

# The Role of Acetaminophen in the Treatment of Osteoarthritis

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## Abstract

The major clinical guidelines recommend the use of acetaminophen (acetyl-para-aminophenol [APAP]) for the treatment of mild-to-moderate symptoms of osteoarthritis (OA) and only recommend the use of nonsteroidal anti-inflammatory drugs (NSAIDs) after APAP failure. This recommendation is based on the efficacy of APAP in treating OA and its relatively benign side-effect profile compared with NSAIDs. NSAIDs are associated with a high risk of adverse events, particularly those of the gastrointestinal (GI) tract. A large number of studies in OA have compared APAP with a variety of selective and nonselective NSAIDs and typically found greater efficacy with NSAIDs. This advantage, however, is mainly the result of increased efficacy in patients with more severe disease, and is viewed as a relatively small analgesic advantage in some studies and meta-analyses. Many of these same studies have reported little or no difference in safety between APAP and NSAIDs, but these results are typically based on short-term studies. Results from meta-analyses on the safety of NSAIDs almost unanimously confirm elevated risk of GI complications. The analgesic mechanism of APAP is still not well understood. However, the notion that APAP has no anti-inflammatory effect has been challenged in recent years with increasing data that suggest it may have an effect on inflammation distinct from that seen with NSAIDs. A variety of mechanistic hypotheses have been proposed.

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## Introduction

There has been an ongoing struggle to understand and to compare acetaminophen (acetyl-para-aminophenol [APAP]) with nonsteroidal anti-inflammatory drugs (NSAIDs), both selective and nonselective, in the symptomatic treatment of osteoarthritis (OA). Within these larger debates are 2 central questions that are often revisited. First, how does APAP compare with NSAIDs for the symptomatic relief of OA? Second, are concerns regarding the safety and tolerability of NSAIDs sufficient to recommend APAP as an initial treatment in OA?

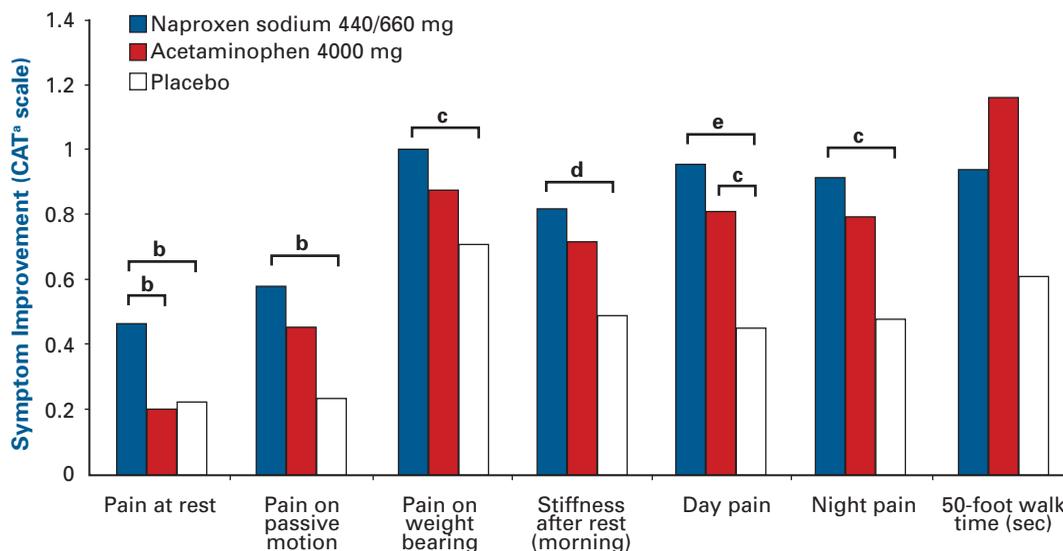
The major clinical guidelines—including those created by the American College of Rheumatology, European League Against Rheumatism (EULAR), Osteoarthritis Research Society International, and the United Kingdom's National Institute for Health and Clinical Excellence—favor APAP, recommending it as the first choice for mild-to-moderate OA-related pain because of its safety and effectiveness.<sup>1-5</sup> The EULAR guidelines additionally state that if APAP treatment is successful, it should be used for long-term analgesia.<sup>3,4</sup> The guidelines further recommend that if APAP fails, NSAIDs should be given at the lowest effective dose to avoid or reduce side effects.<sup>1-5</sup>

Complicating the question of the precise roles of APAP and NSAIDs in the treatment of OA is the fact that OA itself is a rather complex disease. An understanding of the mechanism related to the efficacy of symptomatic treatments for OA, as well as a deeper understanding of OA itself, have occurred in the realm of inflammatory processes (among other aspects of OA). That is, the role of inflammation in OA is now better understood and more prominent in the accepted model of the disease process. Previous assumptions about the anti-inflammatory activity of APAP, or lack thereof, have also evolved and been challenged in recent years.

## Efficacy and Safety Studies of Acetaminophen and NSAIDs

In a milestone study from 1991, Bradley and colleagues found that in the symptomatic treatment of knee OA, APAP 4000 mg/day was comparable to ibuprofen at both an “analgesic dose” (1200 mg/day) and an “anti-inflammatory dose” (2400 mg/day).<sup>6</sup> Since then, numerous studies have compared APAP with various NSAIDs in OA, more often than not for knee OA, and the results generally support that NSAIDs provide greater pain relief than APAP.<sup>7-11</sup>

■ **Figure 1.** Comparative Effects on 7 Symptom Domains for Naproxen Versus Acetaminophen Versus Placebo Over a Period of 7 Days<sup>12D</sup>



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\*CAT; 5-point categorical scale (0-4).

<sup>b</sup> $P < .05$ .

<sup>c</sup> $P < .01$ .

<sup>d</sup> $P = .01$ .

<sup>e</sup> $P < .0001$ .

Moreover, a substantial portion of these individual studies have observed little difference with regard to safety and tolerability among NSAIDs and APAP.<sup>7,8,12</sup> Before describing the inherent problem with these safety results, it is worth noting that several key meta-analyses have come to very different conclusions. For example, a meta-analysis by Zhang et al compared APAP to NSAIDs in OA and found that while efficacy was greater with NSAIDs, gastrointestinal (GI)-related safety issues were also significantly greater with NSAIDs.<sup>9</sup> Furthermore, a 2006 Cochrane review of APAP in OA determined that NSAIDs were more effective than APAP for pain relief, but the magnitude of the difference in treatment effect was “small to modest.”<sup>13</sup> Because the median length of the reviewed studies was only 6 weeks, the safety and tolerability data derived from them for comparative purposes was of limited practical utility since the medications in question are not generally confined to short-term use.<sup>13</sup>

An illustrative example of the limitations of safety data from short-term trials is the 2 VACT (Vioxx, Acetaminophen, Celecoxib Trial) studies. The cyclooxygenase (COX)-2 inhibitors, rofecoxib and celecoxib, demonstrated greater efficacy in knee OA compared with APAP, but no significant differences in the incidence of adverse events (AEs) were observed between the treatment groups.<sup>7</sup> It should be noted that this 6-week study was published approximately 9 months

after rofecoxib was withdrawn from the market due to increased risk of cardiovascular events with long-term use.

Several other studies produced results inconsistent with those from the preponderance of APAP versus NSAID studies. For example, in a 12-week study by Case et al that compared APAP, diclofenac sodium, and placebo in knee OA, not only was the NSAID superior to APAP for symptomatic treatment, APAP was no better than placebo.<sup>10</sup> However, the study population included only 25 patients in the diclofenac group, 29 in the APAP group, and 28 in the placebo group. The authors stated that the study was sufficiently powered to reach their conclusion about APAP, although they acknowledged that subset analysis—to determine which patients responded better among individual treatments—was not possible due to the limited number of patients in the study.<sup>10</sup>

The results of this study were similar to an earlier and larger crossover study by Pincus et al, which compared diclofenac plus misoprostol (for the prevention of GI side effects) with APAP in 218 patients with knee OA. That study found that 57% of subjects preferred treatment with diclofenac/misoprostol, 20% preferred APAP, and 20% had no preference.<sup>11</sup> Consistent with clinical guidelines recommending APAP in mild and moderate OA, a subgroup analysis of patients in the Pincus study found that the greatest difference in efficacy occurred among patients with more

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severe OA, and minimal differences were seen in patients with a milder form of the disease.<sup>11</sup> It should be noted that significantly more patients given diclofenac and misoprostol experienced AEs, particularly GI AEs, compared with patients receiving APAP.<sup>11</sup> For individual GI AEs, significantly more patients in the diclofenac and misoprostol group experienced abdominal pain and abnormal serum glutamic oxaloacetic transaminase levels compared with those given APAP.<sup>11</sup> The incidence of dyspepsia was similar among the 2 treatment groups.

Other studies of APAP compared with placebo have generally found APAP to be superior. Pooled results from 2 identical, multicenter, randomized, double-blind, placebo-controlled studies demonstrated that both APAP and naproxen were better than placebo across 7 symptom domains; naproxen was more effective than APAP; and naproxen, APAP, and placebo had similar safety profiles (although the studies were only 7 days in duration)<sup>12</sup> (Figure 1). Neither patient nor investigator evaluations, however, were significantly different regarding the efficacy of naproxen compared with APAP, but both treatments were rated significantly better than placebo by both patients and investigators.<sup>12</sup> In a 7-day study in knee and hip OA, APAP was preferred nearly 2 to 1 over placebo.<sup>14</sup> In 2004, Pincus et al published results from 2 identical, randomized, double-blind, placebo-controlled, crossover clinical trials in patients with hip and knee OA that compared APAP, celecoxib, and placebo.<sup>15</sup> Pain, as measured by visual analog scores, was not significantly different between APAP and celecoxib in the first study. APAP and celecoxib were both superior to placebo. In the second study, celecoxib was significantly superior to both APAP and placebo, and APAP was not significantly better than placebo.<sup>15</sup> Patients preferred celecoxib, followed by APAP, and then placebo. In a 6-week, double-blind, parallel-group, placebo-controlled trial, APAP was compared with placebo in patients with knee OA. No significant differences in pain intensity were observed between patient groups; however, both APAP and placebo produced significant reductions in pain.<sup>16</sup>

There is some evidence to suggest that APAP confers some risk of GI side effects, particularly at higher doses (approximately  $\geq 2600$  mg/day) and in people predisposed to GI dysfunction. Those taking lower daily doses of APAP experienced significantly fewer GI side effects.<sup>17,18</sup> In a meta-analysis using data from 10 randomized controlled trials with APAP, the safety risk associated with APAP was equivalent to that of placebo.<sup>9</sup>

Some data in animal models shows a potentially harmful effect of APAP on gastric mucosa, whereas other animal studies point to a neutral or even protective effect.<sup>19-21</sup> Rat studies

suggest that the risk of mucosal damage with APAP increases with the presence of several related risk factors, specifically inflammatory disease, hyperacidity, and vagal stimulation; the risk of mucosal damage diminishes or disappears when 1 or more of these risk factors is not present.<sup>22</sup> Additional research is required to further clarify this association.

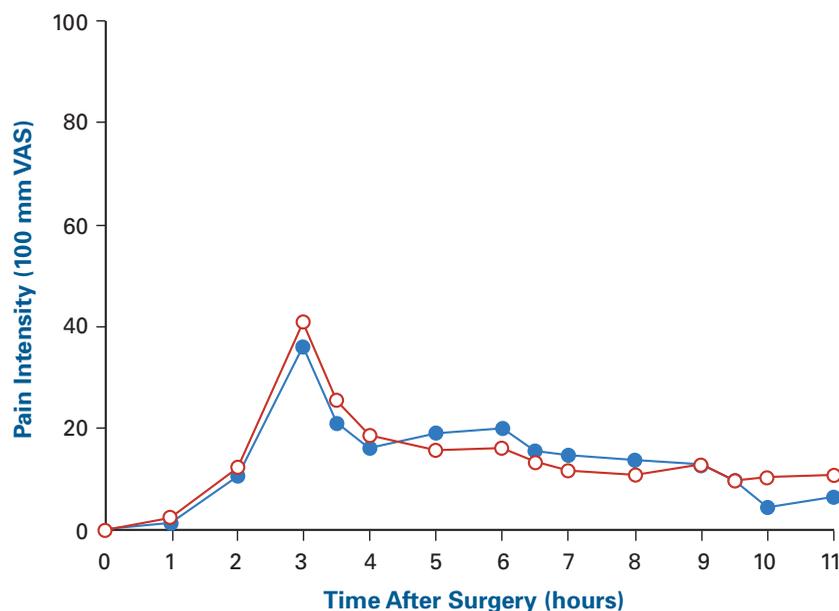
A 2007 analysis of data from the Health Professional's Follow-Up study found that frequent analgesic use—whether with NSAIDs or APAP—is associated with an increased risk for hypertension in male subjects.<sup>23</sup> APAP, when taken 6 or 7 days a week, significantly increased the risk of hypertension. In contrast, data show an increased risk of hypotension in critically ill and febrile patients receiving APAP or its prodrug propacetamol.<sup>24,25</sup>

Several studies of imperfect design have pointed to an increased risk of renal complications with long-term APAP use. In a case-control study, Fore et al observed an elevated risk of exacerbation of chronic renal failure with APAP use.<sup>26,27</sup> A cohort study using data from the Physicians' Health Study, which lasted from 1982 to 1995 and included more than 11,000 subjects, evaluated the risk of elevated creatinine and reduced creatinine clearance among people taking APAP, aspirin, and other NSAIDs. The investigators found that APAP was associated with the lowest risk of renal dysfunction, compared with aspirin and other NSAIDs (which had the highest risk), although none of the relative risk calculations approached statistical significance.<sup>28</sup> In fact, APAP use was associated with a slight, but statistically significant reduction in both the risk of creatinine elevation and reduced creatinine clearance compared with no APAP use. These associations were not observed for aspirin or NSAIDs.

With regard to NSAIDs, the safety picture is quite different. While studies of safety and tolerability are far too numerous to describe in detail here, the widespread perception that NSAID use is associated with a clinically meaningful risk of side effects is well supported by the medical literature. A number of meta-analyses on the risk of side effects with NSAIDs have generally come to the same conclusions: the risk of GI perforation, ulcers, and bleeding is high with NSAIDs, particularly with sustained use and at higher doses.<sup>29-32</sup> Lower doses of over-the-counter (OTC) formulations of NSAIDs are generally safer than the higher doses of prescription NSAIDs, but this difference disappears when OTC formulations are taken at prescription doses.<sup>29</sup>

Prostaglandin analogs, H<sub>2</sub>-receptor antagonists, and proton pump inhibitors have been shown to be somewhat effective in reducing the risk of GI complications associated with

■ **Figure 2.** Mean Pain Intensity Scores of Patients Having Bilaterally Impacted Third Molars Removed on 2 Separate Occasions, Treated Once With Acetaminophen and Once With Ibuprofen<sup>37</sup>



Evaluation of pain was based on the visual analog scale (VAS) reported by 36 patients on the day of surgery for both interventions. For one surgery they received acetaminophen (●) 1000 mg 4 times a day for 3 days. For the other surgery they received ibuprofen (○) 600 mg 4 times a day for 3 days. Reprinted with permission from Björnsson GA, et al. *Br J Clin Pharmacol.* 2003;55:405-412.

NSAIDs, but they do not entirely solve the problem. Two meta-analyses found that use of these add-on agents did have a preventive effect on reducing the risk of GI side effects, specifically ulcers.<sup>33,34</sup> With regard to ulcer complications related to NSAID use, the only reliable studies have been with misoprostol. Although misoprostol has been shown to reduce the risk of ulcers, it is associated with significant side effects, such as diarrhea and nausea, particularly at higher doses.

### Potential Analgesic Effects of Acetaminophen Treatment

In the 1991 study by Bradley et al, APAP demonstrated equivalent efficacy to both a high “anti-inflammatory” dose and a low “analgesic” dose of ibuprofen in knee OA. A subsequent analysis of data from that study provided some revealing context regarding analgesia. The authors examined the impact of inflammation in these patients upon relief of symptoms. They found that reduction in the signs of joint inflammation was similar among the 3 treatment groups and associated with less disability and pain at rest, but that better outcomes were not more or less prevalent in any of the 3 treatment groups.<sup>35</sup> Thus, they concluded at the time, that reducing these anti-inflammatory signs did not necessarily

require the use of an anti-inflammatory agent rather than a “pure analgesic.” This rather counterintuitive conclusion assumed that only the higher-dose ibuprofen had constituted a truly anti-inflammatory agent, a conclusion that would later come under closer scrutiny.<sup>35</sup>

Fourteen years later, in 2006, Brandt et al published data from 2 uncontrolled pilot studies (combined N = 30) that evaluated the effect of APAP and NSAIDs on synovial inflammation, the presumed site of most OA-related pain. Data from these studies showed equivalent effects of APAP and NSAIDs on effusion volume and synovial tissue volume.<sup>36</sup> While these studies were too small to be anything more than suggestive themselves, they do point to the possibility that APAP has a significant effect on inflammation or the reaction to inflammation. This notion is supported by several dental surgery studies, which show that APAP is equivalent to NSAIDs in the reduction of both swelling and pain, and is superior to placebo (Figure 2 and Table).<sup>37-39</sup>

Ultimately, the mechanism by which APAP produces analgesic effects is not well understood. The current view assumes a lack of inflammatory effect by APAP and the potential for weak effects on COX enzymes, although different from that of NSAIDs. It has been speculated that APAP

■ **Table.** Postoperative Swelling<sup>a</sup> (in mm; mean [SD]) After Treatment With Acetaminophen 1000 mg 4 Times a Day for 3 Days and Ibuprofen 4 Times a Day for 3 Days<sup>37</sup>

Days After Surgery	Acetaminophen	Ibuprofen	Difference (95% Confidence Interval)	n
3	18.4 (10.7)	18.4 (14.4)	-0.3 (-4.7, 4.1)	36
6	3.1 (4.6)	2.9 (6.2)	0.2 (-2.4, 2.8)	36

<sup>a</sup>Swelling measured on days 3 and 6 following bilateral third molar surgery. Reprinted with permission from Björnsson GA, et al. *Br J Clin Pharmacol.* 2003;55:405-412.

may inhibit a COX variant, COX-3, an enzyme possessing properties in common with both COX-1 and COX-2, but distinct from either.<sup>40</sup> Subsequent animal study data, however, suggest that COX-3 is probably not relevant to the action of APAP; if anything, APAP appears to have an effect on COX-2, although this activity remains to be fully elucidated.<sup>41</sup>

It is generally accepted that the analgesic activity of APAP occurs via its effect on the central nervous system.<sup>42</sup> Inflammation now assumes a larger role in OA than previously believed, although its role is not clearly understood.<sup>43</sup> The hypotheses that have been generated to explain inflammatory action in OA, as well as the potential analgesic effects of APAP, are too numerous to describe here. What follows is a selection of several possible mechanisms to explain the efficacy of APAP in OA.

- **Nitric Oxide.** Nitric oxide (NO) is associated with inflammation in OA, and OA cartilage produces a high level of NO via elevated upregulation of inducible NO synthase.<sup>43,44</sup> NO is implicated in cartilage catabolism through its inhibition of cartilage matrix macromolecules.<sup>45,46</sup> Furthermore, NO has been shown to enhance matrix metalloproteinase (MMP), which is implicated in articular cartilage fibrillation of OA joints.<sup>47</sup> At the same time, the synthesis of interleukin (IL)-1Ra, which inhibits catabolic pathways in OA, is reduced by NO.<sup>47</sup> The assumed efficacy of APAP, in this regard, is related to APAP's capacity to interfere with central NO mechanisms at the spine.<sup>48</sup> The result of this interference is reduced nociception associated with spinal *N*-methyl-*D*-aspartic acid and substance P receptor activation.
- **Substance P.** Although the role of substance P in pain mechanisms is not entirely clear, there is evidence to suggest a dual mechanism comprising both analgesia and a lowering of pain thresholds.<sup>48</sup> Substance P is also implicat-

ed in the pathogenesis of OA—it mediates inflammatory processes and is present in excess quantity in damaged articular cartilage in patients with OA.<sup>47</sup> APAP has been shown to block pain behavior in rats after activation of substance P receptors.<sup>48</sup>

- **Beta-endorphin.** Beta-endorphin is an opioid peptide, endogenously produced, which has analgesic effects similar to morphine.<sup>49</sup> Beta-endorphin inhibits production of inflammatory cytokines tumor necrosis factor- $\alpha$  and IL-1 $\beta$  as well as MMPs.<sup>50</sup> A study comparing APAP with rofecoxib in patients with knee OA found that while both treatments reduced pain, pain reduction with APAP was correlated with a reduction in beta-endorphin plasma levels, but rofecoxib was not.<sup>49</sup>

### Conclusions

The comparative efficacy of APAP and NSAIDs for the symptomatic treatment of OA tends to favor NSAIDs, although this appears to be an effect of greater efficacy in patients with more severe symptoms. APAP is associated with a low rate of AEs. The rate of AEs is much higher with NSAIDs, but can be partly, yet not entirely, ameliorated by agents that reduce GI complications. Consequently, the major clinical treatment guidelines for OA recommend APAP as the initial treatment for those with mild-to-moderate pain, both for its efficacy and safety. Whereas the analgesic mechanism of APAP has yet to be elucidated, the assumption that APAP lacks an anti-inflammatory effect is challenged by various, albeit inconclusive, data. These data point to the possibility that the inflammatory process in OA is more complex than previously understood. Although APAP may not possess an inflammatory effect analogous to that of NSAIDs, it may possess one by different means.

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