamatórios não esteroides; Dor pós-operatória; Analgésicos; Dor aguda.

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Introduction

Acute pain is an adaptive physiological response to tissue damage, with sudden onset and limited duration. In contrast, chronic pain persists for more than three months, evolving into an autonomous pathological condition supported by neuroplastic mechanisms, such as central sensitization, making its management more challenging[1,2]. According to the International Association for the Study of Pain (IASP) taxonomy, pain is classified into three main mechanisms[3,4]. Nociceptive pain, the focus of this article, results from activation of nociceptors by tissue injury, as in fractures, and is typically described as localized and throbbing. Neuropathic pain results from injury to the somatosensory nervous system and manifests as burning or shock-like pain. Finally, nociplastic pain arises from an alteration in nociception, without evident tissue or neural damage, and is characterized by central amplification of pain, as in fibromyalgia[3,4]. In summary, the mechanisms arise from tissue injury, nerve injury, or pain-processing dysfunction, respectively[3,4,5].

Acute pain has a high prevalence and is the main driver of demand for emergency services. In orthopedic and trauma scenarios, musculoskeletal pain is frequent and often undertreated. Postoperatively, the prevalence of severe pain remains high, affecting 20% of patients in general surgeries and up to 56% in orthopedic trauma surgeries. Uncontrolled pain negatively impacts recovery, delays mobilization, and increases the risk of complications and chronicity. Inadequate management leads to functional limitation and worsening of quality of life, making a multimodal approach essential to optimize outcomes[6-8].

Multimodal analgesia is the gold standard approach for acute nociceptive pain, based on the synergistic combination of drugs with different mechanisms of action, such as NSAIDs, paracetamol, and opioids[9-12]. This strategy aims to modulate pain at multiple points in the nociceptive pathway. The advantages documented include superior analgesia with a reduction in opioid consumption and, consequently, a lower incidence of its adverse effects. The implementation of multimodal protocols results in better clinical outcomes, including shorter hospital stay and higher patient satisfaction[9-12].

The physiology of nociceptive pain begins with the transduction of harmful stimuli into electrical signals by peripheral nociceptors via ion channels, including those of the transient receptor potential (TRP) family[13,14]. These signals are transmitted to the spinal cord, where the release of excitatory neurotransmitters can lead to central sensitization[15]. Pain transmission is modulated by sensitization mechanisms, which amplify it, and by descending inhibitory pathways, which attenuate it, both involving opioid and adrenergic receptors and other pharmacological targets[16]. Understanding this complex signaling network, with multiple points of intervention for drugs such as NSAIDs and opioids, underlies the rationale for multimodal analgesia[13,16].

Practical management of acute pain follows a four-step algorithm: evaluation, initial non-opioid therapy, multimodal escalation, and continuous reassessment[5,17,18]. The first step is a systematic assessment of pain, considering its characteristics, functional impact, and patient risk factors. For mild to moderate pain, first-line therapy consists of non-opioid analgesics such as paracetamol or NSAIDs[17,18]. If the response is inadequate, the approach is scaled multimodally and may include short-acting opioids for moderate to severe pain, prescribed at the lowest effective dosage and for a limited duration[5,17,18]. Frequent reassessment of efficacy and adverse effects, along with an opioid tapering strategy, is a critical component of treatment[5,8,17].

Next, we analyze in detail the main pharmacological classes that form this algorithm, starting with the first-line analgesic.

Paracetamol

Paracetamol (acetaminophen) is recommended as a first-line analgesic for treating acute pain of mild to moderate intensity, owing to its favorable safety profile, tolerability, and proven efficacy at therapeutic doses[11,19,20]. Its usefulness is well established in multiple clinical settings, including musculoskeletal pain, tension headache, and postoperative pain, with a modest benefit, particularly for the rapid relief of moderate pain[21].

The standard dosage for adults is 1,000 mg every 6 hours, administered orally, intravenously, or rectally, and should not exceed the maximum daily dosage of 4,000mg[11,20,22]. In specific populations, such as older patients with chronic liver disease, the dosage should be individualized, with a possible reduction to 2,000-3,000 mg per day[11,19]. For children, the dosage is calculated based on weight, at 10-15 mg/kg per dosage every 4 to 6 hours, with a daily intake of 60-75 mg/kg[20,22].

The risk of hepatotoxicity is minimal when therapeutic dosages are maintained, including in patients with compensated cirrhosis[19]. Liver toxicity becomes a significant concern in cases of overdose, defined by intakes higher than 4,000 mg/day in adults or a single dosage greater than 150 mg/kg[20,22]. This condition can progress to acute liver failure, with paracetamol being the main cause of this condition in Western countries.

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are classified based on their selectivity for cyclooxygenase (COX) isoenzymes. Non-selective (traditional) NSAIDs inhibit both cyclooxygenase (COX)-1 and COX-2, while selective COX-2 inhibitors (coxibs) act predominantly on COX-2. This pharmacological distinction is clinically relevant as it determines the efficacy and safety of each agent, especially in the gastrointestinal, cardiovascular, and renal systems.

Systemic NSAIDs

In terms of analgesic efficacy for acute pain, both traditional NSAIDs and COX-2 inhibitors present comparable results in scenarios such as postoperative pain and gout crises. Meta-analyses demonstrate that coxibs (e.g. etoricoxib, celecoxib) are as effective as non-selective NSAIDs (e.g. diclofenac), with some evidence suggesting a marginal benefit for etoricoxib in acute gout[23]. Therefore, the therapeutic choice should be guided primarily by the patient's individualized risk profile.

The main benefit of coxibs lies in their superior gastrointestinal safety profile. By sparing COX-1 activity, they preserve the synthesis of gastroprotective prostaglandins, resulting in a significantly lower risk of ulcers and gastrointestinal bleeding compared with non-selective NSAIDs[24,25]. This advantage makes them particularly useful in patients at high risk of gastrointestinal events, such as those with a history of peptic ulcer disease, and in perioperative settings in which the preservation of platelet function is crucial[26].

In contrast, cardiovascular safety is of greater concern with coxibs, which are associated with an increased risk of thromboembolic events[24,25]. This risk depends on dosage, treatment duration, and pre-existing risk factors[24,25]. Among non-selective NSAIDs, naproxen is considered the option with the lowest cardiovascular risk, while diclofenac exhibits a risk profile similar to that of coxibs[24]. Regarding renal safety, both classes have similar risks of fluid retention and worsening renal function, warranting caution in patients with comorbidities[26].

In summary, the decision between a non-selective NSAID and a coxib should be individualized. Although equally effective, coxibs offer greater gastrointestinal safety at the cost of increased cardiovascular risk, with similar renal risk[24,25]. Additionally, they are a valuable component in multimodal analgesia regimens, contributing to the reduction of opioid consumption (Table 1)[26].

Topical NSAIDs

Topical NSAIDs are a highly effective therapeutic option for the management of acute pain of peripheral musculoskeletal origin, such as sprains and strains[27-29]. Current guidelines recommend them as first-line therapy for adults with this type of pain, except for low back pain, due to their excellent safety profile compared to oral formulations and their ability to promote significant pain relief and functional improvement[27-29].

The effectiveness of topical NSAIDs is corroborated by high-quality evidence. A relevant metric is the low number needed to treat (NNT) to achieve at least 50% pain reduction within 7 days, ranging from approximately 1.8 for diclofenac to 3.9 for ibuprofen, indicating a substantial clinical benefit[28]. Analgesic efficacy is comparable with oral NSAIDs, but with a significantly lower risk of systemic adverse events[27-29].

In terms of safety, topical NSAIDs have a clear advantage, with rates of local adverse reactions, such as mild skin irritation, similar to placebo[27-29]. Crucially, there is no significant increase in the risk of systemic complications (gastrointestinal, renal, or cardiovascular), which are the main concern with oral NSAIDs. This characteristic makes them a preferred option for patients with contraindications to systemic use, such as older individuals with comorbidities[28]. The recommendation for first-line use applies to most cases of acute peripheral musculoskeletal pain, except for severe injuries that may require a systemic or multimodal approach[27]. In the United States, several formulations of topical NSAIDs are approved by the FDA for this indication[30].

Table 1. Recommendations for safe prescribing of anti-inflammatories: Non-selective inhibitors vs selective inhibitors (COX-2)

Risk domain	Non-selective NSAIDs (e.g. ibuprofen, naproxen, diclofenac)	COX-2 selective inhibitors (e.g. celecoxib, etoricoxib)	Practical implications / Recommendations
Cardiovascular (CV) risk	Varies by drug and dosage. Naproxen appears to have lower CV risk; diclofenac shows COX-2 selectivity and a CV risk profile similar to that of coxibs, especially at higher dosages.	Increased risk of thrombotic events, including myocardial infarction and stroke, has been demonstrated in trials and observational studies; the magnitude is dosage-dependent.	1) Avoid coxibs and diclofenac in patients at high CV risk. 2) Prefer naproxen or similar when an NSAID is needed and CV risk is relevant. 3) Use the lowest effective dosage for the shortest possible time.
Gastrointestinal (GI) risk	Non-selective NSAIDs increase the risk of ulcers, bleeding, and perforation; risk depends on dosage, duration, and patient factors (age, aspirin use, anticoagulation).	Coxibs reduced high-grade GI events in many comparative trials compared with high dosages of non-selective NSAIDs; the relative gastroprotective benefit was more evident when comparisons were not 'fair' in dosage.	4) In patients at high GI risk, coxibs may be considered, but concomitant CV risk should be assessed. 5) Use a proton pump inhibitor (PPI) for GI protection in high-risk patients, regardless of the NSAID chosen.
Renal risk and blood pressure	Non-selective NSAIDs can cause sodium retention, increased blood pressure (BP), and an increased risk of acute renal failure (dehydration, heart failure (HF), and chronic kidney disease). Dosage-dependent effect.	Coxibs also inhibit renal COX-2, which may increase BP and renal risk, similar to the renal adverse effect of classical NSAIDs.	6) Monitor renal function and BP in prolonged use or in patients at risk. 7) Avoid NSAIDs in dehydration, decompensated HF, or severe renal failure.
Dosage-response considerations	Analgesic efficacy and adverse risk increase with dosage; often, dosages for rheumatoid arthritis > osteoarthritis.	CV and GI risk related to dosage and exposure; comparisons between NSAIDs and coxibs should use equivalent dosages to be fair.	8) Prescribe the lowest effective dosage for the shortest possible duration; adjust dosage as indicated (e.g. lower dosages for osteoarthritis).
Comparisons and 'Fair Play' in trials	Historical trials have often used high dosages of NSAIDs compared to coxibs at standard dosages, exaggerating the GI benefit of coxibs.	Studies comparing coxibs with diclofenac (also relatively COX-2 selective) masked the CV signal; critical interpretation is required.	9) Interpret literature critically—recognize dosage and comparator biases; do not extrapolate GI benefits without assessing CV risk.
General clinical strategy	Non-selective NSAIDs may be appropriate when CV and GI risks are low; naproxen is preferable when CV risk is a concern.	Coxibs may be an option to reduce GI risk in patients with high GI risk and low CV risk; avoid in patients with high CV risk.	10) Individualize decision with risk assessment (CV, GI, renal); prefer naproxen if CV concern; consider coxib + PPI at high GI risk and low CV risk; always use lower dosage and duration.

Source: Adapted from Stiller and Hjemdahl (2022)[24]

Local anesthetics

Local anesthetics are essential in the management of acute pain, with several routes of administration, including infiltration, topical application, and transdermal patches, allowing a targeted approach to the injury.

Anesthetic infiltration, such as lidocaine and bupivacaine, is a standard practice for analgesia in minor surgical procedures and soft tissue trauma. The selection of the agent should consider the duration of the analgesic effect and the risk of systemic toxicity, and it is mandatory to adhere to the maximum recommended dosages, such as 4-5 mg/kg for lidocaine, to prevent serious adverse events such as arrhythmias and seizures[20,31]. In acute dental pain, bupivacaine has been shown to be superior to lidocaine in reducing the need for rescue analgesics[32].

For superficial injuries such as burns or wounds, topical application is the route of choice. Cream, gel, or viscous solutions provide effective analgesia with a low risk of systemic toxicity due to limited absorption[20,33]. In burn patients, for example, lidocaine/prilocaine creams may offer pain relief for up to 24 hours following procedures such as skin grafts[33]. In acute toothache due to pulpitis, topical benzocaine showed higher efficacy than placebo[32].

Transdermal lidocaine patches, although approved for neuropathic pain, can be considered as adjuncts in multimodal strategies for acute pain, although the evidence for postoperative pain is limited and the analgesic effects modest[34,35]. They are applied directly to the painful area for up to 12 hours and have a favorable safety profile, with predominantly local adverse reactions. Formulation and route of administration should always be individualized to the clinical scenario and the patient's profile, as recommended by several acute pain management guidelines[20,33].

Muscle relaxants

The use of muscle relaxants and antispasmodics to manage acute pain is limited to specific scenarios, especially in musculoskeletal conditions such as acute low back pain. The prescription of these agents is recommended only for the short term, usually for no more than 2-3 weeks, due to their adverse effects and the lack of evidence to support a sustained benefit[36-39].

The literature shows that muscle relaxants such as cyclobenzaprine and tizanidine can offer modest relief from acute low back pain, especially when first-line analgesics such as NSAIDs are ineffective or contraindicated[36,37,39]. However, the magnitude of this benefit is often small and clinically questionable, with mean reductions of less than 10 points on a 100-point pain scale[37]. There is no evidence to demonstrate the superiority of one agent over another within the same classification[39].

The main limiting factor for muscle relaxants is the significant risk of adverse effects on the central nervous system, especially sedation, which affects up to 50% of patients[36,37,39]. Other common effects include dizziness and drowsiness, which can compromise daytime functioning and increase the risk of falls and accidents, especially in older individuals[36]. The risk of sedation is enhanced by the concomitant use of other central nervous system depressants, such as opioids[38].

Current guidelines recommend that muscle relaxants be considered as second-line therapy, reserved for moderate to severe acute pain that has not responded to NSAIDs, and avoided in cases of mild pain[36,37]. When prescribed, nighttime is preferred to minimize functional impact. Given its risk profile, its use in older individuals is considered potentially inappropriate.

Opioids

The use of opioids for managing acute pain should be judicious, reserved as rescue therapy for cases of moderate to severe pain that do not respond adequately to other analgesic modalities, such as NSAIDs, paracetamol, or local anesthetic techniques[5,8]. The decision to prescribe an opioid requires a detailed assessment of the diagnosis, patient comorbidities, and individual risk for misuse and adverse effects[8,40].

Drug selection should prioritize immediate and short-acting opioids, such as morphine, oxycodone, or hydromorphone, preferably administered orally to facilitate titration[5,41]. Prolonged-release formulations are not recommended for the initial management of acute pain. The starting dosage should be as low as possible to achieve the desired effect, with adjustments based on age, kidney and liver function, and prior opioid exposure[41,42]. In older patients or those using other sedatives, even lower dosages are required[8,42].

The duration of treatment should be as short as possible. For most acute non-traumatic pain conditions, a course of three days or less is usually sufficient, and use for more than seven days is rarely warranted[8,40]. Long-term use is associated with an increased risk of dependence, tolerance, and other serious adverse events[8,40].

A tapering strategy should be established from the outset, with frequent reassessment of opioid need and return to baseline analgesic regimen as soon as pain subsides[8]. It is essential to monitor the patient for signs of excessive sedation, respiratory depression, and constipation, implementing prophylactic measures when necessary[5,8]. In patients achieving dosages ≤ 50 MME/day (milligram equivalents of morphine), vigilance should be increased, and the prescription of naloxone for reversal should be considered[40].

The practical application of this pharmacological arsenal varies significantly across clinical settings, requiring a targeted approach (Table 2).

Prevalent clinical conditions of acute pain

The pharmacological treatment of acute nociceptive pain is highly dependent on the clinical setting, requiring a targeted approach. In acute musculoskeletal injuries, such as sprains, fractures, and bruises—one of the main causes of pain in emergency services—the initial

Table 2. Key aspects of the 2022 CDC recommendations on opioid prescription

Theme / Domain	Key points	Notes and limitations
Scope of application	Patients ≥ 18 years with acute (< 1 month), subacute (1-3 months) or chronic (> 3 months) pain; does not apply to cancer pain, palliative care or end of life.	It requires individualized clinical analysis; it is neither directive nor mandatory.
Prioritized non-opioid therapies	Non-pharmacological and non-opioid modalities should be considered and optimized prior to opioids.	Decision based on patient preferences and conditions.
Opioid initiation	Only when benefits outweigh risks, avoid unnecessary onset of acute pain.	Prevent evolution from acute to chronic use.
Selection and dosage	Start with immediate-release opioids at the lowest effective dosage possible.	Avoid extended release as a first option.
Dosage increases	Avoid rapid increases; reassess risk/ benefit continuously.	Benefit tends to diminish with high dosages.
Duration of initial prescription	Limit the expected duration of severe pain, usually < 7 days.	Avoid over-prescribing and the risk of prolonged use.
Monitoring and follow-up	Evaluate efficacy, adherence, and adverse events on a regular basis.	Use prescription monitoring systems when available.
Risk assessment/mitigation	Investigate risk factors (substance use, comorbidities).	Consider naloxone, treatment contracts, and intensive monitoring.
Tapering and discontinuation	Gradually reduce the dosage when risks outweigh benefits.	Avoid abrupt interruption; the plan must be shared.
Fairness and clinical judgment	Guidelines are voluntary; adapt to reality and the patient.	Avoid rigid application that compromises access to appropriate treatment.

Source: Adapted from Dowell et al. (2022)[8]

management prioritizes the use of NSAIDs (topical or oral) and paracetamol, with opioids being strictly reserved for cases of severe or refractory pain[8,17,27,29]. A similar logic applies to acute low back pain, where NSAIDs and paracetamol form the basis of therapy, and muscle relaxants can be considered as adjuvants, while opioids are indicated only for short periods in situations of severe and disabling pain[8,17]. In the context of postoperative pain, a multimodal strategy is also standard, with short-acting opioids being added for larger procedures, but always with an early tapering strategy[8,17].

The choice of drug is even more specific in other conditions. For acute dental pain, for example, NSAIDs are recommended as a first line and have been shown to be more effective than opioids[8]. In cases of renal colic, NSAIDs are preferred not only for their analgesic potency but also for their action on ureteral spasm, with opioids serving as rescue therapy[8]. In contrast, the pain crisis of sickle cell disease, due to its intensity and refractoriness, often requires staggered analgesia that includes opioids as a central part of treatment[8]. Management in specific populations, such as pediatric populations, follows principles similar to those for adults, with strict dosage adjustments for age and weight in common scenarios such as musculoskeletal and postoperative pain[43]. In all cases, the final therapeutic decision must be individualized, considering the intensity of pain, the patient's comorbidities, and the risk profile of each drug[8,17,27,29].

Specific populations

The pharmacological treatment of acute pain in specific populations requires an individualized approach, with specific adjustments to mitigate risks associated with pharmacokinetic and pharmacodynamic changes[11,44-46]. In older patients, increased sensitivity to adverse effects dictates a more cautious approach. Paracetamol is recommended as a first-line analgesic; however, the maximum daily dosage should be reduced, for example, to up to 2,000 mg/day, due to decreased hepatic clearance and increased risk of toxicity[11,44]. The use of NSAIDs should be avoided whenever possible, given the high risk of gastrointestinal bleeding, renal failure, and cardiovascular events[11,45,46]. If an NSAID is indispensable, preference is given to selective COX-2 inhibitors, associated with gastroprotection, and

prescribed at the lowest dosage and for the shortest possible period[11,45]. Prescription of opioids for older individuals requires lower initial dosages and slow and careful titration, as the risk of respiratory depression, delirium, and excessive sedation is significantly higher in this population[11,44].

In patients with moderate to severe kidney disease, NSAIDs are contraindicated due to the risk of acute deterioration of renal function and sodium retention[11,17,45]. Paracetamol is a safer alternative, although it should be used with caution in advanced stages of the disease. If opioids are necessary, the choice of agent is crucial: morphine and codeine should be avoided due to the accumulation of their active metabolites, and preference should be given to drugs such as fentanyl or hydromorphone, which have less dependence on the renal excretion pathway[46]. In patients with significant liver disease, NSAIDs should also be avoided due to the risk of renal bleeding and decompensation. The maximum dosage of paracetamol should be reduced to 2 g/day, and opioids, whose metabolism is hepatic, should be started at low dosages with close monitoring for signs of toxicity[11,17,46].

For pregnant women, paracetamol is considered the analgesic of choice and is safe throughout pregnancy. NSAIDs, on the other hand, should be avoided, especially in the third trimester, due to the risk of premature closure of the fetal ductus arteriosus[17]. For patients at high cardiovascular risk, NSAIDs should be used with caution, prioritizing lower-risk agents such as naproxen and avoiding selective COX- inhibitors[28,45]. In anticoagulated patients, NSAIDs are formally contraindicated due to the high risk of bleeding, making paracetamol the first-line option[11,45]. In many of these risk groups, the use of topical analgesics, such as NSAIDs or lidocaine, for localized pain represents a safe and effective alternative[8,17].

Safety, interactions, and the rational use of analgesics

The rational management of drugs for acute nociceptive pain requires the application of principles of analgesic stewardship to maximize efficacy and minimize risks through judicious, evidence-based prescribing[17,27]. The basis of this approach is to use the lowest effective dosage for the shortest possible time, with frequent reassessment and a well-defined tapering strategy aligned with the patient's expectations. It should be considered that most cases of acute pain provide substantial relief within 1 to 7 days, making prolonged treatment the exception[17,29].

Gastrointestinal safety is a central concern in oral NSAIDs. Moderate certainty evidence indicates that they increase the risk of adverse events such as abdominal pain and dyspepsia (OR 1.77) compared to placebo or paracetamol[27,29,47]. The risk of serious complications, such as bleeding, is dependent on the dosage and duration of treatment, being higher in older patients and patients with a history of gastrointestinal disease or using anticoagulants. In this context, topical NSAIDs appear as a first-line alternative, presenting similar efficacy to oral ones for localized musculoskeletal pain, but with a significantly lower risk of systemic adverse events[27,29,43]. The use of proton pump inhibitors (PPIs) as gastroprotection is a recommended practice in high-risk patients requiring oral NSAIDs[17,20].

Drug interactions also require clinical attention. NSAIDs may reduce the efficacy of several classes of antihypertensives and substantially increase the risk of bleeding when associated with anticoagulants or platelet antiaggregants[17,20]. Opioids, in turn, are at risk of severe central nervous system depression when combined with other depressants, such as benzodiazepines and alcohol[17,29]. In addition, it is crucial to avoid therapeutic duplication, such as the concomitant use of multiple NSAIDs or different formulations that contain paracetamol in a non-obvious manner, which requires a careful review of the prescription and guidance to the patient[17].

The concept of rational use of analgesics, analogous to that of antibiotics, recommends a careful prescription, with active monitoring of adverse effects and preference for non-opioid and non-pharmacological agents whenever possible[17,27,29]. At hospital discharge, opioids should be prescribed only when strictly necessary, for a limited period (usually ≤ 3 days) and with clear guidance to the patient on the risks and the safe disposal of leftovers, to prevent misuse and dependence[17,27,29,47].

Gaps and lines of research

Despite significant advances in the management of acute nociceptive pain, important gaps remain to be explored. Continued research for analgesics with improved safety profiles, such as NSAIDs that dissociate anti-inflammatory efficacy from gastrointestinal and

cardiovascular risks, remains a priority. In addition, there is a growing need to develop non-opioid alternatives with sufficient analgesic potency for severe pain to further reduce opioid dependence in scenarios such as postoperative and trauma. Future investigations should also focus on the mechanisms of transition from acute to chronic pain, including the role of nociplastic components, to develop more effective preventive strategies. Finally, optimizing multimodal analgesia protocols for specific populations, such as older patients and patients with renal and hepatic comorbidities, requires further robust studies to guide clinical practice with greater safety.

Final considerations

Pharmacological treatment of acute nociceptive pain has evolved from a single-agent-based model to a multimodal, individualized, evidence-based approach. The pillar of this strategy is the rational use of non-opioid analgesics, such as paracetamol and NSAIDs, whose selection must be strictly guided by each patient's risk profile, particularly regarding gastrointestinal, cardiovascular, and renal safety. The combination of drugs with different mechanisms of action enhances analgesic efficacy and, crucially, minimizes the need for opioids, reducing the incidence of their adverse effects. Opioids retain their role as indispensable rescue therapy for severe pain, but their prescription should follow the principles of optimal use: the lowest effective dosage, for the shortest possible duration, and with a clear tapering strategy. The integration of these concepts aims not only at the effective relief of acute suffering but also at improving the patient's functional recovery and preventing chronic pain.

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References

1. Prasad R, Mueller KL, Bruns D, et al. Clinical Practice Guideline for Psychological and Other Nonpharmacological Treatment of Chronic Musculoskeletal Pain in Adults. Washington, DC: American Psychological Association; 2024.
2. Steingrímsdóttir ÓA, Landmark T, Macfarlane GJ, Nielsen CS. Defining chronic pain in epidemiological studies: a systematic review and meta-analysis. Pain. 2017 Nov;158(11):2092-107.
3. Fitzcharles MA, Cohen SP, Clauw DJ, et al. Nociplastic pain: towards an understanding of prevalent pain conditions. Lancet. 2021 May;397(10289):2098-2110.
4. Kaplan CM, Kelleher E, Irani A, et al. Deciphering nociplastic pain: clinical features, risk factors and potential mechanisms. Nat Rev Neurol. 2024 Jun;20(6):347-363.
5. Swarm RA, Youngwerth JM, Agne JL, et al. Adult Cancer Pain, Version 2.2025, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2025 Jul;23(7):e250032.
6. Edgley C, Hogg M, De Silva A, et al. Severe acute pain and persistent post-surgical pain in orthopaedic trauma patients: a cohort study. Br J Anaesth. 2019 Sep;123(3):350-359.
7. Small C, Laycock H. Acute postoperative pain management. Br J Surg. 2020 Feb;107(2):e70-e80.
8. Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC Clinical Practice Guideline for Prescribing Opioids for Pain - United States, 2022. MMWR Recomm Rep. 2022 Nov;71(3):1-95.
9. Hsu JR, Mir H, Wally MK, Seymour RB. Clinical Practice Guidelines for Pain Management in Acute Musculoskeletal Injury. J Orthop Trauma. 2019 May;33(5):e158-e182.
10. American Society of Anesthesiologists Task Force on Acute Pain Management. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology. 2012 Feb;116(2):248-73.

11. Bernard A, Oyler DR, Anglen JO, et al. Best Practices Guidelines For Acute Pain Management In Trauma Patients. Chicago, IL: American College of Surgeons; 2020.
12. Coccolini F, Corradi F, Sartelli M, et al. Postoperative pain management in non-traumatic emergency general surgery: WSES-GAIS-SIAARTI-AAST guidelines. World J Emerg Surg. 2022 Oct;17(1):50.
13. Kumamoto E. Anesthetic- and Analgesic-Related Drugs Modulating Both Voltage-Gated Na+ and TRP Channels. Biomolecules. 2024 Dec;14(12):1619.
14. Mickle AD, Shepherd AJ, Mohapatra DP. Nociceptive TRP channels: sensory detectors and transducers in multiple pain pathologies. Pharmaceuticals (Basel). 2016 Dec;9(4):E72.
15. Phillips WJ, Currier BL. Analgesic pharmacology: I. Neurophysiology. J Am Acad Orthop Surg. 2004 Jul-Aug;12(4):213-20.
16. Khan A, Khan S, Kim YS. Insight into Pain Modulation: Nociceprors Sensitization and Therapeutic Targets. Curr Drug Targets. 2019;20(7):775-88.
17. Amaechi O, Huffman MM, Featherstone K. Pharmacologic Therapy for Acute Pain. Am Fam Physician. 2021 Jul;104(1):63-72.
18. Pharmacologic Stepwise Multimodal Approach for Postpartum Pain Management: ACOG Clinical Consensus No. 1. Obstet Gynecol. 2021 Sep;138(3):507-517.
19. Alchin J, Dhar A, Siddiqui K, Christo PJ. Why Paracetamol (Acetaminophen) Is a Suitable First Choice for Treating Mild to Moderate Acute Pain in Adults With Liver, Kidney or Cardiovascular Disease, Gastrointestinal Disorders, Asthma, or Who Are Older. Curr Med Res Opin. 2022 May;38(5):811-825.
20. Fink PB, Wheeler AR, Smith WR, et al. Wilderness Medical Society Clinical Practice Guidelines for the Treatment of Acute Pain in Austere Environments: 2024 Update. Wilderness & Environmental Medicine. 2024 Jun;35(2):198-218.
21. Stephens G, Derry S, Moore RA. Paracetamol (acetaminophen) for acute treatment of episodic tension-type headache in adults. Cochrane Database Syst Rev. 2016 Jun;(6):CD011889.
22. Martinez-De la Torre A, Weiler S, Bräm DS, et al. National Poison Center Calls Before vs After Availability of High-Dose Acetaminophen (Paracetamol) Tablets in Switzerland. JAMA Netw Open. 2020 Oct;3(10):e2022897.
23. Li M, Yu C, Zeng X. Comparative efficacy of traditional non-selective NSAIDs and selective cyclo-oxygenase-2 inhibitors in patients with acute gout: a systematic review and meta-analysis. BMJ Open. 2020 Sep;10(9):e036748.
24. Stiller CO, Hjemdahl P. Lessons from 20 years with COX-2 inhibitors: Importance of dose-response considerations and fair play in comparative trials. J Intern Med. 2022 Oct;292(4):557-574.
25. Patrício JP, Barbosa JP, Ramos RM, Antunes NF, de Melo PC. Relative cardiovascular and gastrointestinal safety of non-selective non-steroidal anti-inflammatory drugs versus cyclo-oxygenase-2 inhibitors: implications for clinical practice. Clin Drug Investig. 2013 Mar;33(3):167-83.
26. Langford RM, Mehta V. Selective cyclooxygenase inhibition: its role in pain and anaesthesia. Biomed Pharmacother. 2006 Aug;60(7):323-8.
27. Qaseem A, McLean RM, O'Gurek D, et al. Nonpharmacologic and Pharmacologic Management of Acute Pain From Non-Low Back, Musculoskeletal Injuries in Adults: A Clinical Guideline From the American College of Physicians and American Academy of Family Physicians. Ann Intern Med. 2020 Nov;173(9):739-748.
28. Derry S, Moore RA, Gaskell H, McIntyre M, Wiffen PJ. Topical NSAIDs for acute musculoskeletal pain in adults. Cochrane Database Syst Rev. 2015 Jun;(6):CD007402.
29. Busse JW, Sadeghirad B, Oparin Y, et al. Management of Acute Pain From Non-Low Back, Musculoskeletal Injuries: A Systematic Review and Network Meta-Analysis of Randomized Trials. Ann Intern Med. 2020 Nov;173(9):730-738.
30. U.S. Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations.
31. Food and Drug Administration. Xylocaine MPF. FDA Drug Label. Updated 2024 May 13.
32. Miroshnychenko A, Ibrahim S, Azab M, et al. Injectable and topical local anesthetics for acute dental pain: 2 systematic reviews. J Am Dent Assoc. 2023 Jan;154(1):53-64.e14.
33. Romanowski KS, Carson J, Pape K, et al. American Burn Association Guidelines on the Management of Acute Pain in the Adult Burn Patient: A Review of the Literature, a Compilation of Expert Opinion, and Next Steps. J Burn Care Res. 2020 Nov;41(6):1129-1151.
34. Finnerup NB. Nonnarcotic Methods of Pain Management. N Engl J Med. 2019 Jun;380(25):2440-2448.
35. Wick EC, Grant MC, Wu CL. Postoperative Multimodal Analgesia Pain Management With Nonopioid Analgesics and Techniques: A Review. JAMA Surg. 2017 Jul;152(7):691-697.
36. Hegmann KT, Travis R, Andersson GBJ, et al. Non-Invasive and Minimally Invasive Management of Low Back Disorders. J Occup Environ Med. 2020 Mar;62(3):e111-e138.
37. Cashin AG, Folly T, Bagg MK, et al. Efficacy, Acceptability, and Safety of Muscle Relaxants for Adults With Non-Specific Low Back Pain: Systematic Review and Meta-Analysis. BMJ. 2021 Jul;374:n1446.
38. Oldfield BJ, Gleeson B, Morford KL, et al. Long-Term Use of Muscle Relaxant Medications for Chronic Pain: A Systematic Review. JAMA Netw Open. 2024 Sep;7(9):e2434835.
39. Anderson D, Annaswamy TM, Bevevino AJ, et al. Diagnosis and Treatment of Low Back Pain (LBP). Washington, DC: Department of Veterans Affairs; 2022.
40. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016. JAMA. 2016 Apr;315(15):1624-45.
41. Paice JA, Bohlke K, Barton D, et al. Use of Opioids for Adults With Pain From Cancer or Cancer Treatment: ASCO Guideline. J Clin Oncol. 2023 Feb;41(4):914-930.
42. Englander H, Thakrar AP, Bagley SM, et al. Caring for Hospitalized Adults With Opioid Use Disorder in the Era of Fentanyl: A Review. JAMA Intern Med. 2024 Jun;184(6):691-701.

43. Olejnik L, Lima JP, Sadeghirad B, et al. Pharmacologic Management of Acute Pain in Children: A Systematic Review and Network Meta-Analysis. JAMA Pediatr. 2025 Apr;179(4):407-417.

44. Almodibeg B, Forget P. Challenges of acute pain management in older patients. Age Ageing. 2024 Apr;53(4).

45. Ribeiro H, Rodrigues I, Napoleão L, et al. Non-steroidal anti-inflammatory drugs (NSAIDs), pain and aging: Adjusting prescription to patient features. Biomed Pharmacother. 2022 Jun;150:112958.

46. Merrick M, Grange R, Rudd S, Shipway D. Evaluation and Treatment of Acute Trauma Pain in Older Adults. Drugs Aging. 2023 Oct;40(10):869-880.

47. Jones P, Lamdin R, Dalziel SR. Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury. Cochrane Database Syst Rev. 2020 Aug;8:CD007789.