

OTC Analgesics vs Opioids for Pain Management

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doi: 10.12788/jfp.0418

KEY TAKEAWAYS

- The use of opioids in acute pain may be appropriate in some situations, but there are opportunities to reduce exposure to opioids with equally effective monotherapy and combination therapy over-the-counter (OTC) medications.
- There are a number of OTC analgesics that are readily accessible and cost-effective options to treat pain.
- The American College of Rheumatology Osteoarthritis Guideline “strongly” recommends the use of topical nonsteroidal antiinflammatory drugs (NSAIDs) and oral NSAIDs to treat arthritis pain, and it conditionally recommends against the use of opioids (other than tramadol).
- The American Headache Society sug-

gests that OTC NSAIDs and combination medications such as acetaminophen, aspirin, and caffeine are Level A recommendations for reducing migraine pain and other symptoms.

- Nonopioid OTC analgesics, such as NSAIDs and the NSAID/acetaminophen combination, are safe and effective first-line options for managing acute dental pain according to the American Dental Association.
- The American College of Physicians supports the use of NSAIDs as first-line therapy for the treatment of low back pain.

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DISCLOSURES

Dr. Ruoff has no disclosures to report. Taylor Bertsch has no disclosures to report.

ACKNOWLEDGMENT

Editorial support was provided by Taylor Gregory Bertsch, PharmD.

SPONSORSHIP

This activity is sponsored by Primary Care Education Consortium and the Primary Care Metabolic Group and supported by funding from GlaxoSmithKline Consumer Healthcare.

INTRODUCTION

In 2012, healthcare professionals in the United States wrote approximately 259 million opioid prescriptions to manage pain nationwide.¹ Using opioids for pain management on this scale has led to prescription misuse and the potential for diversion, as outlined by the National Institute on Drug Abuse.^{2,3} From 2010 to 2014, the prevalence of diagnosed opioid abuse doubled.⁴ The national economic burden of opioid misuse on an annual basis is staggering: in 2017 it was calculated at over \$1 trillion.^{5,6}

Emergency rooms, as well as primary care settings, have been identified as primary locations where patients may receive opioids for acute pain management, setting the stage for potential misuse.^{7,8} To protect the patient's best interest, while still appropriately managing their acute and chronic pain, recommendations for safe alternatives to opioids have coalesced into a number of evidence-based treatment guidelines. Over-the-counter (OTC) medications, such as nonsteroidal antiinflammatory drugs (NSAIDs), combination analgesics, and acetaminophen, have well-established safety profiles, without the same dependence potential as opioids.⁹

NSAIDs have some associated risks and side effects, such as gastrointestinal issues, renal toxicity, and blood pressure elevation. They are also cost-effective and readily available in the pharmacy setting. An observed reduction in opioid prescriptions within the emergency department (ED) occurred from 2009 to 2018, due to increasing awareness of the opioid crisis.¹⁰ These trends are reassuring, with an increased focus on alternatives like OTC and prescription nonopioid pain relievers, as well as nonpharmacologic approaches as viable options for managing pain.

The World Health Organization (WHO) suggests addressing pain using an analgesic ladder, starting with NSAIDs and combination therapy, escalating to combination therapy with the use of weak opioids, and ending with the use of combination therapy with more potent opioids.¹¹ Frameworks such as the Grading of Recommendations Assessment, Development and Evaluation (GRADE) can assist in determining responsible opioid-prescribing practices for patients experiencing chronic pain lasting over 3 months.¹² This approach takes into consideration the scientific evidence, potential for positive and negative patient outcomes, and patient prefer-

ences. The concerning side effects of opioids include physiologic dependence, sedation, respiratory depression, and constipation. Even though opioids can be used appropriately and offer proven benefits, there are stereotypes and stigmas associated with their use.^{13,14}

The opioid epidemic has caused a shift toward equally effective classes of medication for pain reduction, and OTC analgesics are one of the clear options.¹⁵ Even in the case of acute pain, ED opioid treatment should only be prescribed in the short term.^{16,17} An abundance of expert guideline recommendations and clinical data support the effectiveness of OTC analgesics for acute pain management of arthritis, migraines, dental pain, and back pain. Additionally, these products are first-line options in the WHO analgesic ladder.^{15,18-21} These pain states are among the most commonly seen by healthcare professionals, and targeted patient education on reasonable clinical interventions will assist in reducing opioid misuse. This review summarizes the clinical study data supporting OTC analgesics as first-line options for the previously mentioned pain states.

OSTEOARTHRITIS

The American College of Rheumatology (ACR) 2019 guidelines strongly recommend oral NSAIDs for the treatment of osteoarthritis (OA) of the hand, knee, or hip.¹⁸ ACR guidelines further recommend the use of oral NSAIDs over other oral medications, regardless of the affected body area. The panel for OA of the knee strongly recommends topical NSAIDs, even before considering oral NSAIDs, due to their low systemic exposure. A conditional recommendation for topical NSAID use was determined by the panel for hand OA. The use of acetaminophen was conditionally recommended for hand, hip, and knee OA. Capsaicin (conditional recommendation for knee) and chondroitin sulfate (conditional recommendation for hand) were the only other OTC analgesics recommended.

In contrast to NSAIDs, ACR conditionally recommended against the use of opioids, with the exception of tramadol. This recommendation is mainly based on the high risk of toxicity and dependence associated with long-term opioid therapy coupled with very modest benefit. The ACR panel does conditionally recommend the use of tramadol in hand, hip, and knee OA because there is support for its use when contraindications to NSAIDs exist or other agents fail. ACR notes that opioids may be appropriate in some circumstances, particularly in patients who have exhausted other treatment options.

A recent meta-analysis comparing the effectiveness and safety of NSAIDs and opioids concluded that the clinical benefit from opioid treatment does not outweigh the

potential harm to patients with OA, underscoring the importance of oral and topical NSAIDs in the treatment of OA.¹⁹ The authors also concluded that topical diclofenac, which is available OTC, could be effective and is generally safer because of reduced systemic exposure and lower dose and could be considered as first-line pharmacologic treatment for knee OA.

The SPACE randomized clinical trial compared the effectiveness of nonopioid vs opioid therapies for the treatment of OA.^{15,20} The results further support the use of NSAIDs as a first-line treatment over opioids due to similar effectiveness and fewer medication-related symptoms over a 12-month period. This trial demonstrated no significant difference between opioid and nonopioid therapy groups regarding pain-related function.

Based on the clinical evidence and recommendations of guidelines from the ACR, nonopioid options such as oral and topical NSAIDs should be considered for managing OA pain before opioids. Opioids play a role in OA pain management when other options have failed and risks can be managed.

MIGRAINES

Migraine headaches are the most common primary headache disorder that cause patients to seek treatment in the ED, accounting for approximately 1.2 million visits to the ED yearly.²⁰ Migraines are often debilitating, and pain management efforts need to be enacted swiftly. Opioids are prescribed often, despite guidelines recommending nonopioid pain treatment.²² One study suggested that ED visit times were significantly longer for patients who were treated with opioids vs nonopioids.²¹ The noted difference in visit times averaged 142 minutes (95% CI: 124, 160) for opioids vs 111 minutes (95% CI: 93, 129) for nonopioids ($P = .015$). Opioid misuse is a strong reason to consider other nonopioid medications.

In 2015, the American Headache Society (AHS) conducted an updated assessment of evidence for acute migraine medications.²³ The AHS guidelines concluded that oral NSAIDs and the acetaminophen, aspirin, and caffeine (AAC) combination are effective for acute migraine treatment based on available evidence (Level A). It is recommended that NSAIDs should not be used >10 to 15 days per month. The guidelines also recommend a number of nonopioid prescription medications, particularly in the triptan class.²³ Butorphanol nasal spray was the only opioid considered effective for acute migraine treatment. However, the guidelines point out that it is commonly avoided due to concerns about dependence, addiction, and the development of medication-overuse headache, and it is not recommended for regular use.

Ibuprofen and the AAC combination are the only Food and Drug Administration–approved OTC treatments for migraine in the United States. Strong clinical trial data support their use in the treatment of migraine. Lipton et al published a review of the use of caffeine in the management of headache, including a review of randomized trials of OTC analgesics combined with caffeine.²⁴ Based on the clinical trials reviewed, they concluded that combining caffeine with OTC analgesic medications, such as acetaminophen and aspirin, significantly improves efficacy over analgesics alone. However, they also address the potential for caffeine-containing analgesics to cause medication-overuse headache. The daily use of AACs for migraines is not recommended due to the possible occurrence of “rebound” headaches.²⁵ The use of ibuprofen is also associated with significant efficacy in migraine. Codispoti et al evaluated the efficacy and safety of ibuprofen, 200 mg and 400 mg, compared with placebo and each dosage separately for the treatment of migraine pain.²⁶ Significantly ($P \leq .006$) more patients treated with ibuprofen, 200 mg or 400 mg, reported mild to no pain after 2 hours (41.7% and 40.8%, respectively), compared with those treated with placebo (28.1%). Another randomized, double-blind placebo-controlled dose-finding study evaluated a single 200 mg, 400 mg, or 600 mg dose of a liquiset formulation of ibuprofen over 8 hours.²⁷ This study demonstrated a superior response to ibuprofen vs placebo for pain reduced to mild or none from 0.5 hour (600 mg) or 1 hour (200 and 400 mg) to 8 hours. All 3 ibuprofen doses were also significantly superior to placebo for pain relief and for mild or no limitation of activity.

In summary, nonopioid options, such as ibuprofen and the AAC combination, should be considered for acute migraine treatment prior to opioids based on clinical efficacy and guidelines such as the AHS recommendations.

DENTAL PAIN

The use of analgesics in patients with dental pain is common, yet selecting the appropriate agent to manage this pain has its own complexities. Dentists in the United States prescribe 12% of immediate-release opioids.²⁸ Although opioids do have their place in therapy, evidence suggests that adverse events associated with acute dental pain are most common among children and adults utilizing opioid treatment.²⁹ The American Dental Association (ADA) suggests that effective management of acute pain can be safely achieved with nonopioid pain medications.³⁰ Effective and well-tolerated alternate options for acute dental pain include oral NSAIDs, acetaminophen, and the ibuprofen/acetaminophen combination due to their ability to manage dental pain and their well-defined safety profiles.³⁰⁻³³

While dental pain is most commonly addressed with the use of NSAIDs such as ibuprofen, acetaminophen, or oral opioid combinations, the fixed-dose combination of ibuprofen and acetaminophen has been extensively studied and proven effective in dental pain. A study investigating the efficacy and safety of single and multiple doses of a fixed-dose combination of ibuprofen and acetaminophen (single-dose fixed-dose combination ibuprofen/acetaminophen 250/500 mg) in the treatment of postsurgical dental pain demonstrated that the combination was significantly more effective than ibuprofen 250 mg or acetaminophen 650 mg on a number of efficacy endpoints.³¹

Moore and Hersch conducted an analysis to evaluate the scientific evidence for using the ibuprofen/acetaminophen combination and its effectiveness in managing acute postoperative pain in dentistry.³² The results suggested the ibuprofen/acetaminophen combination may be more effective, with fewer side effects than opioid-containing formulations. The results also indicated that the combination provided greater pain relief than monotherapy with either drug after third-molar extractions. They used the results of this analysis to suggest a stepwise approach to acute postoperative pain management in dentistry (**TABLE**).

Moore et al assessed the benefits and harms associated with analgesic medications used in the management of acute dental pain.²⁹ The ibuprofen/acetaminophen combination had the highest association with treatment benefit and the highest proportion of adult patients who experienced maximum pain relief. Opioids were associated most frequently with adverse events, and pain relief from opioids has been difficult to quantify due to variability in patient dosage and trial design.³³ Overall, the use of NSAIDs, with or without acetaminophen, offered the most favorable balance between benefits and harms.

While opioids remain an important option for consideration with dental pain, clinical evidence and ADA guidelines suggest that nonopioid options, such as ibuprofen, acetaminophen, and the ibuprofen/acetaminophen combination should be considered for managing dental pain over opioids.

BACK PAIN

Low back pain (LBP) is a leading cause of disability in the United States. In 2017, the American College of Physicians (ACP) Clinical Practice Guidelines for Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain were updated.³⁴ For acute and subacute LBP, nonpharmacologic treatment is recommended, but the updated guidelines strongly recommended NSAIDs or skeletal muscle relaxants if pharmacologic treatment is desired. Acetaminophen is no longer recommended. For patients with chronic LBP

TABLE. Analgesic use for dental pain according to pain level³²

Pain level	Oral analgesic options
Mild	Ibuprofen 200-400 mg as needed for pain every 4-6 hours
Mild to moderate	Ibuprofen 400-600 mg fixed interval every 6 hours for 24 hours then Ibuprofen 400 mg as needed for pain every 4-6 hours
Moderate to severe	Ibuprofen 400-600 mg plus acetaminophen 500 mg fixed interval every 6 hours for 24 hours then Ibuprofen 400 mg plus acetaminophen 500 mg as needed for pain every 6 hours
Severe	Ibuprofen 400-600 mg plus acetaminophen 650 mg with hydrocodone 10 mg fixed interval every 6 hours for 24-48 hours then Ibuprofen 400-600 mg plus acetaminophen 500 mg as needed for pain every 6 hours

Source: Adapted from Moore PA, Hersh EV. Combining ibuprofen and acetaminophen for acute pain management after third-molar extractions: translating clinical research to dental practice. *J Am Dent Assoc.* 2013;144(8):898-908. Copyright 2013, with permission from Elsevier.

who have had an inadequate response to nonpharmacologic therapy, treatment with NSAIDs as first-line therapy should be considered. Opioids should only be considered in patients who have failed other treatments and only if the potential benefits outweigh the risks for individual patients.

ACP guideline updates were based on a systematic review of randomized, controlled trials (or systematic reviews) of pharmacologic and nonpharmacologic treatments for LBP.³⁵ Pharmacologic treatments evaluated included NSAIDs, antidepressants, opioids, benzodiazepines, anticonvulsants, corticosteroids, and muscle relaxants, and parameters such as pain, function, and risk were assessed. Several trials demonstrated improvement of LBP in both acute and chronic cases when treated with NSAID therapy vs placebo. A placebo-controlled trial of acetaminophen in acute LBP found acetaminophen was no more effective than placebo.³⁶ For acute LBP, 1 trial made direct comparisons of opioid therapy vs NSAID therapy (oxycodone vs acetaminophen and naproxen), and no significant difference was found between groups with regard to pain control and patient function.³⁵ For chronic LBP, 3 trials in the systematic review reported inconsistent effects of opioids vs NSAIDs for pain relief, and 1 trial found no difference in function.³⁵ The review found that opioids had a higher risk for nausea, dizziness, constipation, vomiting, somnolence, and dry mouth than placebo. However, the trials assessed were not designed to assess long-term harms or the risk for overdose, abuse, or addiction.

Ultimately, opioids may offer benefit in some patients, but clinical evidence and guidelines recommendations, such as those from the ACP, suggest oral NSAIDs should be considered for LBP over opioids.

CONCLUSION

Pain management remains a challenge for clinicians, who are

increasingly looking for alternatives to opioids. A number of nonpharmacologic options can help with pain management, but there remains a need for pharmacologic options when nonpharmacologic options alone are inadequate. Numerous evidence-based treatment guidelines issued by medical societies currently recommend OTC analgesics as initial treatment for arthritis pain, migraine headaches, dental pain, and back pain. These guideline recommendations are based on an abundance of clinical data supporting the efficacy and safety of OTC analgesics. Additionally, mounting evidence suggests that not only are OTC analgesic options safer and better tolerated than opioids, but they are just as effective in many pain states.

Through education and the use of peer-reviewed guidelines, healthcare professionals can minimize the potential for opioid misuse while effectively managing a patient's pain with alternate nonopioid pharmacologic options. ●

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