

Pain Relief in Osteoarthritis: The Rationale for Combination Therapy



Osteoarthritis (OA) affects 21 million people in the United States¹ and is a major public health problem, especially among those over age 65. The economic burden in the United States exceeds the gross national product of most countries. Although pain is the most pressing problem facing people with OA¹, adequate pain relief is frequently not achieved. One could argue that this undertreatment of pain is related to (a) lack of professional medical attention, (b) failure to incorporate nonpharmacological measures such as weight loss and exercise into the treatment plan, and (c) overreliance on monotherapy.

Lack of Professional Medical Attention

Data published by the US Centers for Disease Control and Prevention (CDC) in 1998 highlight the scope of underdiagnosis. According to this CDC survey, only 61% of people with any kind of arthritis have ever been diagnosed by a physician². Many people never seek medical attention, even when arthritis has progressed to the point of limiting daily activities¹. Those who do not seek medical care are left to their own devices regarding appropriate analgesic choices^{1,3}. The chasm that separates a large number of OA sufferers from the medical community could be addressed through health education initiatives that inform the public about the signs, symptoms, and management of OA and encourage those with chronic joint pain to consult a physician.

Failure to Incorporate Nonpharmacological Measures into the Treatment Plan

On a population-wide basis, arthritis limits activity more than any other health condition, including cardiovascular disease, blindness, or diabetes⁴. There is a dynamic interrelationship between activity and joint pain in OA: pain can affect a person's willingness and ability to engage in physical activity, and inactivity can hasten the disability and exacerbate the joint pain associated with OA. For these reasons, nonpharmacological therapy, including education,

communication, weight control (as appropriate), orthotics and exercise, is essential. However, to date, adoption of these measures is often suboptimal⁵.

Overreliance on Monotherapy

Medications widely used to treat OA pain, including analgesics (e.g., acetaminophen, tramadol, capsaicin, narcotics and their derivatives, intraarticular hyaluronates) and antiinflammatory agents [e.g., nonselective nonsteroidal antiinflammatory drugs (NSAID), cyclooxygenase-2-specific (COX-2-specific) inhibitors, intraarticular depo-corticosteroids] have demonstrated efficacy over placebo⁵. In addition, all have at least some data showing improvement in physical function. Publication of clinical trials describing improvement in pain and function indicate that professional journal editors considered the findings noteworthy. But what about the patients? Are the results — in terms of pain relief and physical function — so robust that we can extrapolate with confidence to the patients we see in clinical practice? Will our patients be satisfied with the influence of treatment? One of the striking findings from the OA literature is that for a substantial percentage of patients, analgesic monotherapy does not provide adequate, much less complete, relief of joint symptoms. Many OA sufferers continue to experience significant pain while taking COX-2-specific NSAID; the same is true for patients taking nonspecific NSAID or acetaminophen⁶⁻⁹.

Without specific guidance from health professionals, patients experiencing persistent or periodic (breakthrough) OA pain while on monotherapy will do what seems appropriate to achieve adequate pain relief. These measures often involve taking increased or additional doses of an NSAID, or concomitant use of more than one NSAID, placing these patients at risk for NSAID-related adverse effects, such as gastropathy^{7,9,10}. They may unknowingly take a number of different products containing acetaminophen, placing them at risk for hepatic injury if they consume more than the

*See Efficacy and safety of tramadol/acetaminophen tablets as add-on therapy for
OA pain in subjects receiving a COX-2 NSAID, page 150*

maximum recommended dose of 4 g/day. Considering the prevalence of OA and the frequency of inadequate pain relief with initial therapy, it is reasonable to suspect that NSAID combinations and inadvertent analgesic overdosing caused by self-medication contribute to morbidity and mortality. While the risk of adverse events involving the gastrointestinal (GI) tract is reduced with COX-2-specific inhibitors, it is not completely eliminated. Moreover, this relative safety benefit is eliminated if a patient reaches for a familiar NSAID (prescription or over-the-counter) to treat breakthrough pain^{8,11}.

Combination therapy — employing agents with complementary mechanisms of action — has the potential to benefit patients suffering from OA pain. Acetaminophen, tramadol, opiates, and NSAID differ in their mechanism of action. Use of these agents in combination can potentially provide additive efficacy by modulating neuronal activity at more than one site along pain-processing pathways.

In this issue of *The Journal*, Emkey and colleagues provide evidence supporting the efficacy of combination therapy for pain related to OA¹². This randomized, placebo-controlled trial evaluated the effect of adding tramadol (37.5 mg)/acetaminophen (325 mg) (Ultracet[®]) to therapy with a COX-2 inhibitor in 307 patients with OA whose pain was not adequately controlled by the COX-2 inhibitor (either rofecoxib or celecoxib). Significant improvements in visual analog scale scores for pain relief were found among patients taking combination tramadol/acetaminophen/COX-2 inhibitor compared to those taking placebo plus COX-2 inhibitors ($p = 0.002$). The treatment group also had significant improvements in WOMAC OA Index physical function ($p = 0.049$) and the Medical Outcome Study Short Form-36 role-physical measures ($p = 0.010$). These findings are consistent with results reported by Silverfield and colleagues showing that tramadol plus acetaminophen was an effective adjunct to nonselective NSAID or COX-2 inhibitors for patients with poorly controlled OA pain¹³.

In terms of tolerability, tramadol offers advantages over opiates such as codeine, propoxyphene, oxycodone, and hydrocodone. However, it is worth noting that in the study by Emkey and colleagues rates of many adverse events were significantly higher in the tramadol/acetaminophen/COX-2 group in contrast to the placebo/COX-2 group: somnolence (6.5%/0.7%), nausea (4.6%/0.7%), constipation (3.3%/0.0%), fatigue (2.6%/0.0%), and vomiting (1.3%/0.0%)¹². It is suggested that these GI and central nervous system-related adverse effects are more likely to result from use of opiate-like tramadol than from use of acetaminophen. The overall effect of these adverse events was relatively minor — 13% of tramadol/acetaminophen patients discontinued treatment due to adverse events in contrast to 4% of those taking placebo. Still, since one objective with any pharmacological intervention is to maximize the benefit-to-risk ratio, is it reasonable to ask what treatment benefits might be obtained

from the simple addition of acetaminophen to an NSAID (COX-2-specific or otherwise)?

Survey data from people with OA indicate that this type of combination drug therapy is common practice: 30% of patients with OA report concurrent usage of acetaminophen and either ibuprofen, naproxen, or diclofenac⁷. However, there is a paucity of published data evaluating combination therapy with NSAID/acetaminophen or COX-2/acetaminophen. In patients receiving naproxen (0.5 g/day) for relief of pain associated with OA of the hip, the addition of acetaminophen (4 g/day) resulted in a significant ($p = 0.001$) reduction in overall pain and in pain during movement or at rest versus treatment with naproxen alone¹⁴. The analgesic effect of naproxen (0.5 g/day) combined with acetaminophen (4 g/day) was comparable to that achieved with 1 g/day of naproxen as a single agent, but was associated with a lower incidence of GI complaints. Similarly, combination therapy with acetaminophen and naproxen has been shown to shift the dose-response curve for naproxen to the left on measures of pain, joint index, and global effect in patients with rheumatoid arthritis, implying a dose-sparing effect¹⁵. These studies, while limited, indicate the potential for enhanced efficacy and safety from the combination of an analgesic and an NSAID.

The need for effective pain relief with a low risk of adverse effects for individuals with OA is undisputed. We know that many analgesics “work” to relieve OA pain. But how often do these agents work well enough to get our patients moving again? And what is the optimal treatment strategy for patients in whom monotherapy proves to be inadequate? In asking whether an analgesic (e.g., acetaminophen) is better or worse than an NSAID, are we focusing on the wrong question? Should the combination of analgesics be considered more often? Emkey and colleagues have provided us with valuable data on what to expect when adding tramadol/acetaminophen when COX-2 therapy is not adequate. These are the type of data we need to confront the clinical realities of OA management. Similar studies on the safety and efficacy of other variations of combination therapy will enhance our ability to provide more optimal pharmacological management of the pain of OA.

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