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Topical NSAIDs as First-Line Treatment for Mild to Moderate Osteoarthritis

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Acute musculoskeletal pain occurs in a broad spectrum of diseases and injuries and can be optimally treated with topical nonsteroidal anti-inflammatory drugs (NSAIDs) in many patients. Osteoarthritis (OA) is one of the most common painful musculoskeletal conditions.¹ Osteoarthritis affects 24% of all adults in the US and is a leading cause of work disability, costing \$303.5 billion per year. Osteoarthritis typically affects the knee and hip joints in older patients, with 1 in 10 adults limiting their activities secondary to arthritis.²

Topical NSAIDs are recommended as first-line therapies for acute pain from musculoskeletal injuries (not including low-back pain) in clinical guidelines and are associated with a safety profile that is comparable to that of placebo.^{1,3-5} Oral NSAIDs are associated with an increased risk for adverse events compared with topical formulations.¹

Nurse practitioners (NPs) and PAs in primary care are well-positioned to provide evidence-based care in the treatment of OA and musculoskeletal pain and engage patients in shared decision-making strategies.⁶

Pain

The pathophysiology of pain is an intricate process involving multiple pathways. Transduction occurs when nociceptors, which are found in many parts of the body including blood vessels, viscera, and muscles, are activated by various stimuli. The action potential then is transmitted along afferent nerve fibers to the spinal cord and brain. The gate control theory explains that the perception of pain is an exchange between the nociceptive pain fibers and the non-nociceptive neurons establishing a bottleneck, stopping the action potentials at the injury site. The theory explains the ability of treatments such as acupuncture and transcutaneous electrical nerve stimulation (TENS), as well as why rubbing a painful area, helps to alleviate pain.⁷

Inflammatory markers are released with tissue injury resulting in arteriole dilation, erythema, and warmth to the area. Fluids and cells released into the area result in

edema. Arachidonic acid is then released and broken down by cyclooxygenase-2 (COX-2), which activates the formation of prostaglandins. Prostaglandins maintain the inflammatory process and free and sensitize prostaglandin E₂ (PGE₂). Nonsteroidal anti-inflammatory drugs impede the synthesis of all prostaglandins, thereby decreasing inflammation and pain through interruption of the production of PGE₂. Topical NSAIDs relieve pain through the same mechanism of action as oral formulations but the action is localized to the area of inflammation.⁸

Clinical Guidelines on Managing Acute Pain in Musculoskeletal Injuries

The American College of Physicians (ACP) and American Academy of Family Physicians (AAFP) recommend topical NSAIDs as first-line therapy with or without menthol gel in the treatment of acute pain from musculoskeletal injuries (not including low-back pain) (Table 1).³ Topical NSAIDs relieved pain and stiffness and improved physical function and overall patient satisfaction without an increase in adverse effects.³

Oral NSAIDs and acetaminophen were given a conditional recommendation.³ Oral NSAIDs were shown to relieve the acute musculoskeletal pain and improve function but are associated with an increased risk for gastrointestinal (GI) bleeding, stomach and abdominal pain, and other GI symptoms; in some cases, renal impairment and cardiovascular adverse effects may occur.¹ The older population is especially susceptible to adverse events from oral NSAIDs and these agents can worsen blood pressure control in patients with hypertension. The ACP and AAFP recommend considering patient age and history of hypertension and GI bleeding before prescribing oral NSAIDs. Acetaminophen is effective for the relief of pain, but not as effective as NSAIDs. The combination of NSAIDs with acetaminophen offers no improvement over either alone.³

Acupressure and transcutaneous electrical nerve stimulation (TENS) were also given a conditional recommendation by ACP and AAFP with a low certainty of evidence.³ The risks of opioids (neurologic and GI adverse events, addiction, and overdose) outweigh the benefits in the treatment of musculoskeletal pain and these agents should not be used except in cases of severe injury or intolerance of first-line therapies.³

Table 1. American College of Physicians and American Academy of Family Physicians Guidelines Management of Acute Pain From Non-Low Back, Musculoskeletal Injuries³

Recommendation 1	Topical NSAIDs with or without menthol gel as first-line therapy are recommended to reduce pain, improve physical function, and improve overall patient satisfaction (Grade: strong recommendation; moderate-certainty evidence)
Recommendation 2a	Oral NSAIDs are recommended to reduce pain and improve physical function or oral acetaminophen to reduce pain (Grade: conditional recommendation; moderate-certainty evidence)
Recommendation 2b	Specific acupressure is recommended to reduce pain and improve physical function or TENS to reduce pain (Grade: conditional recommendation; low-certainty evidence)

Recommendation 3 Opioids, including tramadol are not recommended except in the case of severe injuries (Grade: conditional recommendation; low-certainty evidence)

NSAID, nonsteroidal anti-inflammatory drugs; **TENS**, transcutaneous electrical nerve stimulation

In the 2020 American College of Rheumatology (ACR) and Arthritis Foundation (AF) guideline for the management of hand, hip, and knee OA (Table 2), the organizations strongly recommended topical NSAIDs in the treatment of OA of the knee and conditional recommendation for OA of the hand.⁴ Oral NSAIDs were strongly recommended for OA of the hand, knee, and hip. Holistic treatments focusing on mind and body practices such as strength, balance, fall prevention, and self-efficacy, were recommended nonpharmacologic treatments, as well as the holistic treatment of depression. These holistic interventions include yoga, tai chi, cognitive behavioral therapy (CBT), acupuncture, and heat or cold applications.⁴

Weight loss is strongly recommended for knee and/or hip OA in patients with overweight and obesity.⁴ Physical and/or occupational therapy are recommended at various times during the course of the disease. No one form of exercise is recommended over another; rather, emphasis is placed on patient preference.

The treatment plan should be tailored to the patient’s pain, severity, and functionality and patients should be followed to ensure adherence, according to the ACR and AF.⁴ Patients should always take an active part in devising a plan of care and providers should incorporate patients’ beliefs, desires, and comorbidities when finalizing treatment decisions.⁴

Table 2. American College of Rheumatology /Arthritis Foundation Guidelines for Management of Hand, Hip, and Knee Osteoarthritis⁴

Strong Recommendations for Pharmacologic Management

- Topical NSAIDs for knee OA
- Oral NSAIDs for hand, hip, and knee OA
- Ultrasound-guided intraarticular glucocorticoid injection for hip OA

Conditional Recommendations for Pharmacologic Management

- Topical capsaicin for knee OA
- Topical NSAIDs for hand OA
- Intraarticular glucocorticoid injections for hand, hip, knee OA
- Acetaminophen for hand, hip, and knee OA
- Duloxetine for hand, hip, and knee OA Tramadol for hand, hip, and knee OA

Strong Recommendations for the Nonpharmacologic Management

- Exercise for OA of the hand, knee
- Weight loss for overweight or obese patients with hip and knee OA
- Tai chi for hip and knee OA

Conditional Recommendations for the Nonpharmacologic Management

- Balance exercises for knee and hip OA
- Yoga for patients with knee OA

Cognitive behavioral therapy for hand, hip, and knee OA
 Tibiofemoral knee braces
 Acupuncture for patients with hand, hip, and knee OA
 Thermal interventions (locally applied heat or cold) for patients with hand, hip, and knee OA
 Radiofrequency ablation for patients with knee OA
NSAIDs, nonsteroidal anti-inflammatory drugs; **OA**, osteoarthritis

Medications for Osteoarthritis and Musculoskeletal Pain

The goal of OA treatment is to relieve pain and improve function without causing harm to the patient. A 2021 meta-analysis analyzed the efficacy and safety of oral and topical NSAIDs and acetaminophen for knee OA. The study authors found that topical NSAIDs produced improvement in function over acetaminophen but not over oral NSAIDs in the treatment of OA of the knee. The safety profile for topical NSAIDs was superior to both acetaminophen and oral NSAIDs (Table 3).⁹

Table 3. Risk for Adverse Cardiovascular and Gastrointestinal Outcomes⁹

Outcome	Topical NSAIDs vs Acetaminophen (reference)	Topical NSAIDs vs Oral NSAIDs (reference)
Major CVD	0.73	0.74
Venous thromboembolism	0.81	0.73
GI bleeding	0.53	0.71

CVD, cardiovascular disease; **GI**, gastrointestinal; **NSAID**, nonsteroidal anti-inflammatory drug
 Adapted from Zeng et al.⁹

In another meta-analysis comparing NSAIDs to opioids, researchers concluded that topical diclofenac 70 to 81 mg per day should be the first-line treatment for knee OA because of the improved safety and efficacy profile over oral NSAIDs and opioids. The benefits do not outweigh the risks for the use of opioids in the treatment of OA.¹⁰

Topical Diclofenac

Diclofenac is the only topical NSAID currently available in the United States and is supplied in a 1.3% patch, 1% gel, and 1.5% and 2% solution.¹¹⁻¹³ The patch and solution are available by prescription and the gel can be purchased over the counter or by prescription. Recommended adult dosing with the gel is 2 grams applied to a 2.25-inch area up to 4 times daily for joints in the hands, elbows, or wrists. For the knee, ankle, or foot joints, 4 grams should be applied to a 4.5-inch area up to 4 times daily.¹¹ The maximum dose per area is 16 grams per day for the lower extremities, 8 grams per day for the upper extremities, and 32 grams maximum daily for total body dose.¹¹ The diclofenac patch can be applied once or twice daily to the affected area.¹² The 1.5% solution is for 40 drops to each affected knee up to 4 times daily. The drops should be applied 10 at a time and rubbed in evenly before applying the next 10

drops.¹³ The 2% solution is administered via pump.¹⁴ Two pump actuations (40 mg) are applied to each affected knee up to twice daily.¹⁴

As with all NSAIDs, the labeling for topical diclofenac contains a black box warning that NSAIDs may cause an increased risk of serious and potentially fatal cardiovascular adverse events and should not be used in the setting of coronary artery bypass graft surgery.¹¹⁻¹⁴ The lowest possible dose of topical diclofenac should be used in patients with known or risk factors for cardiovascular disease.

Other topical NSAID formulations (eg, ibuprofen, ketoprofen) have shown efficacy in clinical trials but are not available in the United States. All topical agents should be rubbed in thoroughly and applied to clean dry skin. They should not be applied to any open or irritated areas. Hands should be washed thoroughly after application. All have the potential to cause skin irritation.

Conclusion

Topical NSAIDs provide effective pain relief with minimal safety concerns for mild to moderate musculoskeletal pain and are recommended by the ACP, AAFP, and ACR as first-line therapy. The evidence strongly supports the efficacy and safety of topical NSAIDs for use in acute and chronic musculoskeletal conditions. Head-to-head clinical trials of different topical NSAIDs, however, are lacking. Data regarding the contrasts between formulations, concentrations, and use for varying conditions would further define the possible benefits of topical NSAIDs. Further research is needed in these areas.

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