Brief review
New guidelines for topical NSAIDs in the osteoarthritis treatment paradigm

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Keywords

Abstract

Background:
Osteoarthritis (OA), the most common form of arthritis, often affects hands, hips, and knees and involves an estimated 26.9 million US adults. Women have a higher prevalence of OA, and the risk of developing OA increases with age, obesity, and joint malalignment. OA typically presents with pain and reduced function. Therapeutic programs are often multimodal and must take into account pharmaceutical toxicities and patient comorbidities. For example, nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with cardiovascular, gastrointestinal, and renal adverse events. Topical NSAIDs offer efficacy with reduced systemic drug exposure.

Research design and methods
This is a review of current guideline recommendations regarding the use of topical NSAIDs in OA of the hand and knee. Articles were identified by PubMed search (January 1, 2000 to May 21, 2010).

Results:
Several current guidelines for management of OA recommend topical NSAIDs, indicating them as a safe and effective treatment. One guideline recommends that topical NSAIDs be considered as first-line pharmacologic therapy. A US guideline for knee OA recommends topical NSAIDs in older patients and in patients with increased gastrointestinal risk.

Conclusions:
The consensus across US and European OA guidelines is that topical NSAIDs are a safe and effective treatment for OA. Because the research base on topical NSAIDs for OA is small, guidelines will continue to evolve.

Introduction

Estimates of the prevalence of osteoarthritis (OA), the most common form of arthritis, vary depending on the diagnostic criteria applied and the age of the population. Clinically, symptomatic OA is estimated to be present in 12.1% of US adults (26.9 million)\(^1\). OA is the 19th leading cause of burden of disease (measured in disability-adjusted life-years) worldwide\(^2\) and the 12th leading cause of burden of disease in the United States\(^3\). Annual US healthcare expenditures for OA are estimated to be $185.5 billion\(^4\).

Osteoarthritis is a disease of the joint characterized by abnormality and disruption of articular cartilage, changes in the subchondral bone, periarticular muscle weakness, ligamentous contractures, and usually mild proliferative synovitis\(^5,6\). The hand, hip, and knee are the joints most often affected\(^1\). Pain in the joint is the most common reason to consult with a physician. Reduced function closely correlates with pain. Additional clinical findings include synovial and/or...
bony tenderness, <30 minutes of morning stiffness, bony enlargement, and crepitation on motion of the joint; patients with knee OA may experience instability or buckling. Pain from hip or knee OA is often accentuated by weight-bearing activities. Additional health-related problems may include impaired sleep, fatigue, limitations in daily and social activities, and emotional stress. Unsurprisingly, the patient’s health-related quality of life is often significantly diminished.

Osteoarthritis is at least in part a heritable disorder. Before age 40 years, it is more common in men and often related to trauma. Most OA starts between the ages of 40 and 50 years and becomes more prevalent with increasing age, especially in women. Obesity is a risk factor for prevalence of OA of the knee and to a lesser extent for prevalence of OA of the hip and of the hand. Occupations involving bending or joint trauma may also increase OA risk. Varus or valgus deformity of the knee is not only a risk factor for knee OA, but also a predictor of progression of disease.

Most patients with OA have increased risk for the presence of multiple comorbidities (odds ratio = 2.4 for having ≥ 6 comorbid conditions). Cardiovascular, gastrointestinal (GI), and endocrine disorders are among the most common, and metabolic syndrome, a constellation of risk factors for coronary artery disease, is approximately 3-fold more prevalent in patients with OA; the risk of metabolic syndrome is particularly high in younger populations (<65 years) with OA.

Since the release of indomethacin in 1962, oral nonsteroidal anti-inflammatory drugs (NSAIDs) have been an integral part of the multimodal therapy of OA. It has always been appreciated that NSAIDs are not completely safe and that the safety of NSAIDs is further compromised by increasing dose, long-term use, increasing age of the patient, comorbidities, and comedications. The most serious adverse events (AEs) of the NSAID profile are GI, cardiovascular, and renal.

One potential way to mitigate systemic exposure to an NSAID is topical application. Since 2007, two topical NSAID preparations have received approval by the US Food and Drug Administration (FDA) for OA: diclofenac sodium 1% gel and diclofenac sodium 1.5% in 45.5% dimethylsulfoxide. Pharmacokinetic data show that, compared with oral diclofenac (50 mg, 3 times daily), topical diclofenac sodium 1% gel (4 g, applied to one knee 4 times daily) produces much lower mean plasma concentrations (9.7 vs. 162 ng/mL) and peak plasma concentrations (15.0 vs. 2270 ng/mL). Although it seems logical that reduced systemic NSAID exposure would mitigate the risk of NSAID AEs, no studies have compared long-term safety with these or with other topical diclofenac formulations versus oral NSAIDs. Hence, these products bear the same FDA-required safety labeling as oral diclofenac. Historically, there are case-control studies that have reported lower AE rates with topical NSAIDs compared with oral NSAIDs.

The availability of topical NSAID therapy that can achieve effective improvement of OA pain and function with lower risk of NSAID-related AEs is an important development in the OA treatment paradigm. The purpose of this article is to review recommendations for topical NSAIDs in current OA guidelines.

Search methodology

Searches of the PubMed database from January 1, 2000 to May 21, 2010 were conducted using the terms ‘osteoarthritis OR nonsteroidal anti-inflammatory drugs’ and the limit practice guideline and the terms ‘Osteoarthritis AND (Guideline* OR Recommendation*)’. Records were reviewed to identify guidelines on pharmacologic therapy for hand and knee OA.

Scope of current osteoarthritis guidelines

Current OA guidelines include the Osteoarthritis Research Society International (OARSI) recommendations for the management of hip and knee OA, the European League Against Rheumatism (EULAR) recommendations for the management of knee OA and hand OA, the American Academy of Orthopaedic Surgeons (AAOS) guideline for the treatment of knee OA, the National Institute for Health and Clinical Excellence (NICE) clinical guideline for the care and management of OA in adults, the American Geriatrics Society (AGS) guidelines for the pharmacologic management of persistent pain in older persons, and the American Heart Association (AHA) scientific statement on the use of NSAIDs. The American College of Rheumatology (ACR) recommendations for the management of hip and knee OA were published in 2000, before US approval of the first topical NSAID formulation for OA. Because these guidelines do not provide any recommendation with regard to topical NSAIDs and new ACR guidelines are in development and expected to be released soon, the 2000 ACR guidelines are not discussed in this review.

As a collective, these guidelines reflect the expertise of US, European, and international physicians and researchers from a variety of medical disciplines. However, the individual guidelines differ in breadth of expertise. The EULAR and OARSI guidelines were developed primarily by experts in rheumatology, although the OARSI guidelines development team also included experts from orthopedics, primary care, and evidence-based medicine. The AOS, AHA, and AAOS guidelines reflect specialist perspectives in geriatrics and pain, cardiology, and orthopedic surgery, respectively. The NICE guidelines are somewhat unique in having been developed jointly by physicians.
(e.g., rheumatologists, geriatric specialists, primary care doctors, physiotherapists) and a diverse group of scientists and professionals that includes health economists, epidemiologists, information scientists, patient and care representatives, and medical statisticians.

Some of the guidelines (OARSI, EULAR, AAOS) address specific types of OA (knee or hand) and others (AGS, AHA, NICE) are general, but knee OA has the most abundant research and is therefore most influential on recommendations. Generally speaking, the guidelines reflect a holistic approach to OA treatment and place a strong emphasis on nonpharmacologic approaches such as patient education, lifestyle modification, surgery, appliances, and alternative therapy (e.g., acupuncture, electromagnetic therapy). Exceptions are the AGS guidelines, which are focused on pain pharmacotherapy, and the AHA scientific statement, which is focused specifically on use of NSAIDs in patients with or at high risk of cardiovascular disease. Discussion of nonpharmacologic approaches is beyond the scope of this review.

With only one exception, the guidelines are evidence-based and were developed through a regimented process of systematic review of the research literature and expert consensus. Most incorporate a grading system indicating the strength of recommendation, which is based on the quality of evidence (e.g., randomized controlled trial, systematic review, retrospective study, case control-study). The AHA scientific statement is a peer-reviewed document that represents the consensus of experts in cardiovascular disease and stroke, but it is not a formal guideline and does not incorporate levels of evidence or classes of recommendation.

### Guidelines on topical NSAIDs

With the exception of the AHA scientific statement, all guidelines make recommendations for topical NSAIDs (Table 1). However, the specifics of the recommendations differ. The OARSI, EULAR, and AGS guidelines recommend that physicians initiate pharmacologic treatment with acetaminophen/paracetamol and that topical NSAIDs are appropriate candidates for second-line therapy in patients who do not respond to or tolerate acetaminophen/paracetamol. The OARSI guidelines also recommend topical NSAIDs as effective adjuncts and alternatives to oral analgesic/anti-inflammatory agents in knee OA. The EULAR hand OA guidelines and knee OA

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation</th>
<th>Grade</th>
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<tbody>
<tr>
<td>AAOS24</td>
<td>Suggest that patients with symptomatic OA of the knee and increased GI risk (aged ≥60 years, comorbid medical conditions, history of peptic ulcer disease, history of GI bleeding, concurrent corticosteroids and/or concomitant use of antiacogulants) receive one of the following analgesics for pain:</td>
<td>IIB</td>
</tr>
<tr>
<td></td>
<td>- Acetaminophen (not to exceed 4 g/day)</td>
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<td></td>
<td>- Topical NSAIDs</td>
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<td>- Nonselective oral NSAIDs plus gastroprotective agent</td>
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<td></td>
<td>- Cyclooxygenase-2 inhibitors</td>
<td></td>
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<tr>
<td>AGS26</td>
<td>All patients with other localized nonneuropathic persistent pain may be candidates for topical NSAIDs.</td>
<td>Moderate quality of evidence, weak recommendation</td>
</tr>
<tr>
<td>AHA27</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>EULAR hand23</td>
<td>Local treatments are preferred over systemic treatments, especially for mild-to-moderate pain and when only a few joints are affected. Topical NSAIDs and capsaicin are effective and safe treatments for hand OA.</td>
<td>75*, 86%†</td>
</tr>
<tr>
<td>EULAR knee22</td>
<td>Topical applications (NSAID, capsaicin) have clinical efficacy and are safe.</td>
<td>1B</td>
</tr>
<tr>
<td>NICE25</td>
<td>Healthcare professionals should consider offering topical NSAIDs for pain relief in addition to core treatment for people with knee or hand OA. Topical NSAIDs and/or paracetamol should be considered ahead of oral NSAIDs, cyclooxygenase-2 inhibitors, or opioids.</td>
<td>NR</td>
</tr>
<tr>
<td>OARSI21</td>
<td>Topical NSAIDs and capsaicin can be effective as adjunctives and alternatives to oral analgesics/anti-inflammatory agents in knee OA.</td>
<td>Ia</td>
</tr>
</tbody>
</table>

AAOS, American Academy of Orthopaedic Surgeons; AGS, American Geriatrics Society; AHA, American Heart Association; EULAR, European League Against Rheumatism; GI, gastrointestinal; NICE, National Institute for Health and Clinical Excellence; NR, not reported; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International.

*100 mm visual analog scale (0 = not recommended at all; 100 mm = fully recommended).
†Percentage rated A–B on A–E ordinal scale (A = fully recommended, B = strongly recommended, C = moderately recommended, D = weakly recommended, E = not recommended).
guidelines both recommend topical NSAIDs as safe and effective, but the EULAR hand OA guidelines go further by recommending local treatments over systemic treatments for hand OA, especially for mild-to-moderate pain and when only a few joints are affected. According to the AGS guidelines, topical NSAIDs should be considered in all patients with localized nonneuropathic persistent pain because of their demonstrated efficacy and minimal systemic absorption. Topical NSAIDs are noted as a possible strategy for averting NSAID toxicity, and the AGS guidelines recommend use of nonselective NSAIDs and cyclo-oxygenase-2 (COX-2)–selective NSAIDs only with extreme caution and in carefully selected individuals because of the potential for GI, renal, and cardiovascular AEs.

The AAOS guidelines recommend acetaminophen or NSAIDs, with no distinction as to which should be first-line therapy, as long as no contraindications are present. Topical NSAIDs are specifically recommended for patients with symptomatic knee OA who have increased GI risk (i.e., aged ≥60 years, comorbid medical conditions, history of peptic ulcer disease, history of GI bleeding, concurrent corticosteroid use, and/or concomitant use of anti-coagulants); nonselective oral NSAIDs plus a gastroprotectant and COX-2 inhibitors are also recommended for such patients.

The AHA scientific statement is focused more narrowly on minimizing cardiovascular risk and therefore differs from these other guidelines in recommending acetaminophen as well as aspirin, tramadol, and narcotic analogues— all considered to have a high degree of cardiovascular safety— as candidates for initial pharmacotherapy in patients with or at high risk for cardiovascular disease. If acetaminophen, aspirin, tramadol, or narcotic analogues are not tolerated or effective, NSAIDs may be considered, starting with nonselective agents and progressing to NSAIDs with some COX-2 activity and ultimately to COX-2-selective NSAIDs, if necessary.

The NICE guidelines recommend that topical NSAIDs be considered as initial pharmacologic treatment. Both paracetamol and topical NSAIDs are designated as safe pharmaceutical options that should be considered if core treatment (i.e., education, strength and fitness training, weight loss) is insufficient. In contrast, oral NSAIDs are designated as an adjunctive treatment, together with COX-2 inhibitors, opioids, surgery, self-management techniques, and other nonpharmaceutical options. Such treatments are recommended only secondarily to core treatment, paracetamol, and topical NSAIDs.

More recent evidence

As noted in the various guidelines, the research base for topical NSAIDs is smaller than that for oral NSAIDs, and guidelines can be expected to evolve as new studies are performed. However, it is worth noting that the recent evidence update to the OARSI 2008 guidelines supports their earlier recommendations regarding topical NSAIDs. In this update, which reflects research published through January 2009, the reported effect sizes (95% CI) for topical NSAIDs were 0.44 (0.27–0.62) for pain, 0.36 (0.24–0.48) for function, and 0.49 (0.17–0.80) for stiffness, and AE relative risks (95% CI) for topical NSAIDs versus placebo were 0.81 (0.43–1.56) for GI events and 1.45 (0.84–2.50) for GI bleed/perforation. These effect sizes are substantially larger than those reported for oral NSAIDs (0.29 [0.22–0.35] for pain) and acetaminophen (0.14 [0.05–0.23] for pain), and the AE relative risks are considerably lower (oral NSAIDs, 2.70 [2.10–3.50] to 5.36 [1.79–16.10] for GI perforation/ulcer/bleed, depending on type of study; acetaminophen, 3.60 [2.60–5.10] for GI perforation/bleed).

The OARSI 2010 evidence update does not include several clinical trials of the two FDA-approved topical NSAID formulations published in 2009. In two double-blind, randomized, placebo-controlled trials in hand OA (8 weeks) and knee OA (12 weeks), topical diclofenac sodium 1% gel produced significant improvements in OA pain intensity and function relative to placebo by week 1 of treatment. In a 12-week, double-blind, randomized, controlled trial in knee OA, diclofenac sodium 1.5% in 45.5% dimethylsulfoxide solution was demonstrated as superior to placebo for pain, physical function, and patient global assessment, and there was no significant difference in efficacy compared with oral diclofenac (100 mg slow release). Diclofenac sodium 1.5% in 45.5% dimethylsulfoxide solution has not been evaluated in hand OA. Although there was a higher rate of application site reactions with topical NSAIDs versus vehicle in these trials, the drugs were well-tolerated overall, and there were no serious AEs related to treatment.

Treatment algorithm

Figure 1 provides an algorithm for the multimodal treatment of symptomatic OA. Before considering pharmacologic therapy, it is most appropriate to educate patients regarding modifiable factors such as diet and exercise that can help to reduce joint stress and to offer physical aids, such as canes and crutches to unload the joint, knee cages to support the joint, and heat or cold therapy to relieve symptoms. When these measures do not provide adequate relief, physicians should consider pharmacologic therapy with either rapid- or slow-acting medications. Because no single therapy is preferred, pharmacologic therapy should be multimodal and individualized to the patient based on consideration of factors such as comorbidity,
dosing frequency, patient’s existing medication, and cost. Rapidly acting medications include oral and topical analgesics (e.g., acetaminophen, lidocaine, tramadol), anti-inflammatories (e.g., intra-articular corticosteroids), and NSAIDs, which have dual anti-inflammatory and analgesic properties. Topical NSAIDs may be considered before oral formulations, particularly in patients with elevated GI, cardiovascular, or renal risk. Slower-acting medications such as antiresorptives, glucosamine, and chondroitin may also be considered; hyaluronate is both slower and longer acting and may be an option in high-risk patients who are not considered candidates for joint replacement.

## Conclusion

There are two FDA-approved topical NSAID preparations for OA: diclofenac sodium 1% gel and diclofenac sodium 1.5% in 45.5% dimethylsulfoxide. The consensus across US and European OA guidelines is that topical NSAIDs are a safe and effective treatment for OA. Although acetaminophen/paracetamol continues to be the first-choice oral pharmacotherapy in many guidelines, the NICE guidelines recommend that topical NSAIDs be considered with paracetamol before oral NSAIDs, COX-2 inhibitors, or opioids, and the EULAR guidelines for hand OA recommend topical NSAIDs as preferred over systemic treatments for hand OA, particularly for mild-to-moderate pain or when only a few joints are affected. The new ACR guidelines currently in development will provide more up-to-date recommendations.

## Transparency

### Declaration of funding

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### Declaration of financial/other relationships

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### References


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**Figure 1. Treatment algorithm for symptomatic osteoarthritis. COX-2, cyclooxygenase-2; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; PGE2, prostaglandin E2; PPI, proton pump inhibitor; PO, oral; SNRI, selective norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.**
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