

# Efficacy and Safety of Naproxen vs Opioids for the Treatment of Musculoskeletal Pain

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## INTRODUCTION

### Epidemiology & treatment of musculoskeletal pain

Musculoskeletal pain affects 1 in 4 adults globally and is one of the most common medical complaints in the world. Musculoskeletal pain is one of the primary reasons for self-medication and entry into the health care system,<sup>1</sup> while also responsible for serious long-term pain and physical disability. Musculoskeletal pains are the second most frequent cause for an individual to consult a physician, accounting for upwards of 20% of a typical primary care practice.<sup>2</sup> Furthermore, there are data suggesting that musculoskeletal pain is more common today than it was 40 years ago,<sup>3</sup> but whether this is due to heightened awareness of symptoms or increased reporting remains unclear.

Successful management of pain in the acute phase is essential to prevent transition to chronic pain.<sup>4-6</sup> Unfortunately, the prognosis for musculoskeletal pain is often poor, with many patients reporting continued symptoms for 6 to 12 months after first consulting with their primary care physician.<sup>7,8</sup> Musculoskeletal pain can also lead to unhealthy behaviors, including overeating, alcohol/drug abuse, as well as the use of more potent than needed drugs.<sup>9-11</sup>

Fortunately, many types of acute musculoskeletal pain can be appropriately managed and stopped from progressing into chronic conditions with both over-the-counter (OTC)

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### DISCLOSURES

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and prescription analgesics. Prescription opioids are commonly used to treat musculoskeletal pain, although there is increasing awareness of the potential harm of opioid-related adverse events and misuse.<sup>12</sup> Importantly, most musculoskeletal aches and pains are acute in nature and self-treatable with OTC analgesics, and flares associated with chronic conditions may also be appropriate for OTC management. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat musculoskeletal pain and are among the world's most consumed prescription and OTC medications. Every day, approximately 30 million people worldwide use NSAIDs.<sup>13</sup> In the United States, there are an estimated 30 billion doses of NSAIDs consumed annually,<sup>14</sup> with over 100 million prescriptions written every year.<sup>15</sup> In the United States, an OTC analgesic usage rate of 76% was reported, with more women self-medicating than men.<sup>16</sup>

Consumers with musculoskeletal pain need a variety of options to reduce or alleviate that pain. In many cases, naproxen represents an effective, long-lasting option based on its 14-hour half-life. All day pain relief is possible with naproxen, and clinical trials demonstrate greater overall pain relief and duration of pain relief compared to acetaminophen (APAP).

### The opioid crisis

Overprescribing and the availability of inexpensive street drugs have fueled a public health crisis, resulting in opioid dependence, misuse, and addiction in epidemic proportions.<sup>17</sup> Despite having only 4.6% of the world's population, the United States consumes 80% of the world's prescription opioids and 99% of the world's hydrocodone supply.<sup>18</sup> The misuse of prescription pain medication is responsible for almost half a million emergency department (ED) visits per year.<sup>19</sup> Greater than 75% of those visits are the result of diversion, which occurs when people are using drugs that were prescribed to another.<sup>20</sup> Data from the US Centers for Disease Control and Prevention indicate that in 2017 there were about 48,000 opioid overdose deaths. The number of overdose deaths involving opioids in 2017 was 6 times higher than in 1999. On average, 130 Americans die every day from an opioid overdose.

Broader use of nonopioid pharmacotherapy, including the appropriate use of OTC options, is critical to addressing the opioid crisis by preventing addiction resulting from valid prescriptions. Often the initial use of opioids starts through the valid treatment of a medical condition (pain) and, whether the initial medical condition is resolved or not, can lead to addiction. According to the World Health Organization analgesic ladder, APAP or NSAIDs should be used prior to weak opioids (eg, tramadol, codeine). If weak opioids are inadequate to provide effective pain relief, then strong opioids (eg, morphine, oxycodone, fentanyl) are indicated.<sup>12</sup> Nonetheless, it is not uncommon for physicians and dentists to prescribe opioids to treat pain conditions that could be adequately managed with nonopioid medications. For example, 6.4% to 8.0% of opioids dispensed annually by outpatient retail pharmacies in the United States are the result of prescriptions from dentists. Dentists are also the highest percentage prescribers for patients ages 10 to 19 years.<sup>21-23</sup>

Despite the issue of opioid-related adverse events and the fact that opioids are not indicated as a primary treatment for a majority of acute pain conditions,<sup>24,25</sup> they are still prescribed too often as first line treatment.<sup>26</sup> In fact, guidelines by the American College of Rheumatology,<sup>27</sup> American Academy of Family Physicians (AAFP),<sup>28</sup> American Academy of Orthopaedic Surgeons,<sup>29</sup> and Osteoarthritis Research Society International<sup>30</sup> all recommend NSAIDs as first-line treatment for various osteoarthritic conditions. Additionally, guidelines by AAFP<sup>31</sup> and the American College of Physicians and the American Pain Society<sup>32</sup> recommend NSAIDs as first-line treatment for the short-term treatment of low back pain. Acute musculoskeletal injury guidelines by the Orthopaedic Trauma Association recommend NSAIDs as first-line treatment,<sup>33</sup> and a guideline for ankle sprains by the National Athletic Trainers' Association<sup>34</sup> only recommends NSAIDs. Furthermore, the American Dental Association also recommends that dentists consider NSAID analgesics as the first-line therapy for acute pain management.<sup>35</sup>

Younger consumers are especially at risk: 80% of high school students who reported medical use of opioids prior to misuse acquired the substance from their own previous prescription,<sup>36</sup> signifying that even a medically necessary opioid prescription carries the risk for misuse. As OTC NSAIDs are indicated for use for 12 years and up, they are the recommended first-line therapy for this vulnerable population.

### Literature search methodology

A comprehensive and broad literature search for all clinical trials comparing opioids and naproxen was conducted utilizing the National Center for Biotechnology Information and the National Library of Medicine's PubMed database. A more

targeted search for randomized clinical trials comparing opioids and NSAIDs supplemented the main search. Abstracts of all search results were reviewed and the full articles reviewed for any relevant results. Citations in the relevant articles were also reviewed to ensure thoroughness.

## EFFICACY OF NAPROXEN AND OPIOIDS IN TREATING MUSCULOSKELETAL PAIN

### Opioids to treat musculoskeletal pain

A systematic review with meta-analysis by Megale et al<sup>37</sup> that included 23 randomized placebo-controlled trials in older adults (over 60 years of age) found that opioid analgesics had only small effects on decreasing pain intensity (standardized mean difference [SMD] of -0.27; 95% CI, -0.33 to -0.20) and improving function (SMD, -0.27; 95% CI, -0.36 to -0.18), which were not associated with daily dose or treatment duration. Furthermore, the authors found that the odds of adverse events with opioids were 3 times higher (odds ratio [OR], 2.94; 95% CI, 2.33-3.72), while treatment discontinuation due to adverse events had odds 4 times higher (OR, 4.04; 95% CI, 3.10-5.25) when treating patients with opioids. The authors concluded that in this older population, opioid-related risks may outweigh the benefits.

### Comparative efficacy of opioids and naproxen

A comprehensive report by the Swedish Council on Health Technology determined that weak opioids reduce mild-to-moderate osteoarthritis (OA) and low back pain by approximately 40%, and are "just as effective as NSAIDs for OA pain."<sup>38</sup>

Fathi et al conducted a randomized clinical trial to compare the efficacy and safety of oral oxycodone with naproxen to control acute pain in adult patients with soft tissue injury (n=150). The study also evaluated whether patients needed additional doses of analgesics during the first 24 hours after discharge from the ED. The study found that pain scores were similar in the oxycodone and naproxen groups before medication (6.21±0.9 vs 6.0±1.0), 30 minutes after medication (4.5±1.4 vs 4.4±1.2), and 60 minutes after medication (2.5±1.3 vs 2.6±1.3). Twelve (16.0%) patients in the oxycodone group and 5 (6.6%) patients in the naproxen group required more analgesic during the first 24 hours after ED discharge, although this was not statistically significant. Patients in the oxycodone group experienced a statistically significant difference in adverse effects, with the most common being nausea (13.3%), vomiting (8.0%), dizziness (5.3%), drowsiness (4.0%), and pruritis (2.7%). The authors concluded that oral oxycodone is as effective as naproxen in pain control for soft tissue injury but has a less favorable safety profile.<sup>39</sup>

Several other studies have demonstrated hydrocodone and oxycodone to be noninferior to nonopioids in reducing

pain. One study found that neither 5 mg oxycodone/325 mg APAP nor 5 mg hydrocodone/300 mg APAP were superior to 400 mg ibuprofen/1000 mg APAP in the treatment of acute extremity pain in emergency departments.<sup>24</sup> Similarly, adding APAP/oxycodone to 500 mg by mouth naproxen (twice daily) for acute lower back pain did not increase efficacy when compared to naproxen alone.<sup>40,41</sup> Further, the use of oxycodone- or hydrocodone-APAP combination pills increases the risk of under-dosing APAP when attempting to minimize opioid dosing or, conversely, over-dosing APAP when attempting to reach a sufficient opioid effect.<sup>42</sup> These studies support the notion that naproxen and oxycodone/APAP have a similar magnitude of effect, yet differential degrees of adverse effects.

### Naproxen to treat musculoskeletal pain

Not all NSAIDs have demonstrated equivalent efficacy in treating musculoskeletal pain. Unlike APAP, NSAIDs are potent inhibitors of prostaglandin synthesis and target the inflammatory pain encountered with acute infection, tissue injury, and surgical trauma. Therefore it is not surprising that when treating inflammatory pain, NSAIDs have consistently been shown to be more effective than APAP.<sup>43,44</sup>

Jevsevar et al recently conducted a network meta-analysis of data from multiple trials to determine the relative effectiveness of nonsurgical treatments for knee OA, including APAP, ibuprofen, intra-articular (IA) or joint injections of cortisone, platelet-rich plasma, hyaluronic acid, and several NSAIDs (eg, naproxen, celecoxib, and diclofenac). The analysis included 53 randomized controlled knee OA trials, requiring at least 30 participants per treatment group and durations of at least 28 days. The authors found that naproxen has the highest probability for improving function and naproxen was the only treatment showing clinical significance for improving function compared with placebo. Cumulative probabilities revealed that naproxen is also the most effective individual knee OA treatment for improving both pain and function, and when combined with IA corticosteroids, it is the most probable to improve pain and function.<sup>45</sup>

There are numerous guidelines for the treatment of various musculoskeletal conditions that were put forth by medical organizations and associations using publicly available literature and weighting recommendations using level of evidence. The majority of guidelines recommend the use of NSAIDs, including naproxen, for first-line treatment, often over opioids. The **TABLE** summarizes some of these guidelines.

Additionally, it should be noted that naproxen has been shown to be more cost-effective in managing joint pain than opioids, celecoxib, or the standard of care.<sup>46</sup> Finally, treating pain with NSAID analgesics rather than opioids helps fight

the ongoing prescription opioid abuse epidemic.

## SAFETY IN MUSCULOSKELETAL PAIN POPULATIONS

### Safety of opioids in musculoskeletal pain populations

Opioid treatment is associated with many adverse effects, some of them serious and life-threatening. Gastrointestinal adverse effects including nausea, vomiting, cramping, and constipation are notable risks associated with chronic opioid use.<sup>47,48</sup> Opioid-induced constipation is sometimes refractory to treatment<sup>49</sup> and could, in serious cases, lead to bowel obstruction and possibly hospitalization or death.<sup>50</sup> Dry mouth and miosis are other common adverse reactions. Less frequent adverse effects include hypothermia, cardiovascular depression (hypotension, bradycardia), headache, urinary retention, ureteric or biliary spasm, muscle rigidity, myoclonus (with higher doses), and flushing.<sup>51,52</sup> Another possible adverse effect is opioid-induced hyperalgesia, which results in more pain instead of less.<sup>53,54</sup> Opioid neurotoxicity can result in dizziness, confusion, hallucinations, delirium, and/or sedation, leading to accidents and unintended consequences, including falls and fractures.<sup>55</sup> Opioids also have an effect on respiratory physiology, which may lead to unproductive ventilation and obstruction of the upper airway as a result of decreased central respiratory drive, respiratory rate, and tidal volume.<sup>56</sup>

A commonly cited statistic regarding the misuse of opioids is "a 1% risk of addiction."<sup>11,57,58</sup> This statistic comes from a single paragraph letter to the editor of *The New England Journal of Medicine* based on limited exposure with inpatients. There was no description of study methods.<sup>59</sup> Subsequent published studies have demonstrated a risk of addiction to prescription opioids of 3% to 45%, when used as part of long-term treatment. Furthermore, if prescription opioids are used beyond 12 weeks, 50% of patients will continue to use them after 5 years.<sup>60</sup> Other studies have verified that conversion to long-term use after 90 days increases risk of addiction.<sup>61-64</sup>

Zeng et al examined the association of tramadol prescription within a population of patients with OA with all-cause mortality, compared with 5 other analgesic medications, in a sequential, propensity score-matched cohort study in the United Kingdom. The patients in the cohort study had initial prescriptions of tramadol (n=44,451), naproxen (n=12,397), diclofenac (n=6,512), celecoxib (n=5,674), etoricoxib (n=2,946), or codeine (n=16,922). The authors found that during the 1-year follow-up, 278 deaths (23.5/1000 person-years) occurred in the tramadol cohort and 164 (13.8/1000 person-years) occurred in the naproxen cohort (rate difference, 9.7 deaths/1000 person-years [95%

**TABLE** Guidelines for musculoskeletal pain

Condition/indication	Recommendations (Excerpted/adapted from citations, with strength/level of evidence where available)	Supporting guidelines
Arthritis	Oral NSAIDs are conditionally recommended <sup>a</sup> as first-line pharmacologic management of knee, hand, and hip OA.	ACR 2012 Recommendations for the Use of Nonpharmacologic and Pharmacologic Therapies in OA of the Hand, Hip, and Knee <sup>27</sup>
	NSAIDs are superior to acetaminophen for treating moderate to severe OA (Evidence rating A <sup>b</sup> ).	AAFP 2012: Osteoarthritis: Diagnosis and Treatment <sup>28</sup>
	Oral or topical NSAIDs or tramadol (Ultram) should be used in people with symptomatic knee OA (SOR: strong <sup>c</sup> ). No recommendation can be made for or against the use of acetaminophen, opioids, or pain patches (SOR: inconclusive <sup>c</sup> ).	AAOS 2013 Evidence-Based Guideline for Treatment of OA of the Knee (2nd Edition) <sup>29</sup>
	Oral nonselective NSAIDs are recommended as a first-line pharmacologic therapy for knee only OA or for multi-joint OA in people without comorbidities (Quality of evidence: good <sup>d</sup> ).	OARSI 2014 Guidelines for the Non-Surgical Management of Knee Osteoarthritis <sup>30</sup>
Low back pain	NSAIDs, opioids, and topiramate (Topamax) are more effective than placebo in the short-term treatment of nonspecific chronic low back pain. (Evidence rating A <sup>b</sup> ) There is no difference between different types of NSAIDs, and no evidence that acetaminophen is better than placebo.	AAFP 2018 Recommendations for Mechanical Low Back Pain <sup>31</sup>
	For patients with low back pain, clinicians should consider the use of medications with proven benefits in conjunction with back care information and self-care. Clinicians should assess severity of baseline pain and functional deficits, potential benefits, risks, and relative lack of long-term efficacy and safety data before initiating therapy (strong recommendation, moderate-quality evidence <sup>e</sup> ). For most patients, first-line medication options are acetaminophen or NSAIDs. NSAIDs are recommended for acute (<4 weeks) and sub-acute or chronic (>4 weeks) treatment of low back pain.	American College of Physicians and American Pain Society Joint 2001 Guidelines for Low Back Pain <sup>32</sup>
Acute musculoskeletal injury	The panel recommends for the routine use of NSAIDs as part of a comprehensive analgesic plan for operative and nonoperative fracture care (strong recommendation, low-quality evidence <sup>f</sup> ). Because of the potential for misuse of all opioids, the panel recommends that the prescriber should use the lowest effective dose for the shortest period possible (strong recommendation, high-quality evidence).	OTA 2019 Clinical Practice Guidelines for Pain Management in Acute Musculoskeletal Injury <sup>33</sup>
	Nonsteroidal anti-inflammatory drugs, administered orally or topically, reduce pain and swelling and improve short-term function after ankle sprains (evidence category: A). <sup>9</sup>	NATA 2013 Position Statement: Conservative Management and Prevention of Ankle Sprains in Athletes <sup>34</sup>
Dental pain	NSAIDs have been shown to be more effective at reducing pain than opioid analgesics and are therefore recommended as the first-line therapy for acute pain management.	ADA 2019 Oral Health Topics: Oral Analgesics for Acute Dental Pain <sup>35</sup>

**Abbreviations:** AAFP, American Academy of Family Physicians; AAOS, American Academy of Orthopaedic Surgeons; ACR, American College of Rheumatology; ADA, American Dental Association; NATA, National Athletic Trainers' Association; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International; OTA, Orthopaedic Trauma Association.

<sup>a</sup>ACR Conditional recommendations mean that the majority of informed patients would choose the recommended management but many would not, so clinicians must ensure that patients' care is in keeping with their values and preferences.

<sup>b</sup>AAFP evidence rating A- Consistent, good-quality patient-oriented evidence

<sup>c</sup>AAOS Recommendations- Strong: benefits of the approach clearly exceed the potential harm, and/or the quality of the supporting evidence is high. Inconclusive: lack of compelling evidence, resulting in an unclear balance between benefits and potential harm.

<sup>d</sup>OARSI quality of evidence: The methodological rigor of the highest level of evidence used. Meta-analyses and systematic reviews were assigned a quality rating of "Good", "Fair", or "Poor" using the Assessment of Multiple Systematic Reviews Tool (AMSTAR). The Cochrane Risk of Bias Assessment Method was used to rate randomized clinical trials.

<sup>e</sup>The panel strongly recommends that clinicians consider offering the intervention to eligible patients based on benefits clearly outweighing risks.

<sup>f</sup>OTA recommendations and quality of evidence: The grading of the evidence was based on the study designs, number of studies, sample sizes, and consistency of results among different studies. "Strong" = practices in which benefits are sure to outweigh potential harms.

<sup>9</sup>NATA evidence category A: Recommendation based on consistent and good-quality patient-oriented evidence.

CI, 6.3-13.2]; hazard ratio, 1.71 [95% CI, 1.41-2.07]), and mortality was also higher for tramadol compared with diclofenac, celecoxib, and etoricoxib. Compared to codeine, no statistically significant difference in all-cause mortality was observed.<sup>65</sup>

### Safety of naproxen in musculoskeletal pain populations

The safety profile of naproxen is well characterized, and much has been written on this topic. Like all NSAIDs, naproxen presents small, but important, increased CV risk, and particularly an increased GI bleeding risk, both of which are associated with dose and duration of use. However, short-term use has not demonstrated the same safety signals. A review of the clinical pharmacology and cardiovascular safety of naproxen by Angiolillo and Weisman (2017) found that the balance of evidence indicates that the low cyclooxygenase-2 (COX-2) selectivity of naproxen results in a lower cardiovascular risk than that of other NSAIDs, as cardiovascular risk is associated with COX-2 selectivity. The authors concluded that “the over-the-counter use of naproxen is expected to pose minimal cardiovascular risk.”<sup>66</sup>

White et al (2018) recently published a comprehensive review of the cardiorenal safety of the most commonly used NSAIDs, including naproxen, in the context of historical regulatory concerns over COX-2 selective drugs and revised labels and the completion of the PRECISION trial. The thorough review by the authors of the published literature suggests that cardiovascular risk is low when OTC formulations are used as directed by the labels. Data from randomized trials with OTC doses do demonstrate lower rates of CV events compared with higher doses used in studies examining prescription strength NSAIDs. Furthermore, the results of PRECISION demonstrate absolute cardiovascular event rates that were lower than expected with the long-term use of prescription-strength NSAIDs in a population enriched for CV disease. The authors conclude that observational data support the notion of low CV risk for NSAIDs used at OTC doses and durations.<sup>67</sup>

A recent publication by Kyeremateng et al compared the rates of adverse events reported with nonprescription doses of naproxen, ibuprofen, APAP, and placebo in multiple dose, multi-day (7 to 10 days) clinical trials. Retrospective collection of safety data from 8 randomized, controlled trials included patients who consumed a fixed-dose regimen of 220 to 750 mg naproxen per day for 7 to 10 days (n=1494). The authors found that the safety profile of naproxen closely resembles that of placebo, with similar rates of adverse events as ibuprofen and APAP. The most frequently reported adverse events were mild-to-moderate in severity and related to the gastrointestinal system, with no differences between groups.<sup>68</sup>

Of course, the benefit-risk ratio of naproxen for the treat-

ment of musculoskeletal pain should be considered at the individual patient level, with particular regard for any underlying conditions that may increase cardiovascular risk. Lastly, naproxen is nonaddictive, and therefore could help physicians and patients avoid the harm associated with opioid addiction.

### CONCLUSIONS

The balance of evidence suggests that naproxen has a favorable adverse event profile compared to opioids. Naproxen can be used in many types of musculoskeletal pain besides OA and is safe for use by minors aged 12 years and up to effectively treat musculoskeletal pain, with wider safety margins and advantages over other NSAIDs and APAP. Naproxen has the most consistent and demonstrably favorable thromboembolic, and overall cardiovascular, safety profile among the most commonly used non-aspirin NSAIDs.<sup>69-72</sup> All pain guidelines recommend exploring and exhausting nonopioid pharmacotherapy options prior to opioid pharmacotherapy, including the use of NSAIDs such as naproxen. Lastly, even though self-medication with OTC naproxen is an effective and appropriate pain relief option for treating minor aches and pains, health care providers and patients should be properly educated regarding the benefits and risks of naproxen compared to opioids, particularly for those who are, or may be, at risk of adverse effects. ●

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