Q/Which oral nonopioid agents are most effective for OA pain?

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EVIDENCE-BASED ANSWER

A/ **NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS),** when used at the maximum clinically effective dose, reduce osteoarthritis (OA) pain in large joints more effectively than either placebo or acetaminophen (strength of recommendation [SOR]: **A,** network meta-analysis of randomized controlled trials [RCTs]).

When ranked for efficacy, diclofenac 150 mg/d was the most effective (SOR: **A,** network meta-analysis of RCTs). The selective COX-2 inhibitors, such as celecoxib, are not more effective at reducing pain than the nonselective NSAIDs (SOR: **A,** meta-analysis of RCTs). Meloxicam is superior to placebo but marginally inferior to other NSAIDs (SOR: **A,** systematic review of RCTs).

Acetaminophen is no more effective than placebo (SOR: **A,** meta-analysis of RCTs).

Evidence summary

All NSAIDs at maximum clinical doses reduced large joint OA pain more effectively than placebo and acetaminophen based on data from a network meta-analysis of 129 RCTs with 32,129 patients (**TABLE 1**).[1] When various doses of NSAIDs are ranked for efficacy based on their effect size compared to placebo, diclofenac 150 mg/d had the greatest treatment effect, followed by ibuprofen 2400 mg/d.[2] Lower doses of NSAIDs—including diclofenac 70 mg/d, naproxen 750 mg/d, and ibuprofen 1200 mg/d—were not statistically superior to placebo (**TABLE 2**).[2]

Selective vs nonselective. There was no statistical difference in pain relief between the selective COX-2 inhibitor celecoxib and the nonselective NSAIDs naproxen, diclofenac, and ibuprofen (**TABLE 1**).[1]

Meloxicam. A systematic review of 16 RCTs and 22,886 patients found that meloxicam reduced pain more effectively than placebo (10-point visual analogue scale [VAS] score pain difference of –6.8; 95% CI, –9.3 to –4.2) but was marginally less effective than other NSAIDs (VAS score pain difference of 1.7; 95% CI, 0.8 to 2.7).[3]

Acetaminophen. Data from 6 RCTs involving 2083 adults with knee OA indicate acetaminophen did not achieve clinical significance compared to placebo (**TABLE 1**).[1] Another meta-analysis of 5 RCTs involving 1741 patients with hip or knee OA also demonstrated that acetaminophen failed to achieve a clinically significant effect on pain, defined as a reduction of 9 mm on a 0 to 100 mm VAS (–3.7; 95% CI, –5.5 to –1.9).[4] Another network meta-analysis of 6 RCTs including 58,556 patients with knee or hip OA, with the primary outcome of pain (using a hierarchy of pain scores, with global pain score taking precedence) also found no clinically significant difference between acetaminophen at the highest dose (4000 mg/d) and placebo (–0.17; 95% credible interval [CrI], –0.27 to –0.6).[2]

Recommendations

In a systematic review of mixed evidence-based and expert opinion recommendations and guidelines on the management of OA, 10 of the 11 guidelines that included pharmacologic management recommended acetaminophen as a first-line agent, followed by topical NSAIDs, and then oral NSAIDs.

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TABLE 1

Effect sizes[a] of acetaminophen and NSAIDs for OA pain[1]

	Acetaminophen (95% CrI)	Celecoxib (95% CrI)	Naproxen (95% CrI)	Ibuprofen (95% CrI)	Diclofenac (95% CrI)
Placebo	0.18 (0.04 to 0.33)	0.33 (0.25 to 0.42)[b]	0.38 (0.27 to 0.49)[b]	0.44 (0.25 to 0.63)[b]	0.52 (0.34 to 0.69)[b]
Acetaminophen		0.15 (0.00 to 0.30)	0.20 (0.03 to 0.37)[b]	0.26 (0.05 to 0.47)[b]	0.33 (0.12 to 0.54)[b]
Celecoxib			0.05 (–0.08 to 0.17)	0.11 (–0.10 to 0.31)	0.18 (–0.01 to 0.37)
Naproxen				0.06 (–0.15 to 0.27)	0.13 (–0.07 to 0.33)
Ibuprofen					0.07 (–0.17 to 0.32)

CrI, credible interval; OA, osteoarthritis.

[a] Hedges' g effect sizes as translated from different pain scales used in studies.

[b] Met criteria for clinically significant improvement.

The exception is the most recent American Academy of Orthopaedic Surgeons guideline, which continues to recommend NSAIDs but is now unable to recommend for or against acetaminophen.[5] **JFP**

TABLE 2

How different NSAIDs compare[a] to placebo for OA pain[2]

NSAID (mg/d)	Effect size (95% CrI)
Diclofenac	
70	–0.26 (–0.63 to 0.12)
150	–0.57 (–0.69 to –0.45)[b]
Celecoxib	
100	–0.14 (–0.29 to –0.01)
400	–0.32 (–0.46 to –0.18)
Naproxen	
750	–0.05 (–0.43 to 0.33)
1000	–0.40 (–0.48 to –0.33)[b]
Ibuprofen	
1200	–0.30 (–0.86 to 0.25)
2400	–0.42 (–0.55 to –0.30)[b]

CrI, credible interval; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis.

[a] Differences on a 10-cm visual analogue scale as translated from different studies.

[b] Clinically important difference.

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