

Tapentadol in the treatment of osteoarthritis: pharmacological rationale and clinical evidence

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Abstract: Osteoarthritis (OA) is the most prevalent joint disease in older people worldwide. Pain owing to OA is considered one of the most frequent causes of chronic pain; however, current pharmacological approaches have some limitations in terms of efficacy and safety. Of note, descending inhibitory pain pathways are often disrupted in chronic OA pain, and pharmacotherapies targeting those pathways – eg, those that block norepinephrine reuptake may be more appropriate for managing chronic pain than pure μ -opioid receptor (MOR) agonists. Tapentadol is an analgesic molecule, which combines two synergistic mechanisms of action, MOR, and norepinephrine reuptake inhibition. This narrative review will briefly discuss the mechanisms contributing to the onset and maintenance of pain in OA patients; clinical data on the use of tapentadol in this setting will then be presented and commented.

Keywords: osteoarthritis, pain, tapentadol

Introduction

Osteoarthritis (OA) is the most prevalent joint disease in older people worldwide, with the knee and hips being the most affected joints, although hand OA is sometimes reported.¹ It is characterized by the progressive destruction of articular cartilage, synovial inflammation, changes in subchondral bone and peri-articular muscle, and pain.² In particular, pain due to OA is considered one of the most frequent causes of chronic pain.^{3,4} the prevalence of radiographic knee OA is estimated to be up to 28%.⁵

The management of OA may require three lines of pharmacological treatment in order to: 1) manage inflammation, only when it is present in its flares; 2) provide central analgesia, by modulating both ascending and descending pathways; and 3) prevent further joint destruction (which is a generator of peripheral pain), eg, by using condroprotectors.^{6,7}

In particular, the treatment of pain is crucial to the management of the OA patient; however, current pharmacological approaches, including paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs), have some limitations in terms of efficacy and safety, limiting them to short-term use.^{8–12} Another option is represented by tramadol.¹³ Opioid analgesics may relieve OA pain, but are associated with well-known safety concerns.^{14,15} Remarkably, patients with OA are often submitted to total knee or hip arthroplasty if their pain is not well-controlled.¹⁶ However, patients still experience marked pain while in the waiting list for surgery and even after joint replacement.¹⁷

Of note, descending inhibitory pain pathways are disrupted in chronic OA pain, and pharmacotherapies targeting those pathways – eg, those that block norepinephrine reuptake may be more appropriate for managing chronic pain compared with

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pure μ -opioid receptor (MOR) agonists.¹⁸ Tapentadol is a dual-acting analgesic molecule, which combines two mechanisms of action, MOR agonism and norepinephrine reuptake inhibition (NRI).^{19,20} This narrative review will briefly discuss the mechanisms contributing to the onset and maintenance of pain in OA patients; clinical data on the use of tapentadol in this setting will then be presented and commented.

Mechanisms of pain onset in OA

OA pain can be considered a “mixed” pain state.²¹ Indeed, all structures of the joints, with the exception of the cartilage, are innervated by nociceptors, and hence structural alterations do stimulate pain.⁴ Although OA pain presents a wide heterogeneity,^{12,22} neuropathic mechanisms are also involved, since structural changes of joint innervation, such as local loss and/or sprouting of nerve fibers are common in OA. In addition, central sensitization, reduction of descending inhibition, descending excitation, and cortical atrophies were observed in OA;²³ all these mechanisms contribute to transition to chronic pain and enhanced severity.^{12,21} Therefore, central analgesia becomes crucial to avoid the establishment of neuroplasticity phenomena leading to chronic pain.^{24,25} Owing to the chronic pain associated with functional limitation, patients may ultimately need to undergo knee or hip replacements. In most cases, the waiting period prior to surgery is characterized by moderate–severe pain, which limits the patients’ function and activity. Control of pain is also important postoperatively, since severe pain is associated with longer hospitalization, poor compliance with the rehabilitation program, a delay in starting to perform daily activities and an increase in postoperative complications.^{26,27}

On these bases, a molecule able to act both on the nociceptive and the neuropathic components of pain can be highly effective in the treatment of OA pain. Tapentadol meets these requirements.²⁸ Indeed, the pharmacological profile of tapentadol, combining synergistically MOR agonism and NRI in one molecule, appears to be unique and it seems reasonable to propose for tapentadol a new class of centrally acting analgesics, designated MOR-NRI,¹⁹ and can be considered an a priori choice for the treatment of chronic, neuropathic, and mixed pain.²⁹

Tapentadol in the treatment of OA pain: clinical data

Solid clinical data support the efficacy and safety of tapentadol in the treatment of OA-associated pain, in line with

its pharmacological rationale. Studies on tapentadol in this indication encompass both the non-surgical (Table 1) and the surgical setting; some pieces of evidence also support the use of tapentadol prolonged release (PR) in the rehabilitation setting.

Non-surgical setting

In a randomized, double-blind study, Afilalo et al evaluated the efficacy and safety of tapentadol PR compared with oxycodone controlled release (CR) in the management of moderate-to-severe chronic OA-related knee pain.³⁰ In total, 1,030 patients receive tapentadol PR 100–250 mg twice daily, oxycodone HCl CR 20–50 mg twice daily, or placebo for a 3-week titration period followed by a 12-week maintenance period. Tapentadol PR significantly reduced pain intensity from baseline to week 12 of the maintenance period versus placebo and throughout the maintenance period. On the other hand, oxycodone CR significantly reduced average pain intensity from baseline throughout the maintenance period versus placebo but not at week 12. A higher percentage of patients achieved $\geq 50\%$ improvement in pain intensity with tapentadol PR (32.0% [110/344]) compared with placebo (32.0 vs 24.3%; $p=0.027$), while a significantly lower percentage of patients achieved this goal in the oxycodone CR group (17.3%). Incidence of gastrointestinal events was 26.1% with placebo, 43.0% with tapentadol and 67.3% with oxycodone.

In a subsequent open-label, Phase IIIb study, Steigerwald et al evaluated the effectiveness and tolerability of tapentadol PR for severe, chronic OA knee pain inadequately managed or left untreated.¹⁴ In total, 195 patients received tapentadol PR (50–250 mg bid) for a 5-week titration period, followed by a 7-week maintenance period. The mean change from baseline to week 6 in pain intensity was -3.4 ± 2.10 ($p<0.0001$). Significant decreases in pain intensity were also observed at weeks 6, 8, and 12.¹⁴ Improvements from baseline to weeks 6 and 12 were observed in the Western Ontario and McMaster Universities OA index,¹⁴ the EuroQol-5 Dimension health status questionnaire, the Short Form-36 health survey, and the Hospital Anxiety and Depression Scale. The same group evaluated the effectiveness and tolerability of tapentadol PR (50–250 mg twice daily) after rotation from WHO step III opioids in patients with severe OA knee pain who poorly tolerated this latter therapy.³¹ Patients received oral tapentadol PR (50–250 mg twice daily) over a 5-week titration and a 7-week maintenance period. In total, 63 patients received tapentadol PR. The responder rate (ie, patients with reduced pain intensity compared with baseline) at week 6 was 94.3%; mean pain intensity was 4.7 ± 0.66 at baseline, 2.5 ± 1.46 at week

Table I Key elements from clinical trials on tapentadol PR in the treatment of OA-related pain in the non-surgical setting

| Study | Design | Patients enrolled | Tapentadol PR median modal daily dose* | Duration study treatment | Efficacy on pain (primary endpoint) | Safety |
|-----------------------|---|---|--|--|--|---|
| Afilalo 2010 [30] | Randomized, double-blind, active- (oxycodone CR 20–50 mg bid) and placebo-controlled parallel-arm, multi-center Phase III study | 1030 patients with moderate-to-severe chronic OA-related knee pain | TDD: 400 mg Allowed dose range: 100–250 mg bid | 3-week titration + 12-week maintenance | Mean change in daily pain intensity at week 12 vs baseline tapentadol PR vs placebo: -0.7 (95% CI: -1.04 to -0.33) Oxycodone CR vs placebo: -0.3 (95% CI: -0.68 to 0.02) | Patients with at least one TEAE tapentadol PR: 61.1% oxycodone CR: 75.9% placebo: 87.4% Patients with at least one gastrointestinal TEAE Tapentadol PR: 26.1% Oxycodone CR: 43.0% Placebo: 67.3% |
| Steigerwald 2012 [14] | Open-label, Phase IIIb study | 195 patients with chronic OA-related knee pain, not treated or inadequately managed with WHO Step I or II analgesics or co-analgesics | TDD: 256.9 ± 111.38 mg Allowed dose range: 50–250 mg bid Tapentadol IR TDD: 6.7 ± 21.16 mg Allowed dose: 50 mg (≤bid; ≥4 hrs apart) | 5-week titration + 7-week maintenance | Mean change in daily pain intensity at week 6 (3 last days) vs baseline: 3.4 ± 2.10 (p < 0.0001) | Patients with at least one TEAE: 71.0% Patients with at least one gastrointestinal TEAE: 38.5% |
| Steigerwald 2013 [31] | Open-label, Phase IIIb study | 82 patients with severe OA-related knee pain, previously treated and intolerant to WHO Step III analgesics | TDD: 232.7 ± 145.37 mg Allowed dose range: 50–250 mg bid Tapentadol IR TDD: 7.0 ± 17.48 mg Allowed dose: 50 mg (≤bid; ≥4 hrs apart) | 5-week titration + 7-week maintenance | Responder rate at week 6: 94.3% (p < 0.0001) Mean change in daily pain intensity Week 6 vs baseline: -2.2 ± 1.55 (p < 0.0001) Week 12 vs baseline: -2.9 ± 1.40 (p < 0.0001) | Patients with at least one TEAE: 34.9% Week -1 vs Week 12 Nausea: 46.0% vs 24.1% Vomiting: 31.7% vs 7.4% |
| Banerjee 2016 [32] | Randomized, open-label, active- (etoricoxib 30 mg bid) controlled Phase III study. | 218 patients with OA-related knee pain | 100 mg bid | 12 weeks | Steady improvement in pain intensity on VAS and WOMAC, but no significant difference for tapentadol vs etoricoxib Clinical global impression at least satisfactory Tapentadol PR: 80.56% Etoricoxib: 69.09% (p = 0.036) | Patients with at least one TEAE Tapentadol PR: 37.03% Etoricoxib: 49.09% (p = 0.048) |

(Continued)

Table I (Continued).

| Study | Design | Patients enrolled | Tapentadol PR median modal daily dose* | Duration study treatment | Efficacy on pain (primary endpoint) | Safety |
|------------------|---|--|--|---------------------------------------|---|---|
| Serrie 2017 [33] | Randomized, double-blind, active- (oxycodone CR 20–50 mg bid) and placebo-controlled study | 990 patients with moderate-to-severe chronic OA-related knee pain | TDD: 315.2 ±108 mg Allowed dose range: 100–250 mg bid | 3-week titration +12-week maintenance | Mean change in daily pain intensity at week 12 vs baseline Tapentadol PR vs placebo: -0.3 (95% CI: -0.61 to -0.09); $p=0.152$ Oxycodone CR vs placebo: 0.2 (95% CI: -0.16–0.54); $p=0.279$ Mean change in daily pain intensity during maintenance period vs baseline Tapentadol PR vs placebo: -0.2 (95% CI: -0.55–0.07); $p=0.135$ Oxycodone CR vs placebo: 0.1 (95% CI: -0.18–0.44); $p=0.421$ | Patients with at least one TEAE Tapentadol PR: 67.1% Oxycodone CR: 84.9% Placebo: 55.5% Patients with at least one gastrointestinal TEAE Tapentadol PR: 41.7% Oxycodone CR: 67.7% Placebo: 27.3% |
| Biondi 2015 [34] | Post-hoc analysis of three randomized, double-blind, active- (oxycodone CR 20–50 mg bid) and placebo-controlled Phase III studies | 210 elderly patients (≥ 75 years) with moderate-to-severe OA-related knee or low back pain | Allowed dose range: 100–250 mg bid | 3-week titration +12-week maintenance | Mean change in pain intensity at week 12 vs baseline Tapentadol PR vs placebo: $p=0.0075$ Oxycodone CR vs placebo: $p=0.1195$ | Significantly lower gastrointestinal TEAEs, vomiting TEAEs, and composite nausea and vomiting TEAEs for tapentadol PR vs oxycodone CR |
| Lange 2017 [35] | Pooled analysis of two randomized, double-blind, active- (oxycodone CR 20–50 mg bid) and placebo-controlled studies | 2010 patients (≥ 40 years) with moderate-to-severe chronic OA-related knee pain | TTD: 300 mg Allowed dose range: 100–250 mg bid | 3-week titration +12-week maintenance | Mean change in daily pain intensity for tapentadol vs oxycodone CR Week 12 vs baseline: -0.41 (95% CI: -0.65 to -0.16); $p=0.001$ Maintenance period vs baseline: -0.35 (95% CI: -0.58 to -0.12); $p=0.003$ | Patients with at least one TEAE tapentadol PR: 71.6% oxycodone CR: 86.2% placebo: 58.3% Lower relative risk for tapentadol PR vs oxycodone CR Vomiting: 0.35 Pruritus: 0.36 Constipation: 0.51 Nausea: 0.57 Somnolence: 0.63 |

Note: *Median modal daily dose=most frequently used daily dose.

Abbreviations: bid, twice daily; CR, controlled release; IR, Immediate release; OA, osteoarthritis; PR, prolonged release; TEAE, treatment-emergent adverse event; TDD, total daily dose; bid, twice a day; WOMAC, Western Ontario and McMaster University osteoarthritis index.

6, and 1.8 ± 1.4 at week 12 ($p < 0.0001$ for all comparisons).³¹ Prevalence of adverse events (AEs) reported as associated with prior opioids and related to tapentadol treatment at week 12 decreased over time; the most frequent AEs were nausea (46.0 vs 24.1%) and constipation (31.7 vs 7.4%).

In a comparative, randomized, open labeled, controlled study by Banerjee et al, patients received either tapentadol (100 mg twice daily; $n=108$) or etoricoxib (30 mg twice daily; $n=110$) for 12 weeks.³² Steady improvement was seen in pain intensity VAS and WOMAC scores³¹ in both groups; moreover, a higher number of patients reported at least satisfactory response at the end of the study in the tapentadol group ($p=0.036$). AEs were less frequent with tapentadol PR (incidence: 37% vs 49%) with the most common events being nausea (22%) and dizziness (13%) with tapentadol and nausea (20%) and dyspepsia (15%) with etoricoxib.

Serrie et al also conducted a double-blind, placebo or oxycodone CR (20–50 mg bid)-controlled trial to assess the efficacy and safety of tapentadol PR (100–250 mg bid) administered for a 3-week titration and 12-week maintenance period in 990 patients with moderate-to-severe OA-related knee pain. The study did not meet its primary endpoints as both tapentadol and oxycodone did not significantly reduce pain intensity vs placebo after 12 weeks of treatment, nor over the maintenance period. However, the study did not demonstrate assay sensitivity and the finding that both primary end-points for tapentadol PR were not met therefore cannot be interpreted. The overall health status of patients treated with tapentadol was superior to that of patients treated with oxycodone; indeed, more patients in the tapentadol arm completed the study and the percentage of patients that rated, at least, “much improved” at the end of the study was higher (56% vs 42.5% for oxycodone). Tapentadol also showed a better tolerability profile with significantly reduced incidence of constipation (17.9% vs 35% for oxycodone) and of the composite of nausea and/or vomiting (23.8% vs 46.8%).³³

Some retrospective studies have also investigated the efficacy and safety of tapentadol.

In a *post-hoc* analysis of pooled data, Biondi et al specifically evaluated the tolerability and analgesic efficacy of tapentadol PR compared with oxycodone CR in 210 elderly adult patients (≥ 75 years) with moderate-to-severe pain due to OA of knee or low back pain.³⁴ Each study consisted of a 3-week titration and 12-week maintenance period, and patients received placebo, tapentadol PR (100–250 mg bid), or oxycodone CR (20–50 mg bid) for 15 weeks. Overall, the incidences of gastrointestinal treatment-emergent AEs overall and those

of nausea/vomiting were significantly lower with tapentadol PR compared with oxycodone CR group (all $p \leq 0.0206$). Moreover, tapentadol extended release treatment determined a significant reduction in pain intensity from baseline to week 15 compared with placebo ($p=0.0075$), while the difference between the oxycodone CR and placebo group did not reach significance, likely due to a higher treatment discontinuation rate in the oxycodone CR group.

In addition, a pooled analysis of two randomized, double-blind, controlled studies conducted by Lange et al, suggested that tapentadol PR is superior to oxycodone in providing pain relief and improving overall health status in patients with moderate-to-severe chronic OA-related knee pain.³⁵ Both studies consisted in a 3-week titration +12-week maintenance period, and patients were randomized to tapentadol PR (100–250 mg bid), oxycodone CR (20–50 mg bid), or placebo. Tapentadol treatment resulted in a more significant reduction in average pain intensity compared with oxycodone, both after 12 weeks of treatment (mean difference -0.41 [95% CI: -0.65 to -0.16], $p=0.001$) and over the maintenance period (-0.35 [95% CI: -0.58 to -0.12], $p=0.003$). Patients' global impression of change measured by the Short Form-36 score and EuroQoL-5Dimensions health status index were also significantly higher for tapentadol vs oxycodone ($p < 0.001$ for all). In terms of safety, treatment with tapentadol led to a reduced relative risk of vomiting, constipation, nausea, somnolence and pruritus, and to less cases of treatment discontinuation (42.2 vs 64% for oxycodone).

Surgical setting

Hartrick et al assessed the efficacy and tolerability of tapentadol immediate release (IR) in a 10-day randomized, double-blind, active (oxycodone IR) and placebo-controlled trial in patients candidate for joint replacement surgery.³⁶ In total, 659 subjects were evaluated for efficacy. Tapentadol IR (50 and 75 mg) and oxycodone HCl IR (10 mg) were associated with significant reductions in pain intensity compared with placebo, at 2, 5, and 10 days after surgery; however, the incidence of gastrointestinal AEs was significantly lower for both doses of tapentadol IR compared with oxycodone HCl IR 10 mg. Rates of treatment discontinuation were 18% in the tapentadol IR 50-mg group, 26% in the tapentadol IR 75-mg group, 35% in the oxycodone HCl IR 10-mg group, and 10% in the placebo group. A similar 7-day study reached the same conclusions, and tapentadol was also associated with greater overall improvement as assessed by both patients and clinicians.³⁷

The PR formulation of tapentadol in this setting has been evaluated by Haeseler et al, who conducted

a randomized, observer-blinded, active-controlled (oxycodone/naloxone) trial in patients following orthopedic/trauma surgery.³⁸ In total, 133 patients received tapentadol and an equal number oxycodone. Mean pain levels in the first 5 postoperative days were 2.8 ± 1.3 in both groups. Overall, the two treatments showed comparable analgesic efficacy and a similar tolerability profile.

Rehabilitation setting

To date, attention has focused on analgesia in the preoperative period, while studies on the rehabilitation period are scant.³⁹ However, pain control continues to be very important in the rehabilitation phase, since high-intensity pain during rehabilitation is associated with longer hospital stay and poor compliance with rehabilitation protocols, with marked consequences on QoL.

In a still-unpublished open-label study, Rinonapoli et al evaluated 49 patients waiting for knee replacement treated with tapentadol.⁴⁰ In all these patients, the pain numerical rating scale (NRS) was ≥ 6 . The initial dose of tapentadol was always 50 mg twice daily. The dose was increased to 100 mg twice daily after 4–5 days and could be further increased according to clinical needs. Most patients, 31 (63.2%) found sufficient benefit from the therapy at a dose of 300 mg/day. Mean NRS at baseline was 8.35, and it decreased to 5.33 at surgery, 4.96 15 days after surgery and 2.15 at 40 days. Sleep quality also improved increased. The average time to reach the best postoperative scores was 23.9 days.

In the pure rehabilitation setting, Panella et al conducted a 3-week, open study to assess the analgesia and tolerability of tapentadol PR (50–150 mg twice daily; $n=91$) compared with paracetamol 1000 mg bid ($n=53$), in patients in rehabilitation after knee replacement surgery and moderate-to-severe pain.³⁹ During the study, more favorable progress was observed with tapentadol PR: in particular, pain, range of motion, and sleep quality showed a faster improvement in the patients treated with tapentadol PR ($p < 0.01$ vs paracetamol). At the end of the study, the pain intensity reduced by 4.3 points with tapentadol PR versus 2.4 with paracetamol.

Conclusion

OA is a common disease of aged population and one of the leading causes of disability worldwide, associated with marked pain in most patients. Proper control of pain is crucial in OA, also in order to guarantee functional recovery and improve quality of life. In the surgical setting,

control of pain allows improved surgical outcomes. Therefore, most guidelines on knee OA, drawn up by the most authoritative international societies (AAOS, OARSI, ACR),^{11,41} dedicate a specific section to the pharmacological treatment of OA-associated pain, but point out that current therapies for this condition present a number of drawbacks including modest efficacy and poor safety, especially over the long term. Selection of treatment should take into consideration the mechanism of action of the analgesic therapy, which should be able to address both the nociceptive and the neuropathic components.

Remarkably, tapentadol was not considered in those guidelines, partly due to its more recent introduction in the pharmacological armamentarium for OA compared with other therapies. However, current data on the efficacy of tapentadol, especially in its PR formulation, are robust and were collected, in most cases, from well-designed studies in the non-surgical, surgical, and rehabilitation settings. Noteworthy, all studies pointed out the favorable safety profile of tapentadol, a finding of major importance in the long-term therapy. The efficacy and safety of tapentadol PR in this setting were consistent regardless of patients' age.

Most of the published studies have included either oxycodone or paracetamol as comparators. To our knowledge, no study has directly compared tapentadol PR with tramadol; owing to the lack of head-to-head comparisons, we can speculate that the higher risk of AEs and pharmacological interactions with tramadol.⁴² Similarly, only one trial has compared tapentadol with a NSAIDs (etoricoxib),³² showing more pronounced efficacy and improved safety with tapentadol. Given the lack of other direct comparisons, it is not possible to know whether this improved efficacy and safety of tapentadol can be extended to other NSAIDs commonly used in the treatment of OA (eg, ibuprofen, diclofenac).

On these bases, we believe that tapentadol PR can be considered a first-line choice in the treatment of OA-associated pain and future guidelines should include this therapy among the recommended pharmacological therapies.

Key points

- OA is the leading causes of disability worldwide, associated with marked pain in most patients. Proper control of pain is crucial in OA, also in order to guarantee functional recovery and improve quality of life. In the surgical setting, control of pain allows improved surgical outcomes.

- Selection of pain treatment should take into consideration the mechanism of action of the analgesic therapy, which should be able to address both the nociceptive and the neuropathic components; moreover, it should avoid the phenomenon of central sensitization.
- Current data on the efficacy of tapentadol for the treatment of OA, especially in its PR formulation, are robust and were collected, in most cases, from well-designed studies in the non-surgical, surgical, and rehabilitation settings.
- All studies pointed out the favorable tolerability profile of tapentadol, a finding of major importance in the long-term therapy.

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Disclosure

The authors report no conflicts of interest in this work.

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