

## Pain Treatment in Arthritis-Related Pain: Beyond NSAIDs

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**Abstract:** Managing pain from chronic conditions, such as, but not limited to, osteoarthritis and rheumatoid arthritis, requires the clinician to balance the need for effective analgesia against safety risks associated with analgesic agents. Osteoarthritis and rheumatoid arthritis pain is incompletely understood but involves both nociceptive and non-nociceptive mechanisms, including neuropathic mechanisms. Prevailing guidelines for arthritis-related pain do not differentiate between nociceptive and non-nociceptive pain, sometimes leading to recommendations that do not fully address the nature of pain. NSAIDs are effective in treating the nociceptive arthritis-related pain. However, safety concerns of NSAIDs may cause clinicians to undertreat arthritis-related pain. In this context, combination therapy may be more appropriate to manage the different pain mechanisms involved. A panel convened in November 2010 found that among the currently recommended analgesic products for arthritis-related pain, fixed-low-dose combination products hold promise for pain control because such products allow lower doses of individual agents resulting in decreased toxicity and acceptable efficacy due to synergy between the individual drugs. Better evidence and recommendations are required to improve treatment of chronic arthritis-related pain.

**Keywords:** Osteoarthritis, rheumatoid arthritis, analgesia, fixed-dose combination products, NSAID, paracetamol, tramadol.

### INTRODUCTION

Osteoarthritis (OA) and rheumatoid arthritis (RA) cause chronic pain, which may involve nociceptive as well as non-nociceptive components, including neuropathic components, due to peripheral inflammation and central sensitization [1, 2]. Despite our modern wealth of analgesic options, managing moderate to severe chronic pain remains clinically challenging for several reasons. These reasons include: the heterogeneity of the patient populations, the progressive nature of the disorders, the multiple pain mechanisms involved, the presence of comorbidities and co-medication in predominantly frail and elderly patients, and the efficacy and safety profiles of available pain medications [3]. OA and RA patients frequently require lifelong pain management regimens, ruling out those pharmacological therapies effective for acute pain but inappropriate for long-term use.

In fact, many analgesic agents carry a substantial degree of risk, which has created barriers in pain management, in that clinicians may undertreat pain in an effort to enhance patient safety and minimize potential side effects [4]. Since chronic pain itself is associated with considerable mortality [5-7], public health organizations today view effective analgesia as a fundamental human right [8-10]. **Not treating pain is not an option.**

### ISSUES IN OA PAIN

OA is a prevalent disorder characterized by the progressive destruction of articular cartilage associated with subchondral bone remodeling, formation of osteophytes, and secondary inflammation of synovial membranes [11, 12]. Its principal symptom is pain, which is mediated by a number of factors. Amongst others, innervation and vascularisation of the articular cartilage may be involved, and compressive forces and hypoxia may stimulate these new nerves, causing pain even after inflammation has subsided [13]. Innervation of the joint tissue and angiogenesis have been described as main pathophysiological pathways causing the deep joint

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pain described by some OA patients [13, 14]. The pain of OA includes both nociceptive and non-nociceptive components and is associated with abnormally excitable pain pathways in the peripheral and central nervous systems [15, 16]. Quantitative sensory testing in OA patients reveals that OA patients have lower thresholds for mechanical and thermal pain than healthy controls [1, 17] and increased sensitivity to pressure, ischemia, and innocuous stimuli [18]. OA patients were shown to have lower pain thresholds than control subjects at the forehead, a non-painful area of the body unaffected by OA [19]. Such findings suggest that OA pain is also centrally mediated [20]. Functional magnetic resonance imaging (fMRI) studies have identified several brain regions involved in OA pain processing, indicating the complexity of OA pain mechanisms [21].

OA is prevalent in the global geriatric population [22]. In general, long-term analgesia is challenging in the elderly, a challenge not always addressed in the literature or guidelines. Since few randomized clinical trials enroll geriatric patients, and even fewer enroll elderly patients of diverse races and ethnicities, there are limited data available in the literature for this particular population. Furthermore, elderly patients often have comorbidities, which may increase the risk of drug-drug interactions and limit the range of drugs to be used. Age-associated differences in drug sensitivities should be considered when treating older patients [23], although the heterogeneous nature of the geriatric OA population precludes clear-cut uniform guidelines for all elderly OA patients. Opioids have been shown to be effective in the elderly, but must be used under close clinical supervision [24].

### ISSUES IN RA PAIN

RA is a progressive disorder characterized by periods when the disease is active punctuated by periods of remission. Patients may suffer persistent or intermittent pain, which can be moderate to severe. RA is an inflammatory disease that causes destruction of cartilage and underlying bone. Since the joint capsule and synovium are densely innervated, pain can be intense and may be triggered by even gentle stimulation or slight movement of the affected joint [25]. The local inflammatory response is mediated by the immune system along with resident non-immune cells (synovial fibroblasts). Local inflammation triggers the release of multiple factors, including pro-inflammatory cytokines, histamines, bradykinins, serotonin, prostaglandin E<sub>2</sub>, and others. Peripheral nociceptors become sensitized owing to the altered cytokine balance. Cellular cascades initiate central sensitization [25]. RA patients have lower thresholds for pressure pain than healthy controls, further suggesting altered central pain processing [26, 27]. Enhanced cortical responses to noxious stimuli in RA patients suggest cellular changes affecting pain-processing signals [28]. Peripheral sensitization, central sensitization, and inflammation interact in RA patients in ways not yet completely understood.

### MEETING DETAILS

In November 2010, a panel convened in Paris, France, to discuss the management of moderate to severe pain from

different etiologies with special emphasis on NSAIDs, paracetamol and fixed-dose combination products. Following presentations by several authors of this article, all authors discussed and reviewed pain management and available guidelines/recommendations based on their own clinical experiences. Their final consensus on pain management for the indications osteoarthritis and rheumatoid arthritis is summarized in this publication and incorporates additional articles which were deemed relevant in discussions during the draft stages.

### CURRENT ANALGESICS USED TO TREAT ARTHRITIS-RELATED PAIN

The focus of rheumatology is the best possible patient care and management of disease-related pain and impact on the patient by understanding the underlying pathophysiological aspects of this inflammatory disease process. Greater understanding of pain mechanisms and growing appreciation for pain control have, however, caused rheumatologists to consider new approaches in pain management. Whereas central pain mechanisms are increasingly addressed in the pharmacological therapy for fibromyalgia patients, it is less clear how to manage the centralized pain processes in OA and RA patient populations. Therefore, it has been proposed that clinicians change the concept of pain control in arthritis-related pain to one of "pain-modifying analgesic drugs" [29]. The following drugs are the main categories of pharmacological agents used for pain control in OA and RA patients. It should be noted that all treatment options may be combined with nonpharmacological approaches.

#### Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Both selective and nonselective cyclooxygenase (COX) inhibitors have antipyretic, anti-inflammatory and analgesic effects and are widely used in treating many painful conditions, including rheumatic diseases [30]. NSAIDs are effective and widely available in over-the-counter formulations and in prescription products. Examples include ibuprofen, naproxen, diclofenac, and celecoxib. NSAIDs are frequently used without considering the relative contraindications since most NSAIDs are sold over the counter [31]. Conventional NSAIDs are associated with gastrointestinal (GI) side effects [32]. Estimates of the number of deaths from NSAID-related gastrointestinal bleeding vary widely and figures of approx. 3500 to 16,500 per year are quoted for the US in a recent FDA report [33]. Both conventional NSAIDs and COX-2 inhibitors are associated with increased cardiovascular risk [34-37]. NSAIDs may increase blood pressure [38], particularly in hypertensive patients [39]. Of all NSAIDs, naproxen seems to pose the least cardiovascular risk [37, 40], although naproxen is associated with the same risk for myocardial infarction as other NSAIDs [35].

Contrary to some clinical assumptions, gastrointestinal risk is present at first dose with a non-selective NSAID, and co-therapy with a proton pump inhibitor (PPI) does not guarantee complete protection [41]. COX-2 selective NSAIDs, especially in combination with a PPI, provide prophylaxis against NSAID gastropathy [42]. The incidence

and severity of gastrointestinal adverse events associated with NSAID therapy increases with advancing age, limiting their clinical utility in the geriatric population, particularly in concomitant use with low-dose aspirin, taken by many elderly patients for cardioprotection [43, 44]. NSAIDs should be used at the lowest effective dose for the shortest possible period of time in chronic pain populations. In addition to the above mentioned risks, NSAIDs may interact with many other medicinal products [45-48] and special caution and close monitoring is recommended in particular for elderly patients and patients with a history or symptoms indicative of gastrointestinal disorders, patients with renal, cardiac or hepatic impairment, a history of hypertension, asthma, seasonal allergic rhinitis, systemic lupus erythematosus (SLE) and mixed connective tissue disorders [45-48]. Very rarely serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported in association with the use of NSAIDs [45-48]. Accumulated toxicity and the above-mentioned potential risks are the main reasons that there are no suitable agents for long-term treatment [49, 50].

### Paracetamol

The antipyretic and analgesic effects of paracetamol (acetaminophen or APAP) have been known since the late 19th century. It is often considered a first-line approach to pain management [51], although there is a risk of hepatotoxicity at high doses. Even at recommended therapeutic doses of paracetamol up to 4 g/d, otherwise healthy adults can exhibit abnormally high levels of aminotransferase [52]. Although high doses of paracetamol are known to be toxic, such supratherapeutic doses of paracetamol are sometimes prescribed and dispensed [53]. Paracetamol is widely available over the counter and in prescription products and many combination products contain paracetamol, but patients may equate the drug's familiarity with safety and wrongly consider it more or less harmless. Twelve percent of patients believe that it is not possible to ingest a toxic dose of paracetamol [54]. Furthermore, even patients who understand the potential toxicity of paracetamol may be unaware that it is found in a wide range of over-the-counter products from cold medicines to headache remedies. Patients taking such over-the-counter products may be unaware of "hidden paracetamol" in such products and unaware of the risk of high cumulative doses [54].

Paracetamol was shown in one study to significantly increase blood pressure in ambulatory patients with coronary artery disease [55]. The frequency of use of paracetamol has been independently associated with a moderately increased risk of hypertension in men [56]. There is some evidence in the literature to suggest that paracetamol may have an anti-inflammatory effect in patients with OA of the knee [57]. Although earlier reports describe paracetamol as having no or minimal anti-inflammatory effects, increasing reports suggest, that in addition, it may have a beneficial effect on inflammation distinct from the anti-inflammatory effects of NSAIDs [58]. Further study in that field is warranted.

### Tramadol

Tramadol is considered a weak opioid on the WHO pain ladder [59]. Due to its differences to other opioids, it will be discussed separately here. Tramadol's analgesic effect derives from a combination of an agonist action at mu-opioid receptors (low affinity of parent drug, much higher affinity of its M1, O-desmethyl, metabolite) and inhibition of neuronal reuptake of serotonin (5-HT, 5-hydroxytryptamine) and norepinephrine [60]. Tramadol has been shown to decrease pain intensity in OA patients and to improve function; active-controlled studies show that tramadol provides analgesic benefits similar to diclofenac and superior to paracetamol [61]. Extended-release formulations of tramadol have been shown effective in treating chronic pain associated with OA as well as offering improvement in pain-related sleep disorders [62].

Tramadol may be associated with a risk of dependence or abuse; the prevalence of abuse/dependence over a 12-month period in patients with chronic non-cancer pain was, however, equivalent for tramadol and NSAIDs, and significantly less than for hydrocodone [63]. In patients prone to convulsive disorders, the risk of convulsions may increase if tramadol is taken concomitantly with medication that lowers the seizure threshold. Some cases of serotonergic syndrome have been reported with the therapeutic use of tramadol in combination with other serotonergic agents such as selective serotonin re-uptake inhibitors (SSRIs) [64]. Recommended dosing should not exceed 400 mg/d, and should be reduced or closely supervised in geriatric patients ( $\geq 75$  years) and those with cirrhosis or renal dysfunction [30]. Tramadol has no known anti-inflammatory effects.

### Opioids

Since 1990, opioids have been recommended in the setting of long-term non-cancer pain syndromes [65]. Growing public health concerns about prescription opioid abuse and particularly about the diversion of prescribed products to the street have focused greater scrutiny on opioid prescribing practices [66-68]. Another concern regarding opioids is the perceived high danger of addiction. Various studies have, however, demonstrated that opioid analgesics for chronic pain conditions are not associated with a major risk for developing dependence [69]. Concern about opioid diversion and misuse has led to the development of so-called abuse-deterrent formulations, as a means for supporting opioid access while limiting abuse and its consequences [70, 71].

Opioids are effective in treating chronic pain [72] but are associated with side effects, including nausea, constipation, and somnolence. Opioids may be appropriate for use in the elderly under close supervision, sometimes at reduced doses [24], or as low-dose transdermal treatment, e.g., buprenorphine [73, 74]. Recently, tapentadol extended-release has shown promise in the treatment of moderate to severe chronic pain related to OA [75, 76].

In summary, clinicians may be cautious in prescribing opioids to treat OA or RA for clinical, legal, or public health reasons [77].

### Tricyclic Antidepressants

Amongst other mechanisms, tricyclic antidepressants (TCAs, e.g. amitriptyline, dothiepin, and imipramine) inhibit serotonin and norepinephrine reuptake and neuronal sodium channels [78]. Various tricyclic TCAs differ with regard to their antinociceptive effects, and the non-serotonergic properties of TCAs are believed to substantially contribute to these differences [79].

TCAs provide significant pain relief in RA patients versus placebo [80-83]. The use of TCAs in arthritis has found such a wide distribution that it has been proposed that these agents along with anticonvulsants should be described as “pain-modifying drugs” [29]. TCAs offer arthritis patients an analgesic benefit apart from their antidepressive effects. It has been speculated that at least part of this benefit relates to improvement of fatigue and sleep disorders [84]. TCAs are associated with certain adverse events, which include sedation, dizziness, blurred vision, constipation, and dry mouth, which can be treatment limiting. Dry mouth can be of particular concern for RA patients with secondary Sjögren’s syndrome [20]. Cardiac toxicity is a concern with TCAs, and the NeuPSIG guidelines (Neuropathic Pain Special Interest Group) recommend prescribing TCAs with caution in patients with ischemic cardiac disease or ventricular conduction abnormalities [85]. Some TCAs, e.g. amitriptyline, are listed on the recently revised Beers list (American Geriatrics Society) of potentially inappropriate medication use in older adults with a strong recommendation to avoid using them because they are highly anticholinergic, sedating, and cause orthostatic hypotension [86]. Since arthritis primarily occurs in the elderly, TCAs are usually not suitable.

### Anticonvulsants

Anticonvulsants, e.g., gabapentin and pregabalin, bind to the  $\alpha_2\delta$  subunit of calcium channels and modulate the release of neurotransmitters, including glutamate, noradrenalin, serotonin, and substance P. As such, these agents may provide analgesic relief for patients with central sensitization. However, the mechanisms of action of these drugs are still poorly understood [87]. While known to be effective analgesics for fibromyalgia, these agents have not been studied in RA and OA populations. Pregabalin was shown in a preclinical study to be effective in reducing pain in an OA model [88]. Both agents are associated with adverse events. In a meta-analysis of pregabalin in adult acute and chronic pain patients, 18% to 28% of participants discontinued the study owing to adverse effects (n=19 studies with 7,003 patients) [89].

### Serotonin Norepinephrine Reuptake Inhibitors

Serotonin norepinephrine reuptake inhibitors (SNRIs), inhibit serotonin and/or norepinephrine reuptake selectively, e.g., duloxetine and milnacipran. Overall, SNRIs are better tolerated than TCAs but may be less effective analgesics; they are not recommended as first-line drugs for analgesia in

RA patients, although they may be useful to manage sleep-related symptoms [84]. A recent study found duloxetine was an effective analgesic in patients with OA of the knee [90].

### Corticosteroids

Due to their potent anti-inflammatory effects, corticosteroids have been shown to be effective adjuvant analgesics in a variety of painful rheumatic conditions, including RA and other autoimmune disorders [91]. Concerns about especially long-term toxicity [92], and adverse events may reduce the clinical utility of these agents for long-term care [23]. According to the NICE guidelines for RA, patients with established RA should only continue long-term treatment with glucocorticoids when the long-term complications of glucocorticoid therapy have been fully discussed, and all other treatment options (including biological drugs) have been offered [49]. Long-term complications of glucocorticoid therapy include glucocorticoid-induced osteoporosis and risk of fracture [93], immunosuppression [94], elevated risk of infections, weight gain, thinning skin, muscle weakness, Cushing’s syndrome, onset of diabetes or worsening of existing diabetes, hypertension, glaucoma, cataracts, and delayed wound healing [95].

### Topical Agents

Topical products, such as lidocaine, diclofenac, capsaicin, and salicylate, allow the patient to obtain localized pain relief. They are mainly used in combination with systemic agents in the treatment of pain associated with rheumatic disease. Topical agents may be analgesic sparing in combination regimens [96]. Side effects include skin irritations, which are typically mild. Topical diclofenac has been reported to be effective in relieving pain caused by OA of the knee [97-99]. Topical 1% diclofenac sodium gel was shown to be an effective analgesic in a study of 385 primary hand OA patients, with about 9% of diclofenac patients experiencing adverse events (compared to 4% in placebo group) and 5% of diclofenac patients discontinuing therapy because of adverse events (2% in placebo group) [100]. In another study of 216 patients with OA of the knee treated with topical diclofenac to manage flares, diclofenac was effective in reducing pain but caused skin irritation in 39% of patients, with 5% choosing to discontinue therapy [101]. Topical NSAIDs do not appear to have gastrointestinal adverse effects typical of oral NSAIDs [102], but long-term studies are warranted to confirm this. OA treatment with topical lidocaine (5% lidocaine medicated plaster) as monotherapy or add-on therapy resulted in significant improvements in pain intensity [103-105], physical function, and stiffness [103]. The use of topical capsaicin in OA is discussed controversially: topical capsaicin is recommended for hand OA but not for knee OA according to the ACR guidelines (American College of Rheumatology) [106], whereas according to a recent review “concerns exist that capsaicin-induced nerve desensitization is not fully reversible and that its autonomic nerve effects may increase the risk of skin ulcers in diabetic patients” [107].

## COMBINATION THERAPIES

The multimechanistic nature of OA, RA and most other chronic pain indications suggests that a multimodal or combination approach to analgesia may be appropriate to manage pain. Combining two analgesic agents may allow for an additive or synergistic effect, which can affect both the drug's analgesic efficacy as well as its side effect profile [108, 109]. Additive effects mean that the effects of both agents are combined. Synergistic effects result in a global effect that is greater than the sum of its parts. It is important to understand that additive and synergistic effects may imply side effects as well as efficacy. Furthermore, additive and synergistic effects may occur, yet fail to be clinically relevant. For these reasons, combination therapy holds promise in theory, but must be carefully evaluated and tested in actual clinical practice.

Fixed-dose combination analgesic products offer certain practical advantages, in that they are convenient, reduce the pill burden, and may allow for lower dosages that might be insufficient if the compounds were taken individually. Fixed-dose combination analgesics should have complementary mechanisms of action and evidence supporting their safety and effectiveness. A drawback to fixed-dose combination analgesic products is inflexibility, in that the doses may not be ideal for the particular patient, and the fact that for continuous pain relief, generally a medication intake several times a day is required.

Paracetamol is often a component of combination products. A potential concern for such products is that they may obscure the patient's cumulative dose of paracetamol (which should not exceed 4 g in healthy adults [110]). Typical combination products with paracetamol include opioid combinations (codeine, tramadol, oxycodone, etc.). These products may be opioid sparing, because they provide effective analgesia at lower opioid doses than opioids taken in monotherapy [111]. Synergistic analgesic benefits have been demonstrated for the fixed dose combination tramadol/paracetamol [112, 113].

The Appendix lists all fixed-dose combination products with paracetamol that have been investigated for OA and RA pain treatment. They include paracetamol + strong opioids (oxycodone), + weak opioids (tramadol, codeine), and + NSAIDs (ibuprofen, etodolac, aceclofenac).

## PAIN CONTROL FOR OA AND RA PATIENTS

Paracetamol is effective in treating certain types of OA. The drug is considered as first-line treatment for mild to moderate pain [114]. However, OA patients often prefer NSAIDs for better pain relief [115]. NSAIDs are targeted therapy for pain management in RA patients, but are not appropriate for long-term disease control [49, 116-118].

Fixed-dose combination products are seldom mentioned in available OA and RA guidelines [49, 50, 116-120]. The NICE guideline initially recommends paracetamol for all OA pain or topical NSAIDs for hand and knee OA ahead of oral NSAIDs, COX-2 inhibitors or opioids [50]. Topical capsaicin should be considered an adjunct to core treatment

for hand and knee OA, and intra-articular corticosteroid injections an adjunct in all OA pain. The OARSI guideline recommends the initial administration of paracetamol for mild to moderate knee or hip OA, and topical NSAIDs and capsaicin as adjuncts or alternatives to oral analgesics in knee OA pain [119]. Weak opioids and narcotic analgesics can be considered for refractory pain but stronger opioids should only be used for severe pain in exceptional circumstances. The evidence presented included fixed-dose combinations of opioids and paracetamol. Both the NICE and OARSI guidelines recommend the use of oral NSAIDs at the lowest effective dose [50, 119]; long-term use should be avoided [119]. The recent ACR recommendations list topical capsaicin, topical NSAIDs, oral NSAIDs (including COX-2 inhibitors) and tramadol for initial pain treatment of hand OA, and advise against intra-articular therapies and opioid analgesics [106]. They recommend a similar approach for knee and hip OA which includes paracetamol, oral NSAIDs, tramadol, and intra-articular corticosteroid injections. Topical NSAIDs are recommended in knee OA (in particular for patients  $\geq 75$  years instead of oral NSAIDs) but there is no recommendation in hip OA. Topical capsaicin is not recommended in knee OA. Opioid analgesics are strongly recommended only in symptomatic knee or hip OA following insufficient response to both nonpharmacological and pharmacological treatments and where patients are not suitable for total joint arthroplasty.

Early use of DMARDs in RA patients is of high importance [121, 122]; however, as pain is a major complaint in these patients, they commonly take analgesics from the very beginning. According to EULAR, symptomatic patients presenting with early arthritis should be treated with NSAIDs after careful evaluation of gastrointestinal, renal, and cardiovascular status [116]. The BSR guideline for long-term RA management recommends a stepped approach with NSAIDs co-prescribed with a proton pump inhibitor in the short term [117]. The NICE guideline suggests analgesics (for example paracetamol, codeine or compound analgesics [=fixed-dose combinations]) to potentially reduce the need for long-term NSAID or COX-2 inhibitor treatment [49].

## PANEL CONSIDERATIONS

The panel reached several general and specific conclusions on pain management for arthritis patients. While patient safety must be paramount, clinicians must address chronic pain associated with OA and RA. Not treating pain is not an option. Pain guidelines must offer clinicians better recommendations by taking into account the impact of pain as well as the multiple mechanisms of RA and OA pain. It is particularly important that clinicians realize that arthritis pain is not limited to nociception, but rather that non-nociceptive, neuropathic, and central mechanisms are also important components of OA and RA pain.

NSAIDs and paracetamol are commonly used, often recommended, and effective agents for the management of pain. However, they are not without potential risks, especially in the elderly and patients with renal,

gastrointestinal, or cardiovascular disease. High doses and long-duration use of NSAIDs to manage moderate to severe pain have been associated with tolerability issues and serious adverse events as well. Their role in the management of the chronic pain associated with OA and RA is thus limited. Higher doses of paracetamol have been associated with liver toxicity, and since paracetamol is a “hidden” ingredient in many over-the-counter products and other combination products, the hepatic injury is of particular concern. Fixed-dose combination products including paracetamol may offer the drug and the combined agent in relatively low doses. Despite such lower-dose paracetamol treatment, patients should be educated in general about the dangers of paracetamol toxicity and cautioned about the amount of paracetamol contained in any combination products they may be prescribed.

Fixed-dose combinations of paracetamol provide a multimechanistic analgesic approach, which may be appropriate to address the pain of OA and RA. Fixed-dose weak opioid/paracetamol combination products have been shown to be effective in managing various types of moderate to severe pain, including the pain of OA and RA, with good tolerability. Tramadol, because of its opioid and nonopioid mechanisms of action, appears to be a promising opioid component in combinations for treating OA and RA pain.

Arthritis-related pain is generally characterized by flares of pain and periods of remission or relatively diminished pain. To manage long-term arthritis pain, a low-dose fixed-dose combination product should be considered as the primary analgesic, providing safe and acceptable multimechanistic pain relief. NSAIDs should only be used to manage acute flares associated with inflammation. This is the reverse of a common treatment regimen in which patients take chronic NSAID therapy and use opioids to manage pain from flares. Potential advantages of using a low-dose opioid combination product include a broader analgesic spectrum, complementary pharmacokinetic profile, potentially synergistic analgesic benefits, and improved ratio of efficacy to adverse effects.

## CONCLUSION

Despite the wealth of analgesic options, treating arthritis-related pain is still a challenge for clinicians balancing efficacy with safety aspects. Growing understanding of the multiple mechanisms of arthritis pain has given clinicians greater appreciation for a multimechanistic approach. The use of combination products, such as tramadol and paracetamol for long-term pain management, is a good option with proven evidence for relieving pain. NSAIDs are effective pain relievers and helpful as add-on treatment for the painful flares of arthritis. They are not safe at high doses or for long-term use, especially in the frail and elderly. Revised guidelines are required to help clinicians to better understand safe, effective treatment options for arthritis-related pain.

## LIST OF PANEL PARTICIPANTS

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## CONFLICT OF INTEREST

ML received consultancy honoraria from Merck the Netherland, Pfizer Europa and Grünenthal GmbH and speaker honoraria from Pfizer Europa. JVP received consultancy honoraria from Grünenthal GmbH, Baxter, Endo Pharmaceuticals, and Hospira. HUM received consultancy honoraria from Grünenthal GmbH. IMM received consultancy honoraria from Boehringer Ingelheim, Grünenthal GmbH, Merck Sharp & Dohme Corporation, and Takeda Pharmaceuticals Europe and has received lecture fees from Almirall, Astra-Zeneca, Boehringer Ingelheim, Bristol Myers Squibb, Esteve, Grünenthal GmbH, Eli Lilly and Company, Merck Sharp & Dohme Corporation, Novartis, and Sanofi-Aventis. SN has received consultancy honoraria or research grants from the following companies in the past five years: Grünenthal GmbH, Johnson and Johnson, Endo Pharmaceuticals, Cephalon, Alphapharma, King Pharmaceuticals, Allergan, ProStakan, and Covidien. JOB received consultancy honoraria from Grünenthal GmbH. SP received consultancy honoraria from Grünenthal GmbH. RBR is a speaker, consultant, and/or basic science investigator for several pharmaceutical companies involved in analgesic research, but receives no royalty (cash or otherwise) from the sale of any product; he received consultancy honoraria from Grünenthal GmbH.

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## APPENDIX

**Fixed-Dose Combination Therapies for Osteoarthritis and Rheumatoid Arthritis Pain. Only Combinations of Paracetamol with Other Analgesic Agents were Included. The List of Studies was Obtained Through PubMed Searches and Reference Lists of Pain Review Articles**

Study	N	Agent(s)	Comparator	Results	Comments
<b>Strong Opioid/APAP Combinations</b>					
Raffaelli 2010 [123]	29 RA patients with chronic moderate to severe pain, not taking biologics	Oxycodone/APAP started at 5/325 mg and titrated to attainment of good pain relief	None	42% had good clinical response (EULAR) and 50% showed 20% improvement. Mean daily dose at end of study was 13.8 (±6.8) mg/720.4 (±291.0) mg	Mild to moderate nausea and vomiting; no serious AEs. Patients were allowed antiemetic drugs and laxatives as needed.
Corsinovi 2009 [124]	154 women nursing home residents with moderate to severe OA pain	Oxycodone/APAP (average dose 16/900 mg) and codeine/APAP (average dose 115/1916 mg)	Conventional therapy (NSAIDs, APAP, COX-2 inhibitors)	Oxycodone/APAP and codeine/APAP significantly reduced mean pain at six weeks versus conventional therapy (p<0.001 and p=0.004, respectively)	AEs did not differ significantly among groups. Patients were all elderly females.
<b>Weak Opioid/APAP Combinations</b>					
Mullican 2001 [125]	462 patients with OA or LBP	Tramadol/APAP (37.5/325 mg) (average dose 131/1133 mg)	Codeine/APAP (30/300 mg) (average dose 105/1054 mg)	Tramadol/APAP was as effective as codeine/APAP and better tolerated	Codeine patients had significantly higher rates of somnolence and constipation, while tramadol patients had higher rate of headache (NS)
Palangio 2000 [126]	469 chronic pain patients (31% had arthritis, n=145)	1 tablet of hydrocodone/ibuprofen 7.5/200 mg daily (HI-1) or 2 tablets of same (HI-2)	Codeine/APAP 30/300 mg	HI-2 offered significantly greater pain relief than HI-1 or comparator; no efficacy differences between HI-1 and comparator	No significant difference in AEs by group (83% HI-2, 80% HI-1, and 81% Comparator) but significantly more HI-2 patients discontinued therapy due to adverse events compared to HI-1 (26% vs 15%, p=0.013)
Conaghan 2011 [127]	220 patients with hip and/or knee pain ≥60 years of age	7-day buprenorphine patches (range 5-25 µg/h) + APAP 1000 mg qid	Codeine/APAP range 16 mg/1000 mg qid to 60 mg/1000 mg qid	Non-inferiority of patch+APAP to codeine/APAP combination regarding analgesic efficacy Comparable incidence of AEs	High withdrawal rates in both groups
Emkey 2004 [128]	306 OA patients taking a COX-2 inhibitor	Tramadol/APAP (37.5/325 mg) as add-on (average dose 154/1332 mg)	Placebo as add-on	Tramadol/APAP patients had significantly better scores on VAS, pain relief and function; 13% of tramadol and 4% of placebo patients discontinued because of AEs	
Park 2011 [129]	97 knee OA patients in sub-study (part of larger study, n=112)	Tramadol/APAP (37.5/325 mg) Mean dose 3.23 tablets/day	NSAID	No significant differences in analgesia or AEs	
Alwine 2000 [130]	403 patients with OA or low back pain	Tramadol/APAP (37.5 mg/325 mg) 1 to 3 tablets per day	4-week active control, thereafter open label (24 m)	Tramadol/APAP rated "excellent" or "very good" by 39% of patients and 40% of investigators, average daily dose was 157 mg/1363 mg.	24% of patients discontinued due to AEs

(APPENDIX) contd.....

Study	N	Agent(s)	Comparator	Results	Comments
Rosenthal 2004 [131]	Subset of 113 patients $\geq$ 65 years with painful OA flares (from larger study of 308 patients) on stable NSAID or COX-2 inhibitor therapy $\geq$ 3 months	Tramadol/APAP (37.5/325 mg) as add on (mean daily dose 168/1.458 mg)	Control continued NSAID or COX-2 inhibitor therapy	Tramadol/APAP patients had significantly reduced daily pain intensity and significantly greater average daily pain relief	23% of tramadol/APAP and 9% of control patients reported treatment-related AEs. Tramadol/APAP vs control rates of constipation and somnolence were 4.3% vs 2.3% and 2.9% vs 2.3%, respectively.
Silverfield 2002 [132]	308 OA patients with flare on stable NSAID or COX-2 inhibitor therapy	Tramadol/APAP (37.5/325 mg) as add on	Control continued NSAID or COX-2 inhibitor therapy	Tramadol/APAP patients had significantly reduced daily pain intensity and significantly greater average daily pain relief	AEs occurred in 24% of tramadol/APAP and 8% of control group; 13% of tramadol/APAP and 5% of control patients discontinued for AEs
Lee 2006 [133]	277 RA patients on stable NSAID and/or DMARD therapy for $\geq$ 1 month	Tramadol/APAP (37.5/325 mg) as add on	Control continued NSAID and/or DMARD therapy	Tramadol/APAP patients had significantly greater pain relief and lower daily pain intensity	AEs were 57.6% in tramadol/APAP group vs 22.4% in control (p<0.001)
Choi 2007 [111]	250 patients with pain from knee OA on stable NSAID therapy	Tramadol/APAP (37.5/325 mg) Mean daily dose 112.5/1.975 mg	Patients were randomized to titration and non-titration groups	Tramadol/APAP reduced pain in both titration and nontitration groups	This was a safety study; discontinuation rate was significantly lower in titration group with nausea, vomiting and dizziness the most common AEs (all significantly more frequent in the nontitration group).
<b>NSAID/APAP Combinations</b>					
Doherty 2011 [134]	892 patients with chronic knee pain (85% had OA)	Two active arms: 1 tablet or 2 tablets daily of ibuprofen/APAP 200/500 mg	Two comparative arms: Ibuprofen 400 mg or paracetamol 1000 mg	At day 10, 2 combination tablets were significantly better than APAP monotherapy; at 13 weeks, significantly more patients found combination therapy (1 or 2 tablets) excellent or good versus APAP monotherapy	Decreases in hemoglobin ( $\geq$ 1 g/dl) occurred in all groups but was twice as frequent in patients taking 2 combination tablets daily compared to monotherapy
Pareek 2010 [135]	220 patients with knee OA flare	Etodolac 300 mg/APAP 500 mg BID	Etodolac 300 mg BID	Etodolac/APAP significantly reduced pain intensity (p<0.001) and improved function	Results noticeable within 30 minutes of first dose; AEs similar in both groups
Pareek 2009 [136]	199 patients with OA flares	Aceclofenac 100 mg/APAP 500 mg BID	Aceclofenac 100 mg BID	Aceclofenac/APAP was superior to monotherapy in pain intensity differences, sum of pain intensity differences, and patients' / investigators' assessments	Combination had more rapid onset of action; AEs similar in both groups (about 10%)

AE=adverse event, APAP=paracetamol, LBP=low back pain, NS=not significant, OA=osteoarthritis, VAS=visual analogue scale (pain measurement).

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