The value of paracetamol/codeine combination in orthopedic practice: integrating scientific evidence and real-life clinical experience

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Introduction

Musculoskeletal pain (MSP), including conditions such as low back pain and knee osteoarthritis, is a leading cause of disability worldwide.[1-3] It significantly affects personal well-being, work performance, and overall quality of life, while contributing to rising healthcare costs.[4]

In Italy, osteoarthritis affects approximately 20.6% of the general population, with prevalence rates reaching 63.0% in women and 50.9% in men over 85 years of age.[5]

Given the strong association between MSP conditions and aging, its incidence is expected to increase as the global population becomes older.[1] However, current medical treatments provide only partial relief.[1]

Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently prescribed for acute MSP, yet their use in elderly populations requires caution.[1]

Guidelines from the American Geriatric Society, the American College of Rheumatology, and the European League Against Rheumatism, recommend limiting the use of NSAIDs to the lowest effective dose for the shortest duration due to the risk of severe adverse events, gastro-intestinal, renal, and cardiovascular side effects.[1,6] Despite these concerns, inappropriate use of NSAIDs and/or overuse remain widespread.[6-9]

Paracetamol (acetaminophen) is one of the most commonly used analgesics, both over the counter and by prescription due to its strong analgesic and antipyretic effects.[1]

Unlike NSAIDs, paracetamol has minimal anti-inflammatory activity and a clinically significant lower risk of gastrointestinal and vascular side effects, making it the first-line analgesic for patients in whom NSAIDs are contraindicated.[1,10]

Combining drugs with distinct mechanisms of action may provide a strategy to enhance efficacy while maintaining tolerability.[10] Administrating reduced doses of two or more drugs from different pharmacological classes, concurrently can achieve effective pain relief, by targeting multiple pathways, while simultaneously minimizing dose-dependent adverse effects.[10]

Pharmacokinetics of Paracetamol and Codeine

The effectiveness and safety of the paracetamol/codeine combination depend on their distinct pharmacokinetic properties.[11]

Paracetamol is rapidly absorbed from the gastrointestinal tract, reaching peak plasma concentrations within 30 to 60 minutes.[1] It is primarily metabolized in the liver via glucuronidation and sulfation, with a small fraction undergoing oxidation by the cytochrome P450 (CYP2E1) enzyme system, which produces the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI).[1,11] This metabolite is normally detoxified by glutathione; however, in cases of overdose, depletion of glutathione can lead to hepatotoxicity.[1] Paracetamol has an elimination half-life of 2 to 3 hours and is excreted in the urine, primarily as conjugated metabolites.[1,11]

Codeine, a weak opioid, is absorbed quickly after oral administration, with peak plasma levels occurring within 1 hour.[11] It undergoes extensive hepatic metabolism via CYP2D6, which converts a portion (5–10%) into morphine, its active metabolite responsible for analgesic effects.[11-13] The degree of analgesia varies among individuals due to genetic polymorphisms in CYP2D6, resulting in some patients being poor metabolizers (low morphine conversion and reduced analgesia) or ultra-rapid metabolizers (excessive morphine conversion and increased risk of opioid toxicity).[12]

Codeine has an elimination half-life of approximately 3 hours and is primarily excreted in the urine as inactive glucuronide conjugates.[11]

Scientific Evidence Supporting Paracetamol/Codeine Use

The combination of paracetamol and codeine is a well-established cost-effective and widely accessible treatment option for various pain conditions.[10,14] Paracetamol/codeine should be used in case of moderate acute pain that is not adequately controlled by other analgesics, such as paracetamol, used alone.[14] When accessing the overall risk-benefit profile for each individual patient, this combination could represent the treatment of choice for patients with elevated risk of cardiovascular events or those undergoing primary or secondary prevention treatment of stroke and acute coronary syndromes.[14] However, treatment strategies should always be meticulously evaluated taking into account the actual benefits and individual risk profiles within the context of patient's specific clinical condition.

A Cochrane Analysis concluded that the combination of paracetamol and codeine provides clinically significant pain relief and prolongs duration by approximately one hour, compared

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to the same dose of paracetamol alone, in patients suffering moderate postoperative pain.[10]
Polat *et al*. demonstrated the superior efficacy of paracetamol/codeine (300mg/30mg) over naproxen sodium/codeine (550mg/30mg) in terms of both pain relief and reduced tramadol consumption, within the first 24 hours following lumbar disk surgery.[15] Additionally, the codeine/paracetamol combination (30mg/300mg) may serve as a clinically viable outpatient opioid alternative to oxycodone/paracetamol (5mg/325mg).[16]
Buccelletti *et al.* further reported that paracetamol/codeine (1000mg/60mg) is comparable to ketorolac (15mg) for managing non-traumatic and post-traumatic pain, but demonstrates superior efficacy in acute pain, particularly in patients with fractures and muscular pain.[17]
Effective management of acute pain necessitates an analgesic with a rapid onset of action.[1] Fast dissolving tablet formulations have been developed to facilitate quicker analgesia.[1] Specifically, effervescent paracetamol formulations have demonstrated several biopharmaceutical and pharmacokinetic advantages over conventional paracetamol formulations.[18] The effervescence mechanism accelerates tablets disintegration, thereby enhancing drug dissolution and absorption while also protecting the active pharmaceutical ingredient from degradation in the stomach. Collectively, these properties contribute to increase bioavailability and a more rapid onset of analgesic action.[18]
This paper explores the clinical value of the paracetamol/codeine combination for musculoskeletal pain conditions, based on insights gathered from an opinion meeting with six orthopedic specialists. The objective was to collect real-life clinical experiences and perspectives on its use in routine practice.

Methods

Six orthopedic specialists shared their experience to evaluate the clinical relevance of the paracetamol/codeine combination in real-world orthopedic practice; a structured discussion was followed by a systematic approach to gathering and analyzing insights. The meeting aimed to achieve the following steps:

Brainstorming: Experts explored various aspects of the paracetamol/codeine combination, identifying key clinical scenarios where its use may be beneficial.

Research & Evidence Review: Participants discussed their real-life experiences and considered existing scientific literature to support or challenge their perspectives. This stage also involved analyzing alternative treatments and potential counterarguments to ensure a comprehensive evaluation.

Outlining Core Considerations: The discussion focused on three primary topics:

- The appropriate use of the paracetamol/codeine combination in orthopedic practice.
- Identifying the ideal patient profile, considering factors such as age, comorbidities, pain severity, and whether the condition is acute or chronic.
- Determining the preferred oral formulation (conventional tablets vs. effervescent formulations) based on pharmacokinetic advantages and patient adherence.

Drafting Key Findings: The specialists consolidated their opinions into a structured framework, highlighting both clinical advantages and limitations.

Revising & Refining Conclusions: The discussion outcomes were refined to ensure logical coherence, clarity, and alignment with existing evidence.

Final Review & Proofreading: The final consensus statement was reviewed for accuracy, ensuring that recommendations were well-supported and clearly articulated.

Through this systematic approach, the expert panel aimed to provide clinically relevant, evidence-based insights into the role of the paracetamol/codeine combination in orthopedic pain management.

Results

The initial topic of discussion focused on the appropriate use to the paracetamol/codeine combination in orthopedic practice, specifically in relation to the type (surgical, traumatic or osteoarticular) and severity. The panel unanimously agreed that paracetamol or NSAIDs alone should be the first-line treatment of mild traumatic pain. However, in cases of moderate traumatic pain, the paracetamol/codeine combination serves as an effective alternative, when NSAIDs or paracetamol alone prove insufficient.
Despite this general framework, it highlighted that patient-specific characteristics play a more critical role in treatment selection than pain classification alone. Frail patients, such as elderly or those with cardiovascular and/or gastrointestinal comorbidities, are better suited for paracetamol-based regimen than NSAIDs, due to the latter's potential risks in this population. Effective pain management during the acute phase is crucial for the overall success of therapy. In the post-surgical setting, early intervention significantly enhances pain control. The expert panel unanimously agreed that the combination of paracetamol or NSAIDs with an opioid analgesic (such as codeine or tramadol) is a highly effective approach, within the first month following surgery.

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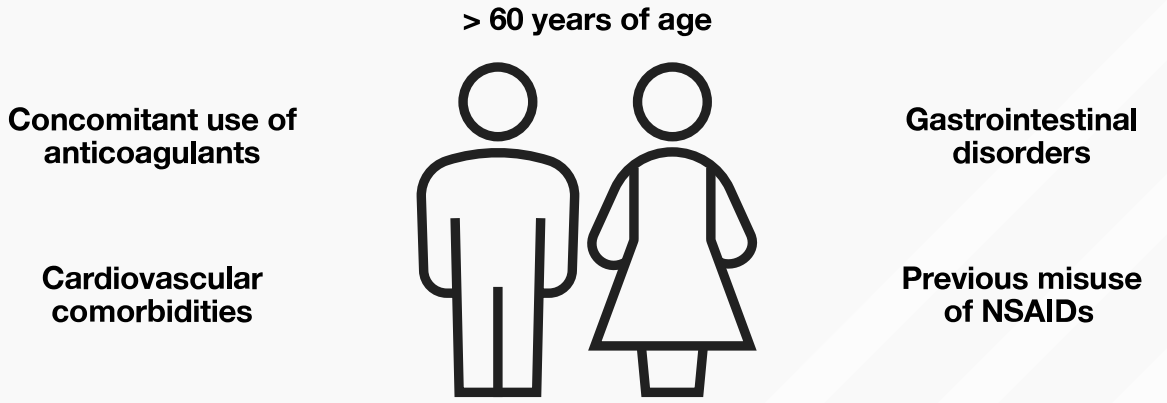

Figure 1. Patient Profile for Paracetamol/Codeine Combination in Orthopedic Practice

For chronic conditions, like osteoarthritis, the preferred strategy for managing pain involves the use of paracetamol or NSAIDs in combination with an opioid, irrespective of pain severity. Given that degenerative arthritis is predominantly age-related, the paracetamol/codeine combination is frequently favored in clinical practice. This preference is driven by the increasing number of frail patients, who constitute the majority of individuals affected by this condition.

The second topic of discussion focused on defining the characteristics of a typical frail patient, in orthopedic practice. The expert panel identified the paracetamol/codeine combination as a potential treatment of choice for moderate acute pain, in patients exhibiting at least one of the following criteria: age over 60 years, concurrent use of anticoagulants, cardiovascular comorbidities, gastrointestinal disorders, or a history of NSAIDs misuse; in elderly patients, half of the dose should be initially used. These recommendations are based on a comprehensive risk-benefit assessment tailored to each individual patient. **(Fig. 1)**.

According to the participants, the most common orthopedic conditions in the paracetamol/codeine combination is particularly beneficial for the ideal patient profile include low back pain, knee osteoarthritis, and post-traumatic pain.

The third point of discussion focused on the preferred oral formulation. The panel unanimously agreed that effervescent tablets offer a more rapid absorption over conventional tablets due to their faster absorption, leading to a more rapid onset of action, which is crucial for the effective management of acute pain. Additionally, effervescent formulation is often better tolerated by frail and multi-treated patients, as they may be easier to ingest and integrate into complex medication regimens.

Discussion

This expert panel concluded that paracetamol/codeine combination represents an effective alternative to NSAIDs for the treatment of acute moderate pain in frail patients. The participants shared their prescribing practices and clinical experience, which were further supported by existing literature, where paracetamol/codeine appears to be effective in the treatment of pain from any source, with an acceptable incidence of adverse events.

The combination therapy, involving pharmacologically distinct agents, acting both centrally and peripherally, specifically aims to enhance efficacy and tolerability.[14] The synergistic interaction between paracetamol and codeine generally ensures effective pain relief making a not-inferior alternative to NSAIDs.[14]

Based on the experience of participants, the common adverse effects of paracetamol/codeine were nausea, vomiting, and constipation, whereas common side effect of NSAIDs were gastrointestinal bleeding, particularly in patients with a history of gastritis, peptic ulcer, or previous surgery.[14] These events represent a potential risk associated with NSAIDs use, particularly at high doses and with long-term administration.[14] Additionally, NSAIDs should be used with caution particularly in patients with chronic heart failure, or those receiving aspirin for secondary prevention of coronary or neurological events.[14]

Furthermore, when physicians are dealing with carriers of CYP2D6 gene multiplications (about 3% in many Caucasian populations),[12] it is very important to watch out for the onset of extreme sleepiness, confusion and shallow breathing, since ultrarapid codeine metabolism resulted in a 1.5-fold higher morphine exposure, compared to extensive metabolizers.[12] A study about the possible effect of CYP2D6 genotype on codeine efficacy and adverse effects showed that, in a cohort of 987 adult patients undergoing ambulatory surgery, the CYP2D6

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Table 1. Overview of evidence on the paracetamol/codeine combination

Reference/design	Population	Treatment	Primary endpoint	Conclusions
Colini Baldeschi, *et al.*[22] Randomized, open label, controlled study	**38 patients** (median age 64.7 years) with moderate low back pain caused by osteoarthritis	Patients were randomized 1:1 to receive orally codeine/paracetamol (30 mg/500 mg) and tramadol/ paracetamol (37.5 mg/325 mg), every 8 hours, for 4 weeks	Analgesic efficacy (NRS), Oswestry Disability Index (ODI); Quality of Life (SF-36); tolerability and safety	Codeine/paracetamol association showed slightly higher values in pain improvement and was better tolerated in terms of adverse events and drop out
Buccelletti, *et al.*[17] Cross sectional, observational, prospective, cohort study	**200 patients** > 18-year-old presenting to the ED for localized traumatic or inflammatory pain involving only extremities	87 patients were treated with paracetamol/codeine (1000 mg/60 mg) and 113 patients with ketorolac (15 mg), both orally	Numeric scale (NRS), recorded at the time of enrolment (T0), 30 minutes (T1) and 2 hours (T2) after the administration of analgesic therapy	Paracetamol/codeine exerted significantly higher analgesic activity in patients with fractures and muscular pain (T2 p = 0.030 and T2 p = 0.044, respectively), compared to ketorolac
Chang, *et al.*[16] Prospective, randomized, double-blind clinical trial	**215 ED patients** (21–64 years of age) with acute extremity musculoskeletal pain, who were discharged home	Patients were randomized to receive orally a 3-day course of oxycodone/ paracetamol (5 mg/325 mg; n=111) or codeine/ paracetamol (30 mg/300 mg; n=104)	The between-group difference in improvement in mean NRS pain score, measured at 2 hours following the most recent ingestion of the study drug	Mean decrease over 2 hours was 4.5 NRS units in the oxycodone/paracetamol group vs 4.2 NRS units in the codeine/paracetamol group, for a clinically and statistically nonsignificant difference of 0.2 NRS units (95% CI 20.4–0.9 NRS units
Polat, *et al.*[15] Randomized, partially blinded, controlled, study	**60 patients** undergoing general anesthesia for an elective single level unilateral microsurgical lumbar discectomy	Patients received oral paracetamol/codeine (300 mg/30 mg; Group P; n=20), naproxen sodium/ codeine (550 mg/30 mg; Group N; n=20), or placebo tablets (Group C; n=20) 30 minutes prior to induction of anesthesia. Patient-controlled analgesia was supplied postoperatively using tramadol	Pain intensity, tramadol consumption, and side effects, recorded every 1 hour, 2 hours, 6 hours, 12 hours, and 24 hours after surgery	Tramadol consumption was lower in Groups P (86 ± 39.52 mg) and N (138 ± 52.28 mg) compared with Group C (250 ± 31.46 mg) (p <0.001). Furthermore, the tramadol consumption level was lower in Group P than in Group N (p<0.001)

genotype appears to be of minor importance for the analgesic efficacy of oral paracetamol–codeine combination therapy, but it may affect the risk of constipation.[19]

In conclusion, the paracetamol/codeine combination represents an effective pain management strategy, with a positive and acceptable risk profile, particularly in frail patients and those at risk of NSAID-related complications.

For osteoarthritis-related pain, paracetamol and NSAIDs remain the first-line therapy, as recommended by the World Health Organization (WHO) and several experts.[20,21] However, the potential for severe side effects associated with NSAIDs, particularly in older patients, should be carefully considered when selecting the most appropriate treatment option.[21]

Colini Baldeschi *et al.* demonstrated that the paracetamol-codeine combination was superior to paracetamol-tramadol in terms of efficacy and tolerability with fewer adverse events and lower dropout rates in patients with moderate low back pain, due to osteoarthritis.[22]

Furthermore, existing literature highlights that paracetamol/ codeine combination provides greater pain relief compared to NSAIDs or paracetamol alone in elderly patients with moderate to severe osteoarthritis-related pain.[23] This combination has also shown a positive impact on functional status and depressive symptoms, which are commonly associated with chronic pain conditions. A rapid onset of action is another key factor in pain management, which can be achieved through fast dissolving tablets.[18] Effervescent paracetamol/codeine tablets enhance drug absorption, and hence more rapid analgesia than oral tablets, while maintaining tolerability and safety profile.[18] **Table 1** summarizes multiple studies evaluating the efficacy and safety of the paracetamol/codeine combination, across different pain conditions.

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Conclusions

Real-life clinical experiences have reinforced evidence supporting the use of paracetamol/codeine combination, in orthopedic practice. Low back pain, knee osteoarthritis, and more generally, osteoarthrosis, all prevalent among elderly and frail patients, are key conditions where this combination therapy proves beneficial. Given the gastrointestinal and cardiovascular risks associated with NSAIDs, paracetamol/codeine presents itself an effective alternative for pain management in this patient population, when NSAIDs or paracetamol alone prove insufficient. Furthermore, the availability of formulations enhances the speed of drug absorption, leading to a faster onset of action, which is particularly valuable in acute pain management.
Studies and clinical experience confirm that paracetamol/codeine is generally non-inferior to NSAIDs in terms of efficacy, while offering a more favorable safety profile for long-term use. However, it remains essential for specialists to regularly assess therapy progression to optimize treatment outcomes.
In conclusion, the paracetamol/codeine combination in effervescent tablets may represent an effective therapeutic option, with an acceptable risk profile, for frail patients requiring treatment for osteoarthritis-related pain, offering a well-balanced alternative to NSAIDs.

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