Managing Patient Pain: A Focus on NSAID OTC Formulations for Relief of Musculoskeletal and Other Common Sources of Pain

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Most Americans use over-the-counter (OTC) analgesics for short-term relief of mild-to-moderate pain. The literature demonstrates the efficacy of these agents through meta-analyses, comparator studies (primarily at prescription dosages), and through trials that have assessed the efficacy of agents at OTC dosages for the management of a variety of common conditions. This article will provide education to better enable clinicians to counsel their patients regarding the use of OTC analgesics and help them appropriately select agents, based on such factors as dosing, duration of action, condition for which pain relief is required, and pharmacologic profile. The safety of these agents has been extensively covered, as have issues that may result from off-label long-term use; therefore, we will not include that information here.

Many Americans experience frequent pain for which OTC pain relievers are commonly used, with demonstrated efficacy. A 3-month survey of adults revealed that, during that time, 29% of participants experienced low back pain; 17%, migraine or severe headache; 15%, neck pain; and 5%, face or jaw pain.[1]

The importance of OTC analgesics is evidenced by the fact that their sales constitute 16.5% of the US nonprescription drug market.[2] In 2017, sales of OTC analgesics totaled more than $4.1 million.[3] 86% of Americans believe that responsible use of OTC medications helps lower the cost of health care.[4] A poll of more than 2000 US adults revealed that approximately 30% regularly use OTC analgesics for arthritis or other pain management needs.[5]

The take-away message for clinicians is that consumers use these products regularly to relieve minor aches and pains due to headache, toothache, musculoskeletal pain, menstrual pain, fever, common cold, and influenza. They believe that they are effective and contribute to their health, well-being, and quality of life.[6]

Based on widespread use of OTC analgesics among consumers and the high level of consumer confidence in these agents, clinicians should be prepared to discuss OTC analgesic use with their patients, both to ensure that patients use these agents safely (see "Safety of OTC nonsteroidal anti-inflammatory drugs [NSAIDs] and analgesic agents," page S68) and because these agents differ significantly; they are not interchangeable as treatments for all pain. Some have shown greater efficacy in the management of specific pain syndromes but show limited use for other ailments.

Family physicians have an opportunity to help patients use these agents properly, select them appropriately, use them at the correct dosage, understand common side effects, and be aware of any potential drug–drug interactions.[5] Clinicians in practice often find that patients believe OTC formulations to be less effective than the same drugs provided in prescription formulations. They may also believe that OTC formulations are safer than prescription products because they are available without a prescription.[7,8]

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Safety of OTC nonsteroidal anti-inflammatory drugs and analgesic agents

Gastrointestinal risk factors represent an issue of concern; before recommending a nonsteroidal anti-inflammatory drug (NSAID), clinicians should consider patient risk factors, including longer duration of NSAID use, age 60 years or older, history of peptic ulcer disease, and general frailty, as well as alcohol use and concomitant use of corticosteroids and anticoagulants.[1] Reports in the medical literature have shown a significant decrease in hospitalization associated with NSAID use, attributable to widespread use of proton pump inhibitors (PPIs), better NSAID prescribing, and decreased prevalence of *Helicobacter pylori* infection. Gastroprotective therapy should be considered with administration of a nonselective NSAID; should dyspepsia occur, PPI co-therapy should be introduced, along with either dosage reduction or a switch to a different NSAID.[2] It should be noted that PPIs do not protect the lower intestine, which can ulcerate. Naproxen has been cited as the best option in patients with high cardiovascular risk and low or moderate gastrointestinal risk.[2,3]

Topical and oral NSAIDs have been compared in studies of patients with rheumatoid arthritis. Topical agents showed reduced risk of cardiovascular events, compared with oral agents.[4]

At a joint meeting on April 24 and 25, 2018, the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the US Food and Drug Administration met and reviewed safety data from the Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen (PRECISION) trial, which evaluated the safety of celecoxib and prescription ibuprofen and naproxen in 24,081 patients. Cardiovascular safety was similar among all 3 agents, with noninferiority noted for celecoxib. The participants discussed findings related to a possible interaction between NSAIDs and low-dose aspirin, based on in vitro platelet aggregation studies; however, the committees concluded that no impact has been demonstrated clinically, and therefore questioned the overall clinical relevance of the findings.[5]

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Clinicians should be able to help patients select the most appropriate OTC agent for specific conditions, using the lowest effective dosage for the minimum duration of time as part of an overall pain management plan for appropriate patients.

EFFICACY OF OTC NSAIDs

NSAIDs and other analgesics, available as OTC formulations, as well as prescription pain relievers, have been evaluated sufficiently for experts to develop recommendations for use (**TABLE 1**).[1] Significantly, acetaminophen, ibuprofen, and naproxen show sufficient evidence for first-line treatment of acute mild-to-moderate pain.[9-12]

MECHANISMS OF ACTION

Specific NSAIDs and acetaminophen differ significantly in terms of dosing, half-life, and duration of effect, with implications for effectiveness in addressing specific patient needs for pain relief.

Acetaminophen

Acetaminophen has a mechanism of action similar to that of NSAIDs, particularly selective cyclooxygenase-2 (COX-2) inhibitors. Generally, it provides weaker analgesic activity than NSAIDs or selective COX-2 inhibitors.[13] It is thought to inhibit cyclooxygenase-1 (COX-1) and COX-2 by metabolizing their peroxidase function. It inhibits phenoxyl radical formation from an essential tyrosine residue and thus inhibits cyclooxygenase activity of COX-1 and COX-2 and prostaglandin synthesis. Acetaminophen shows selectivity for inhibition of the synthesis of prostaglandins and related factors in the presence of low levels of arachidonic acid and peroxides. It demonstrates little activity with high levels of arachidonic acid and peroxides. For these reasons, it does not suppress the severe inflammation of conditions such as rheumatoid arthritis and acute gout, but does inhibit inflammation associated with tooth extraction.[14]

Acetaminophen is absorbed rapidly and distributed quickly throughout the body, with peak plasma concentration attained within 30 to 60 minutes; delay may occur with food intake.[14] With repeated doses, plasma concentration reaches steady-state level in 10 to 15 hours. Higher steady-state levels are not achieved with continued dosing. These results are consistent with the short elimination half-life of 2 to 3 hours and the recommended dosing interval of 4 to 6 hours.[15]

Over-the-counter NSAIDs

NSAIDs share similar mechanisms of action, inhibiting the synthesis of prostaglandins, fatty acid derivatives that are widely distributed in tissues and are involved in the production of pain, fever, and inflammation.[16] NSAIDs achieve these

TABLE 1 Key recommendations for practice

Recommendation	Rating
Acetaminophen, ibuprofen, and naproxen are good, effective first-line treatments for mild-to-moderate acute pain	A[9-12]
Selective COX-2 NSAIDs are second-line medications for mild-to-moderate pain, with similar efficacy to nonselective NSAIDs but at increased cost	A[11]

Abbreviations: COX-2, cyclooxygenase-2; NSAIDs, nonsteroidal anti-inflammatory drugs.

A = consistent, good-quality, patient-oriented evidence.

Adapted from: Blondell et al. *Am Fam Physician*. 2013;87:766-772.[1]

effects through inhibition of the cyclo-oxygenase enzymes. Their demonstrated anti-inflammatory and analgesic activities stem from effects on prostaglandins that sensitize tissues to pain and inflammation-producing mediators. It is assumed that, in the presence of infectious states, antipyretic activity also results from inhibition of prostaglandin synthesis.[16]

Aspirin is rapidly hydrolyzed, primarily in the liver, to salicylic acid. This is conjugated with glycine, thus forming salicyluric acid, and glucuronic acid. Both are excreted primarily by the kidneys. Because of rapid hydrolysis, plasma concentrations of aspirin rarely exceed 20 μg/mL at ordinary therapeutic dosages. The peak salicylate level for uncoated aspirin occurs in about 2 hours but is delayed by enteric coating. The plasma half-life of aspirin is approximately 15 minutes; however, when metabolized to salicylate, half-life increases, particularly with higher dosages.[17]

Ibuprofen features a linear blood level dose–response relationship with single doses up to 800 mg. In chronic conditions, a therapeutic response may be observed within a few days; most often, it occurs by 2 weeks.[18] After a satisfactory response is achieved, the clinician should review the dosage and adjust as appropriate. For mild-to-moderate pain, recommended dosing is 400 mg every 4 to 6 hours, as necessary. Trials have shown that exceeding the recommended dosage does not increase efficacy.[18]

Naproxen, in low dosages (≤660 mg/d naproxen sodium), features analgesic and antipyretic actions, although a full anti-inflammatory activity response requires higher dosages. Within 20 minutes of intake, significant plasma levels and initiation of pain relief occur. Rapidly and completely absorbed from the gastrointestinal tract, naproxen, at 440 mg, achieves peak plasma level (C_{max}) of 53 to 66 g/mL approximately 1 to 1.5 hours after intake. Food consumption may delay absorption of caplets and will delay absorption of liquid gels. Dose-linear kinetics are observed with use of as much as 550 mg twice daily. Plasma concentrations of the active component, unbound circulating naproxen (about 10 ng/mL), provide analgesic effects; they correspond to a total naproxen plasma concentration of 15 μg/mL. The volume of distribution of naproxen is small, about 0.1 L/kg of body weight. Within 2 days, steady-state concentrations are observed, with no significant accumulation. More than 99% of circulating naproxen is albumin-bound.[16]

NSAIDS AND ACETAMINOPHEN FOR PAIN RELIEF ASSOCIATED WITH COMMON PAIN SYNDROMES

Meta-analyses and comparator studies show evidence for effectiveness of NSAIDs and acetaminophen.

NSAIDs and acetaminophen are somewhat effective in the management of common pain syndromes, such as osteoarthritis. This chronic condition has been estimated to carry an estimated lifetime risk of 45%,[19] underscoring the importance of clinician counseling concerning pain associated with this condition and the need to provide strategies for pain relief. A 2018 meta-analysis[19] investigated the comparative effectiveness of nonsurgical treatment—NSAIDs, acetaminophen, and intra-articular (IA) options (corticosteroids, platelet-rich plasma, and hyaluronic acid [HA])—for management of knee osteoarthritis. In their review of 56 studies, most of which were high-quality, the authors assessed the effect of treatment on pain, via conversion to a 0 to 100 visual analog scale, and function, assessed through conversion to a 0 to 100 Western Ontario and McMaster Universities Osteoarthritis Index.

All active treatment regimens demonstrated significant improvement in pain compared with placebo. For function, only naproxen showed clinically significant improvement. Neither IA interventions nor options available OTC (ibuprofen and acetaminophen) showed improvement over placebo. The authors concluded that naproxen was the most effective single treatment and may produce the greatest likelihood of improvement of both pain and function when combined with an IA corticosteroid. They noted that, although caution should accompany the routine use of NSAIDs in chronic arthritic conditions, evidence indicates that naproxen is less likely than other NSAIDs to be associated with adverse cardiovascular events. Furthermore, the meta-analysis supports the use of naproxen as the conservative treatment of choice, most likely to improve pain and function associated with knee osteoarthritis, followed by IA interventions, ibuprofen, and celecoxib (**TABLE 2**[19]). The authors speculate

TABLE 2 Improvements in pain, function, and pain and function associated with common interventions for knee osteoarthritis[19]

Rank	Outcomes		
	Pain and Function	Pain	Function
1	Naproxen	Corticosteroid	Naproxen
2	Corticosteroid	Ibuprofen	Diclofenac
3	IA PRP	IA PRP	Celecoxib
4	Ibuprofen	Naproxen	Ibuprofen
5	Celecoxib	Celecoxib	IA PRP
6	Diclofenac	HA	Corticosteroid
7	HA	Diclofenac	HA
8	IA placebo	IA placebo	Acetaminophen
9	Acetaminophen	Acetaminophen	IA placebo
10	Oral placebo	Oral placebo	Oral placebo

Abbreviations: HA, hyaluronic acid; IA, intra-articular; PRP, platelet-rich plasma.

that the effect of NSAIDs specifically on function may result from the fact that knee-joint effusion contributes to limited knee-joint function; impaired function often is secondary to inflammatory factors that lead to joint effusion. They note that the limited benefit of acetaminophen for improving pain and function—combined with the potential for hepatic toxicity—make this agent a lower-level treatment choice.[19] A recent Cochrane review of IA steroids as a treatment for knee osteoarthritis showed no benefit compared with placebo.[20]

Similar findings were reported in a 2015 report seeking to establish rational treatment algorithms for management of knee osteoarthritis. In a meta-analysis of treatments for osteoarthritis, 129 trials (32,129 participants) were assessed in terms of pain-related outcomes. Naproxen, ibuprofen, diclofenac, IA HA, and IA corticosteroids were shown to be significantly statistically superior to acetaminophen, the only agent that did not meet criteria for clinically significant improvement in pain. Seventy-six trials (24,059 participants) were included in the analysis of physical function outcomes; only IA corticosteroids were not statistically significantly superior to oral placebo. Naproxen, ibuprofen, diclofenac, and celecoxib showed greater statistical significance than did acetaminophen. Fifty-five trials (18,267 participants) were analyzed regarding stiffness outcomes. Naproxen, ibuprofen, diclofenac, and celecoxib showed statistically significant improvement over oral placebo and acetaminophen. Acetaminophen was the only agent that showed no clinically significant improvement from baseline.[21]

The benefits of prescription-dosage agents for long-term use have been established.[21] In a study of osteoarthritis of the hand, researchers noted that naproxen, which provides the least cardiovascular risk among NSAIDs, may be a beneficial component to pain management. Still, the optimal NSAID likely differs for the individual patient, as these agents have effects on multiple sites as well as both peripheral and central pathways associated with analgesia. It is possible that NSAIDs offer potential benefits for treatment of inflammation associated with various conditions.[22]

The effects of dosage escalation also provide important information that may help clinicians individualize treatment. Among agents available in OTC formulations, a significant linear dose effect in treatment was significant only for naproxen, based on a review of 8973 manuscripts, including 76 randomized trials and a total of 58,451 patients.[23]

NSAIDS AND ACETAMINOPHEN AT OTC DOSES FOR PAIN RELIEF

These analgesics have also been studied in low-dosage formulations for a variety of conditions.

Osteoarthritis

Studies involving low-dosage OTC formulations provide guidance for clinicians in helping to aid patient selection of pain relief products, as noted in the studies summarized below.

The specific effects of OTC NSAIDs on pain and function were evaluated in a recent post hoc pooled analysis (n = 818). Patients 65 years or younger received naproxen, 660 mg/d. A separate subgroup analysis assessed older patients who received a lower dosage of naproxen (440 mg/d). Compared with placebo, the use of naproxen provided significant improvements in pain and physical function ($P<.05$); efficacy was similar among both younger and older patients. Both investigators and patients rated treatment as "good" to "excellent" significantly more often ($P<.001$).[24]

Benefits of NSAIDs, including OTC formulations when possible, were also reported in long-term clinical and economic evaluations of patients with osteoarthritis and cardiovascular disease and diabetes. In patients with multiple comorbidities, regimens that included naproxen and ibuprofen were more effective and cost-effective in managing pain than were opioids, celecoxib, or pharmacotherapeutic standard-of-care acetaminophen and corticosteroid injection.[25]

Multicenter, randomized, double-blind, placebo-controlled trials compared the analgesic efficacy and safety of nonprescription dosages of naproxen, ibuprofen, and placebo in patients with osteoarthritis of the knee. A total of 444 patients were randomized—all for 7 days—to a daily dosage of naproxen sodium, 660 mg; naproxen sodium,

440 mg (patients ≥65 years); ibuprofen, 1200 mg; or placebo. Naproxen (440 mg and 660 mg) and ibuprofen were clinically effective at relieving pain compared with placebo, and reduced the mean symptom score by 30% to 45%. Compared with placebo, naproxen (440 mg and 660 mg) significantly improved all 7 symptoms from baseline, and ibuprofen significantly improved 5 symptoms. For patients ≥65 years (n = 183), naproxen, 440 mg, showed significant superiority in comparison with placebo for all symptoms other than pain on weight-bearing; ibuprofen showed a significant reduction only in day pain. No significant differences in adverse event reporting were noted among groups.[26]

Acute muscle soreness

OTC formulations are commonly used for relief of acute muscle soreness, a common complaint among consumers. In a study, OTC naproxen, 220 mg for 3 days, was administered to patients who underwent a series of exercises consisting of knee extensions designed to produce muscle soreness and strength loss associated with exercise. Three days after exercise, participants in the placebo group experienced more loss of concentric (P<.0064) and isometric (P= .0213) strength and greater thigh soreness when rising from a seated position (P<.0393). Investigators concluded that naproxen is likely to protect muscle strength and function during early stages of increased physical activity, with less muscle injury and soreness.[27] Other investigators have reported similar results.[28] It has been suggested that naproxen improves recovery by attenuating expression of the inflammatory response to muscle injury.[29] High dosages of ibuprofen have shown similar efficacy; however, moderate dosages have not been shown to alleviate soreness.[30]

Pain relief following dental procedures

Multiple NSAIDs and acetaminophen have demonstrated efficacy in addressing pain associated with dental procedures. Both OTC and prescription formulations are commonly used to relieve pain. The efficacy of OTC products—along with the efficacy of opioids and prescription NSAIDs—for pain management was assessed in a survey completed by 2765 patients. At 5-day follow-up after a variety of procedures associated with significant pain, both OTC and prescribed NSAIDs demonstrated relief sufficient to manage most postoperative dental pain.[31]

In a study, lower-dosage naproxen submicron particle capsules provided effective analgesia in acute postsurgical dental pain; the authors propose additional studies to assess the utility of this agent as a treatment for other acute pain conditions.[32] In a double-blind randomized study (n=41), patients evaluated the efficacy of naproxen gel for relief of pain resulting from the placement of orthodontic elastic separators. Naproxen was associated with significantly lower mean pain scores at all time points (P<.001), compared with placebo.[33]

Ibuprofen has also been shown to effectively manage dental pain after removal of the third molar, with administration every 4 to 6 hours. For more severe pain, a combination of 400 to 600 mg ibuprofen with 500 mg acetaminophen, every 6 hours for 24 hours, has been recommended.[34] Acetaminophen has been shown to decrease swelling after oral surgery.[35]

Postoperative pain

The effect of NSAIDs has also been evaluated in multiple studies for postoperative pain. In 9 studies (n = 784), naproxen sodium 550 mg (equivalent to 500 mg naproxen) demonstrated that the number needed to treat was 2.7 (95% confidence interval, [CI] 2.3-3.2) for at least 50% pain relief over 4 to 6 hours. The authors concluded that oral administration of naproxen at dosages in the range of 400 mg and 500 mg provided effective analgesia for adults who experience moderate-to-severe postoperative pain.[36]

Pain associated with headache

NSAIDs provide relief from headache. Ibuprofen has been shown to provide relief from acute migraine in about one half of affected patients, but providing *complete* relief from pain and associated symptoms for a minority. For all efficacy outcomes, the number needed to treat was better with 400 mg than with 200 mg, compared with placebo. More rapid pain relief was seen with the use of soluble formulations.[37]

Naproxen has been compared with sumatriptan for both initial and recurrent migraine attacks. It has been suggested that naproxen may be useful in combination with sumatriptan for patients with unrelieved recurrent headache because this strategy has been shown to provide more pain relief than either agent alone when used for the initial treatment of acute migraine.[38] It may also be useful to add an oral anti-emetic dopamine antagonist to naproxen.[38] Clinicians who are called on to decide which medication to prescribe for headache recurrence should be guided by considerations that include cost, contraindications, side effects, and the patient's overall previous experience with the medication.[38]

Pain associated with dysmenorrhea

Primary dysmenorrhea generally begins within 2 years after onset of menstruation, with symptoms that include low backache, nausea and vomiting, headache, and diarrhea.[39] Dysmenorrhea results from withdrawal of progesterone, which activates the COX-2 enzyme and decreases hydroxyprosta-

glandin dehydrogenase. The resulting increased secretion of prostaglandins leads to increased strength of uterine contractions and pain.[40] NSAIDs are widely used to relieve pain and are significantly more effective than placebo (odds ratio, 7.91; 95% CI, 5.65-11.09). Little evidence suggests superiority of individual NSAIDs, although NSAIDs provide greater pain relief than acetaminophen.[39]

CONCLUSIONS

Clearly, NSAIDs and acetaminophen differ significantly regarding their utility in managing specific pain conditions. Correct dosing is likely to be important for the individual patient who has difficulty remembering to take medication on schedule or for whom only short-term pain relief is required. Similarly, duration of effect may guide the clinician's and patient's decision-making. However, data clearly show that these agents are effective and safe when used correctly in patients without contraindications. They provide a low-cost option for patients and help empower them to participate in their care and discuss options and treatment goals with their clinicians. ●

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