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Acetaminophen or NSAIDs for the treatment of osteoarthritis

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Although non-pharmacological interventions are the cornerstone of osteoarthritis management, analgesics are an important component of treatment during the symptomatic periods of the disease. In this respect, current practice guidelines advocate the use of a simple analgesic, acetaminophen, or a non-steroidal anti-inflammatory drug (NSAID), given either systemically or topically as first-line or second-line drug therapies. The present paper aims first to assess the evidence for the efficacy and safety of these medications. Given the increasing importance of patient involvement in decision-making, the following key practical issue regarding acetaminophen and NSAIDs will then be addressed: 'which drug do patients prefer?' Regarding NSAIDs, a further question concerns the place for non-selective agents and cyclo-oxygenase-2 (COX-2) selective inhibitors (coxibs) in the light of new warnings and contraindications concerning coxibs in patients with increased risk of cardiovascular thrombotic events.

Keywords: osteoarthritis; pain; non-steroidal anti-inflammatory drugs; coxibs; topical treatment; acetaminophen.

Osteoarthritis (OA) is a leading cause of pain and disability, especially in the elderly. Although non-pharmacological interventions are the cornerstone of OA management, analgesics play a central role during the painful periods of the condition.[1–3] In this respect, current practice guidelines advocate the use of a simple analgesic, acetaminophen (paracetamol), or a non-steroidal anti-inflammatory drug (NSAID), given either systemically or topically as first-line or second-line therapies in patients with symptomatic OA.[1–3] The present paper aims first to assess the evidence for the efficacy and safety of these drug treatment modalities. Given the increasing importance of patient involvement in decision-making, the following key practical issue regarding acetaminophen and NSAIDs will then be addressed: 'which drug do patients prefer?' In

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fact, patients' preferences may differ from those of their doctors or evidence-based guidelines.[4] Regarding NSAIDs, a further question concerns the place for non-selective agents and cyclo-oxygenase-2 (COX-2) selective inhibitors (coxibs) in the light of new warnings and contraindications concerning coxibs in patients with increased risk of cardiovascular thrombotic events.

WHAT IS THE EVIDENCE FOR THE EFFICACY OF ACETAMINOPHEN AND NSAIDS?

The question of whether acetaminophen is more effective than placebo for OA has been considered in the meta-analysis by Zhang et al.[5] The literature search identified four placebo-controlled randomized clinical trials published to July 2003. The two earliest trials were available for the assessment of clinical response rate, defined as the percentage of patients reporting at least moderate to excellent or $>50\%$ pain relief or symptomatic improvement. As such, acetaminophen had a higher response rate than placebo in both studies.[5] However, the results were heterogeneous and not relevant for pooling.[5] The two latest trials allowed the effect size (ES) to be calculated. There is no current operational definition for what constitutes a sufficiently large ES for a therapeutic intervention to be considered useful, but a value of 0.2 is considered clinically small, 0.5 is moderate (and would be recognized clinically), and >0.8 is large.[2,6] The pooled ES for pain reduction (primary outcome measure) was 0.21 (95% confidence interval [CI]: 0.02–0.41), whereas the pooled ES for the total WOMAC (Western Ontario and McMaster Universities) OA index score was 0.14 (95% CI: -0.06 to 0.34).[5] It should be remembered that the WOMAC inquires about the three domains of pain, stiffness, and function, but that most of its 24 questions relate to function.

Two further placebo-controlled trials of acetaminophen in large-joint OA have been reported after July 2003.[7,8] In the first one, the proportions of patients with knee OA meeting the primary endpoint (30% decrease in global knee pain during physical activity in the past 24 hours) were the same for acetaminophen (52.6%) and placebo (51.9%) at the end of the 6-week study period.[7] However, this negative result might be ascribable to several unusual features and caveats, especially selection bias, unexpectedly high placebo response, and high drop-out rate.[9] When the data from the second study, namely PACES-b[7], were included in the above-mentioned meta-analysis, the ES for both pain relief (0.23; 95% CI: 0.13–0.34) and changes in overall WOMAC index (0.16; 95% CI: 0.06–0.28)[9] were very similar to those reported by Zhang et al.[5]

Numerous studies have shown the efficacy of oral NSAIDs in the management of symptomatic OA. A meta-analysis of published randomized placebo-controlled trials concluded that NSAIDs—including coxibs—can reduce pain and functional disability in knee OA better than placebo (ES: 0.32, 95% CI: 0.24–0.39, and 0.29, 95% CI: 0.18–0.40, respectively).[6] However, the current analysis did not support the long-term use of NSAIDs for this condition.[6] NSAIDs might be more effective in hip OA; based on a systematic review of non-aspirin placebo-controlled trials, the ES for pain relief was 0.69 (95% CI: 0.12–1.26).[3]

Taken together, these data indicate that acetaminophen is slightly better than placebo in relieving pain while having limited effects, if any, on other aspects of OA symptomatology, especially disability. On the other hand, oral NSAIDs provide small to moderate beneficial effects on pain as well stiffness and function. Interestingly, the meta-analysis by Zhang et al[5], which included eight trials directly comparing acetaminophen