Highlights of new publication on efficacy and safety of NSAIDs and opioids in the treatment of osteoarthritis

Effectiveness and safety of non-steroidal anti-inflammatory drugs and opioid treatment for knee and hip osteoarthritis:

network meta-analysis

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The following piece was developed as a summary of a global meta-analysis publication, and some of the data presented may not align with approved indications from market to market. In the United States, Voltaren Gel is indicated for OA pain of the knee, hand, wrist, elbow, foot, and ankle. Please consult the FDA-approved labeling for directions and further information on how to use Voltaren safely and effectively.

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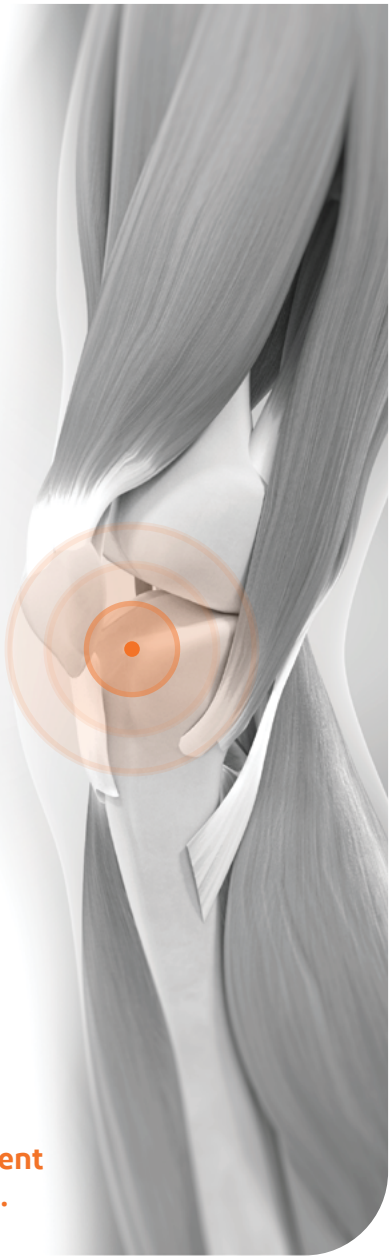
Background



Osteoarthritis (OA) is a chronic, progressive, degenerative joint disease with the hallmark symptom being pain. OA-related pain results in functional limitation, disability, and impaired quality of life. Since no disease-modifying therapy is yet available, the aim of treatment is to reduce pain, minimize disability, and improve quality of life.

The treatment of OA can pose significant challenges for clinicians. **Non-steroidal anti-inflammatory drugs (NSAIDs) remain the mainstay of pharmacologic treatment for OA pain.**

However, given the potential for adverse side effects, clinical considerations aimed at risk mitigation from the safe use of NSAIDs must be carefully weighed. In general, it is recommended to use the lowest dose possible for the shortest time needed to limit systemic exposure.

Gastrointestinal **Renal** **Cardiovascular**

Evidence suggests that opioids offer modest efficacy, but they cause significantly more side effects and carry the risk of dependence and overdose. Despite the notable risks associated with opioids, they remain among the most prescribed drugs for OA pain in the US, UK, Canada, and Australia.

Topical NSAIDs have become increasingly recommended in OA treatment guidelines based on demonstrated efficacy and low systemic exposure.

Methods

Searches for eligible studies were conducted using data sources that included Cochrane Central Register of Controlled Trials (CENTRAL), Medline, Embase, and ClinicalTrials.gov. Searches were conducted from inception through June 2021.

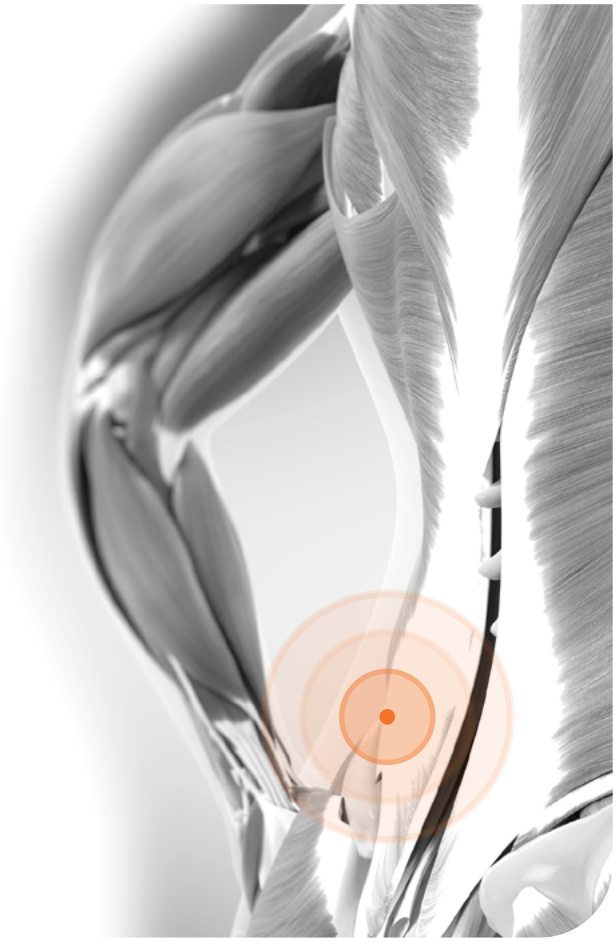
Eligible studies were defined as randomized, clinical studies of knee or hip OA that compared any of the following interventions: **NSAIDs, opioids, acetaminophen, or placebo. Only those studies with an average of ≥100 participants per arm were considered to reduce small study bias.**

- **The primary outcome:** Reduction in pain; estimated the probability for the effect of experimental intervention to reach the between-group minimum clinically important difference (MID) of −0.37 standard deviation units to facilitate the interpretation of treatment effects. An effect size (for pain) of 0.37 corresponds to a between-group difference of 9 mm on a 100-mm visual analogue scale.
- **Secondary outcome:** Physical function
- **Others:** Discontinuations or withdrawals due to adverse events (AEs)

The authors of this meta-analysis aimed to assess the effectiveness and safety of different preparations and doses of NSAIDs, opioids, and acetaminophen to help health care providers manage knee and hip OA pain and physical function.

Results

- Data from 181 publications describing 192 clinical trials were included in the analysis. This included a total of 102,829 study participants. The mean age of participants ranged from 48 to 72 years and the percentage of female patients ranged from 13% to 91%. The average time since OA diagnosis was 6.6 years. Ninety active interventions were examined in this meta-analysis (68 NSAIDs, 19 opioids, 3 acetaminophen), with celecoxib being the most frequently investigated intervention (44 trials).



- Diclofenac 150 mg/day and etoricoxib 60 mg/day appeared to be the most effective interventions for pain relief. Diclofenac 150 mg/day had an effect size of −0.56 and etoricoxib 60 mg/day had an effect size of −0.65, corresponding to 14-mm and 16-mm differences on a 100-mm visual analogue scale. The probability that these interventions have treatment effects that are more pronounced than the between-group MID was 99.9%
- Diclofenac 150 mg/day and etoricoxib 60 mg/day had similar rates of increased AEs vs placebo (odds ratio 1.27 and 1.56, respectively). However, etoricoxib demonstrated a lower risk of discontinuation due to an AE and lower risk of experiencing a serious AE
- Topical diclofenac, regardless of dose, had the largest effect on pain and physical function compared to other topical treatments. The lowest dose of 70 to 81 mg/day had a 92% probability of having a minimum clinically relevant improvement on pain while a dose of 140 to 160 mg/day had 96.3% probability. Both doses demonstrated a better safety profile than oral diclofenac
- Opioid interventions did not appear to have a clinically relevant effect on pain and demonstrated significantly worse safety profiles
- Acetaminophen 3900 to 4000 mg/day had the lowest effect on OA pain, with an effect size of −0.15, corresponding to a 4-mm difference on a 100-mm visual analogue scale
- All interventions improved physical function compared to placebo except for nabumetone 1000 mg/day and acetaminophen <2000 mg/day

Study Strengths

- This meta-analysis included a 2.5-fold to 5-fold increase in the number of trials and patients analyzed compared with previous reviews specific to NSAIDs, opioids, or acetaminophen
- The comprehensive nature of this meta-analysis allowed for the generation of more granular evidence and statistical precision, particularly in regard to comparisons between formulations and doses
- The exclusion of small studies (<100 participants/arm) helped to minimize the risk of bias
- Treatment-effect estimates were consistent for 1, 6, and 12 weeks of follow-up, which provided evidence for the strength of the study data

Study Limitations

- The average treatment duration was less than 3 months, so safety findings are not generalizable to long-term use
- The studies analyzed did not allow for the consideration of comorbidities, which is an essential element of clinical practice
- Only a small proportion of the studies analyzed reported cause-specific (i.e. gastrointestinal, cardiovascular) AEs. Therefore, a comparison of these events between interventions and doses was not possible. These events are particularly important in weighing treatment options in patients with comorbidities
- The authors note that this meta-analysis did not include enough trials to determine the impact of topical NSAID formulation (patch, gel, cream) on their effectiveness and safety profiles

Conclusions

While this meta-analysis provides a larger and more granular view of the use of NSAIDs and opioids for the treatment of OA pain, the results are not unexpected and align with the OA treatment guidelines set forth by major medical societies such as Osteoarthritis Research Society International (OARSI) and American College of Rheumatology (ACR). In general, this meta-analysis reinforces the following:

- Topical NSAIDs are an efficacious, first-line treatment option with a proven safety profile and low systemic exposure
- Oral NSAIDs are highly efficacious for the treatment of OA pain, but should be carefully considered due to associated AEs, particularly in patients with comorbidities
- Acetaminophen had a significantly smaller-size effect on OA pain and function and may be most appropriate for those with intolerance or contraindication to NSAIDs
- The clinical benefit of opioids does not outweigh the harm they might cause in patients with OA regardless of dose or formulation
- In general, acetaminophen and opioids should be reserved for patients who are intolerant to NSAIDs or have exhausted other treatment options