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Tapentadol prolonged release in the treatment of musculoskeletal pain: an innovative pharmacological option

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Abstract. – Musculoskeletal pain, encompassing back and osteoarthritis (OA) pain, represents the most frequent source of chronic pain in western countries, and it is particularly frequent in older adults. Remarkably, back and OA pain present, in most cases, both a nociceptive and a neuropathic component of pain. Treatment selection should, therefore, properly consider the ability of a drug to act on both components, reducing the possibility of plastic changes in the central nervous system, and consequently promoting physical rehabilitation.

The pharmacological profile of tapentadol, combining synergistically μ-opioid receptor (MOR) agonism and norepinephrine reuptake inhibition (NRI) in one single molecule with a concomitant reduction in the burden of adverse events, is unique, to date, and makes this drug particularly suitable for the treatment of back pain and OA-associated pain, especially when a neuropathic component is present.

Tapentadol is an innovative dual-acting analgesic molecule, which combines two mechanisms of action, namely MOR agonism and NRI. This narrative review will briefly discuss the pharmacological action of tapentadol and its rationale of use in back pain and OA.

Key Words:
Low-back pain, OA pain, Tapentadol.

Introduction

Musculoskeletal pain is one of the conditions most frequently encountered in clinical practice. It can affect patients of all ages but is particularly common in older adults and in senior patients.

In particular, low back pain (LBP) remains the most frequent chronic pain condition worldwide, with a lifetime prevalence of >70% in western countries[1,2]. This condition is associated with a major impact on the healthcare system and, often, with multiple comorbidities, such as depression, anxiety disorders, and sleep disturbances[3]. Although sometimes neglected compared with LBP, neck pain is also a common disabling disease, with a prevalence that can be up to 23% and an associated major need of medical visits and physiotherapy[4]. Noteworthy, it has been well established that chronic LBP or neck pain – collectively, back pain – results from the transition to chronic pain processes involving central sensitization and plastic alterations of the involved structures, presenting a neuropathic component in the majority of cases[5]. Proper selection of treatment, aiming at targeting the underlying pathophysiology, is therefore of paramount importance in this setting[6].

Another major cause of chronic pain is osteoarthritis (OA), the most prevalent joint disease in older people worldwide[7,8]. While the progression of pain is activity-induced in the early stages of OA, in the intermediate stages pain becomes more and more frequent and progresses to constant pain, which also interferes with activities of daily living[9]. OA pain has long been considered as nociceptive, but mounting evidence suggests that neuropathic pain, both peripheral and central sensitization, also plays a major role, thus making innocuous stimuli, such as normal joint movements, painful (allodynia) and the response to become exaggerated (hyperalgesia)[9].

Tapentadol (Grunenthal, Aachen, Germany) is an innovative dual-acting analgesic molecule, which combines two mechanisms of action, namely μ-opioid receptor (MOR) agonism and norepinephrine reuptake inhibition (NRI). This narrative review will briefly discuss the pharmacological action of tapentadol and its rationale of use in back pain and OA.

Pharmacological Mechanisms of Tapentadol

Two complete overviews of the pharmacology of tapentadol have been recently published, and

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the reader is therefore suggested to refer to those papers for a deeper description of this topic[10,11]. In brief, tapentadol is a nonracemic compound endowed with analgesic, antihyperalgesic and antiallodynic properties[10]. It presents no active metabolites.

Tapentadol was developed by a rational drug-design program aimed at defining a molecule characterized by dual MOR and NRI activity[12,13], therefore making it the first and, so far, unique member of a new class of analgesic compounds, MOR-NRI[11]. Indeed, despite a 50-fold lower affinity for MOR than opioids and relatively moderate NRI activity (Ki = 0.48 μM for rat synaptosomal uptake inhibition), tapentadol potency was comparable to that of morphine across a variety of preclinical pain models, and this molecule exerts an analgesic efficacy comparable to that of classical opioids, such as oxycodone and morphine[12,14]. This activity cannot be explained by a mere additive effect, but rather by a synergistic interaction between the two distinct mechanisms of action, MOR agonism, and NRI[10,11]. Therefore, tapentadol addresses both the nociceptive and the neuropathic components of pain. More precisely, the MOR agonism is the most effective component against moderate to severe acute pain, whereas NRI is predominant in neuropathic pain models and in the progression to chronic pain[10].

Importantly, the two mechanisms do not interact synergistically on the burden of adverse effects[15]. Indeed, a very recent study showed that only 40% of the effect of tapentadol is dependent on MOR activation compared with the classic opioids at equianalgesic concentrations, therefore leading to a more favorable tolerability profile compared with strong classical opioids[15]. Moreover, tapentadol shows minimal serotoninergic activity, thus reducing the risk of emesis during long-term treatment[11]. In line with this pharmacological evidence, tapentadol, in its prolonged-release (PR) formulation, was better tolerated than opioids in terms of incidence of specific adverse events (AEs), such as gastrointestinal events, hypertension, pulmonary dysfunction, endocrine toxicity, and convulsions, in studies up to 4 years of duration[16]. The lack of action on the serotoninergic system markedly reduces – or even abolishes – the risk of secondary depression[16] in a population of patients who are often on antidepressants. Tapentadol is also associated with a very low, if not negligible, potential of abuse[16].

Collectively, the above-mentioned pharmacological properties of tapentadol lead to its efficacy and safety in different settings, including back pain and OA[17-20].

Tapentadol in the Treatment of LBP

Rationale of Use

Chronic LBP is a heterogeneous condition, in which both nociceptive and neuropathic pain mechanisms are usually involved[3]. However, the neuropathic component – arising from injury affecting the nerve roots and damaged lumbar discs – is often neglected when selecting treatment[3,17]. Moreover, studies on the analgesic treatment of back pain are usually of short duration (<3 months), and evidence of long-term efficacy and safety is limited[17].

According to the above-described, well-grounded pharmacological rationale, tapentadol PR appears to be a particularly suitable option for the treatment of back pain, also given the relative efficacy of other therapies that only address the nociceptive component of pain[17,21]. A landmark paper discussing the role of tapentadol PR in this setting has recently been published[17]. We, therefore, present here only a brief comment on the clinical evidence of this molecule in the treatment of back pain.

Clinical Data

The efficacy and safety of tapentadol PR have been comprehensively studied in patients with LBP and neck pain, as extensively reviewed in a recent paper[17]. An overview of the most relevant studies is provided here, while details are presented in Table I.

The first trial of tapentadol in LBP, with a randomized, double-blind, placebo-controlled design[22], randomly assigned, approximately 1,000 patients to tapentadol PR 100-250 mg twice daily, oxycodone controlled-release (CR) 20-50 mg twice daily or placebo for a period of 15 weeks (3-week titration period and 12-week maintenance period). The reduction in pain intensity was similar with tapentadol PR and oxycodone CR; however, tapentadol PR was associated with a significantly lower incidence of nausea and vomiting, as well as a reduced incidence of gastrointestinal AEs (43.7% *vs.* 61.9%). Tapentadol PR also showed similar analgesic effect and improved tolerability than strong opioids[23]. In a randomized, double-blind trial, tapentadol PR showed an analgesic effect similar to that of tapentadol PR+pre-

Table II. Key elements from clinical trials on tapentadol PR in the treatment of low-back pain. *Median modal daily dose=most frequently used daily dose.

Study	Design	Number of patients	Tapentadol PR median dose	Duration	Efficacy	Safety	Ref
Buynak 2010	Prospective, randomized, double-blind, active-(oxycodone CR 20-50 mg twice daily) and placebo-controlled phase III study	981 patients	TDD: 313.2±116.7 mg Allowed dose range: 100–250 mg twice daily	3-week titration + 12-week maintenance	LSMD (95% CI) in pain intensity (NRS-3) during maintenance period *vs.* baseline: – Tapentadol PR *vs* placebo: -0.7 (-1.06, -0.35); $p<0.001$ – Oxycodone CR *vs.*placebo: -0.8 (-1.16, -0.46); $p<0.001$	Patients with at least one TEAE: – Tapentadol PR: 75.5% – Oxycodone CR: 84.8% – Placebo: 59.6%	22
Gálvez 2013	Open label, multicenter, phase IIIb study	125 patients with low tolerance to step III opioids	TDD (week 6): 322.8±120.73 mg Allowed dose range: 50–250 mg twice daily	5-week titration + 7-week maintenance	Response rate week 6: 80.9%; $p<0.0001$ Mean±SD change in pain intensity (NRS-3) *vs.* baseline Week 12: -1.3±2.10; $p<0.0001$	Patients with at least one TEAE: 68.0% (78.6% mild-to-moderate)	23
Baron 2015	Randomized, double-blind, active-(tapentadol PR + pregabalin) controlled, multicenter, phase IIIb study	445 patients	Titration: 300 mg/day Maintenance: 500 mg/day vs 300 mg/day + pregabalin 300 mg/day	5-week titration + 8-week maintenance	LSMD in pain intensity (NRS-3) from randomization to end of study for tapentadol PR *vs.* tapentadol PR/pregabalin: -0.066 (95% CI: -0.57-0.43); $p<0.0001$	Patients with at least one TEAE: Tapentadol PR: 63.6% Tapentadol PR + pregabalin: 64.8%	24
Baron 2016	Randomized, open-label, active- (oxycodone/naloxone PR 10 mg/5 mg-40 mg/20 mg) controlled, phase IIIb/IV study	258 opioid-naïve patients	Allowed dose range: 50-250 mg twice daily	3-week titration + 9-week maintenance	Mean change (LS mean) in pain intensity (NRS-3) from baseline to final evaluation tapentadol PR: -3.7 (0.25); $p<0.001$ *vs* baseline and vs oxycodone/naloxone PR	Patients with at least one TEAE: Tapentadol PR: 76.9% Oxycodone/naloxone PR: 83.6%	14
Baron 2016	Open-label, continuation arm of randomized phase IIIb study	59 patients	300 mg/day	8 weeks	Mean±SD change in pain intensity (NRS-3) from baseline to end of study: -5.3±1.78; $p<0.0001$	Patients with at least one TEAE: 50.8%	25
Guillén-Astete 2017	Retrospective observational study	91 patients in the ED	25 mg/day (n=23) 50 mg/day (n=68)	30 days	OR (95% CI) of reassessment in ED for tapentadol *vs* other treatment Days 8-14: 0.252 (0.100-0.635); $p=0.001$ Days 15-30: 0.277 (0.136-0.563); $p<10^{-4}$	–	26
Notar o 2017	Prospective, observational, monocentric study	27 patients	Allowed dose range: 100-500 mg/day Most frequent dose: 100-200 mg/day (initial dose) and 300 mg/day (after 3 weeks)	6 months	Reduction in NRS score at rest: 44% after 9 days; $p<0.001$ Reduction in NRS score on movement: 27% after 3 days; $p<0.001$ Reduction in PD-Q score: 35% after 21 days; $p<0.01$	Tolerability at 6 months: well-tolerated in 70% of patients	27
Finco 2018	Long-term prospective, single-center, observational study	27 patents refractory to other treatments	Median dose: 300 mg/day	3-week titration 30 months mean FU	Pain intensity: Reduction >40% in all the patients; $p=6.71x10^{-19}$ SF-12 score from baseline to last FU (IQR) Physical component: from 30.3 (38.2-28.0) to 55.5 (56.7-54.3); $p=2.34 \times 10^{-19}$ Mental component: from 30.5 (31.8-26.6) to 50.1 (52.6-45.8); $p=1.03 \times 10^{-15}$ PGIC score: "*definite*" or "*considerable improvement*" at 12 months: 92.6%	Patients with at least one AE: 70.4%	28

*composite endpoint of 3 efficacy components (≥30% improvement of pain, pain-related disability, QoL) and 3 safety components (normal bowel function, no CNS side effects, no TEAE-related discontinuation) LBP: low back pain, ED: emergency department; bsl: baseline; NRS-3: numerical rating scale-3; RCI: repeated confidence interval; QoL: quality of life; RR: response rate; CNS: central nervous system; SF-12: Short Form-12 Health Survey; CGIC: clinician global impression of change scale; PGIC: patient global impression of change scale; LSMD: least square mean difference; IQR: interquartile range

gabalin, but with improved tolerability profile (dizziness: 16.9% *vs.* 27.0%, p=0.03)[24]. Another randomized, controlled, open-label, phase IIIb/IV trial, compared tapentadol PR and oxycodone/naloxone PR in opioid-naive patients affected from severe chronic LBP with a neuropathic pain component[14,25]. Patients were assigned to tapentadol PR 50 mg twice daily or oxycodone/naloxone PR 10 mg/5 mg; after a titration period of 21 days, the maximum twice-daily doses allowed were 250 mg for tapentadol PR and 40 mg/20 mg for oxycodone/naloxone PR[14]. Tapentadol PR was superior over oxycodone/naloxone PR in the reduction of pain intensity from baseline to the final assessment. Moreover, improvements in painDETECT and Neuropathic Pain Symptom Inventory scores were greater with tapentadol PR, and this molecule showed a more favorable tolerability profile than oxycodone/naloxone PR[25].

Several 'field-practice' studies[26-28] have investigated the effectiveness of tapentadol PR for the treatment of LBP, further confirming the effectiveness and safety of this molecule in less stringent conditions than those applied in clinical studies, and up to a 51-month follow-up. In particular, in a prospective study by Finco et al[28], conducted in 27 patients with chronic LBP refractory to other pharmacological treatments, all patients reported a significant improvement of pain intensity and quality of life (QoL) at a maximum follow-up of 51 months (Figure 1).

Interestingly, tapentadol PR has also been tested in the management of chronic neck pain[4], given its dual action on the nociceptive and neuropathic components of pain. In an Italian observational study, Billeci et al[4] evaluated 54 patients with moderate-to-severe chronic neck pain on a starting dose of tapentadol PR of 100 mg/day (dosage could then be adjusted as necessary; mean final dose: 205 mg/day). Pain intensity at movement decreased over time; at baseline, 70% of patients showed a neuropathic component, and this percentage was reduced to 23% at 12 weeks. Tapentadol PR was associated with improved mobility in all planes of motion.

Tapentadol PR in the Treatment of OA Pain

Rationale

Proper treatment of pain is crucial to the management of OA. However, current pharmacological approaches, such as paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs), present limited efficacy and safety[29]. Opioids analgesics may relieve pain in this setting but are associated with some safety concerns[30].

Therefore, there is a major need for new pharmacological options, characterized by marked efficacy and a favorable tolerability profile. In particular, given the major contribution of the neuropathic component to OA pain, tapentadol can be considered a suitable pharmacological option in patients with OA pain[18]. In a recent review, the rationale of use of tapentadol PR in this setting is extensively discussed, together with a detailed presentation of available clinical data[18].

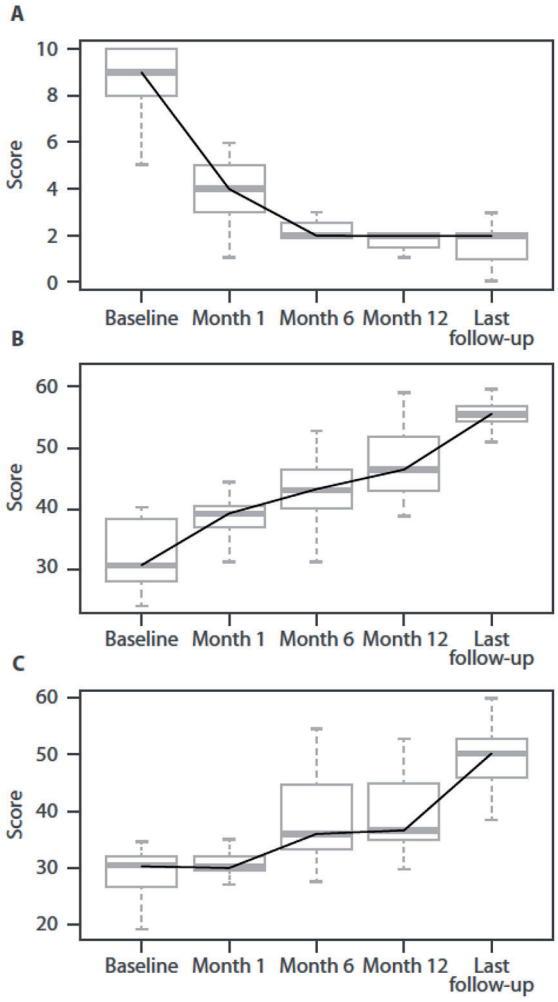

Figure 1. Numeric Rating Scale of Pain during the last 72 hours (NRS-3) **(A)**, Physical Health Composite Scale (PCS) **(B)**, Mental Health Composite Scale (MCS) **(C)** in the study by Finco et al in patients with chronic LBP (maximum follow-up, 51 months) [adapted from Finco 2018][28]. The curves represent a graphical elaboration from available data and are presented for display purposes only.

Clinical Data

Well-grounded clinical data lend support to the efficacy and safety of tapentadol PR in the treatment of OA-associated pain, especially in the non-surgical setting, but also in surgical patients. Evidence on the use of this molecule in the rehabilitation setting has also been published. Table II shows details of the studies in the non-surgical setting.

With respect to the non-surgical setting, Afilalo et al evaluated the efficacy and safety of tapentadol PR (100-250 mg twice daily) compared with oxycodone CR in a randomized, double-blind trial of 1,030 patients with moderate-to-severe chronic knee pain associated with OA[31]. Overall, tapentadol PR was associated with a more evident reduction in pain intensity, compared with oxycodone, and allowed a higher percentage of patients to achieve ≥50% improvement in pain intensity versus baseline, compared with placebo and oxycodone (32.0%, 24.3%, and 17.3%, respectively). Incidence of gastrointestinal AEs was 43.0% with tapentadol PR and 67.3% with oxycodone. The efficacy of tapentadol PR in knee pain owing to OA was also shown in a subsequent open-label trial, which also demonstrated improved functionality parameter (Western Ontario and McMaster Universities OA index) with this treatment[30]. Tapentadol PR was effective and safe in patients who interrupted WHO step III opioids due to poor tolerance[32]. In a comparative, open-label, controlled study[33], patients were randomly assigned to either tapentadol (100 mg twice daily; n=108) or etoricoxib (30 mg twice daily; n=110) for 12 weeks. A higher number of patients reported satisfactory response with tapentadol PR at the end of the study, compared with NSAIDs. Moreover, the incidence of AEs was lower with tapentadol PR (37% *vs.* 49%). Some retrospective studies have also investigated the efficacy and safety of tapentadol, further supporting the effectiveness of this molecule in the non-surgical setting[34,35].

The use of tapentadol PR in the surgical setting has been evaluated in a randomized trial versus oxycodone/naloxone in patients following orthopedic/trauma surgery[36]. Overall, the two treatments showed comparable analgesic efficacy and a similar tolerability profile.

In the rehabilitation setting, Panella et al[37] published the results of a 3-week, open-label study evaluating the efficacy and tolerability of tapentadol PR (50-150 mg twice daily; n=91) compared with paracetamol 1000 mg twice daily (n=53), in patients in rehabilitation after knee replacement surgery. More evident improvement was observed with tapentadol PR than with paracetamol, in particular, on pain intensity, range of motion, and sleep quality.

Tapentadol and QoL

Pain reduction is commonly – and correctly – considered the immediate outcome of any analgesic therapy. However, mounting attention is being paid to some outcomes that go beyond the mere reduction of pain intensity, such as QoL and functional recovery[38].

The link between pain and QoL/functional recovery appears straightforward to understand: a patient with reduced pain will experience an improvement of QoL and a recovery of the function of the affected area(s). Improved QoL and functionality will also increase productivity and working ability, reducing at the same time the need for other medical therapies[38]. A recent paper by Panella et al[38] extensively discusses this issue.

The role of analgesic therapies on the improvement of QoL and functional recovery has been poorly explored to date. However, four studies of tapentadol PR have specifically investigated the effect of this molecule on QoL and functionality[14,24,35,39,40]. In 2010, Lange et al[40] performed a pooled analysis of three phase III randomized studies in patients with chronic OA of the knee or LBP, which compared tapentadol PR (100-250 mg twice daily) with placebo or oxycodone CR (20-50 mg twice daily). At the patient global impression of change (PGIC), 56.7% of patients treated with tapentadol PR reported their overall status to be "much improved" or "very much improved", compared with 37.4% of patients in the placebo group and 49.8% of those treated with oxycodone CR ($p<0.001$). An advantage for tapentadol PR was also observed by analyzing the SF-36 questionnaire: in particular, significant improvements from baseline to endpoint were observed with tapentadol PR compared with placebo in physical functioning, role-physical, bodily pain and vitality scores ($p<0.05$ for all comparisons), and with oxycodone CR in all domains but general health. Similar findings were reported for the EQ-5D questionnaire and the health status index score.

Six years later, Hofmann et al performed a systematic comparison of three randomized trials on tapentadol PR and oxycodone CR in the treatment of chronic OA pain and LBP, for a total of 2,989 patients[39]. Overall, statistical analysis showed the superiority of tapentadol PR in health-related QoL compared with oxycodone

Table II. Key elements from clinical trials on tapentadol PR in the treatment of OA-related pain in the non-surgical setting. *Median modal daily dose=most frequently used daily dose.

Study	Design	Number of patients	Tapentadol PR median modal daily dose*	Duration	Efficacy	Safety	Ref.
Afilalo 2010	Randomized, double-blind, active-(oxycodone CR 20-50 mg bid) and placebo-controlled parallel-arm, multicenter phase III study	1,030 patients	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: -0.68-0.02)	Patients with at least one TEAE: – Tapentadol PR: 61.1% – Oxycodone CR: 75.9% – Placebo: 87.4%	31
Steiger-wald 2012	Open-label, phase IIIb study	195 patients not treated or inadequately managed with WHO step I or II analgesics	TDD: 256.9±111.38 mg Allowed dose range: 50-250 mg bid	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%	30
Steiger-wald 2013	Open-label, phase IIIb study	82 patients intolerant to WHO step III analgesics	TDD: 232.7 ± 145.37 mg Allowed dose range: 50-250 mg bid	5-week titration + 7-week maintenance	Responder rate at week 6: 94.3% (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%	32
Banerjee 2016	Randomized, open-label, active- (etoricoxib 30 mg bid) controlled phase III study	218 patients	100 mg bid	12 weeks	Improvement in pain intensity on VAS and WOMAC 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)	33
Biondi 2015	*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)	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	34
Lange 2017	Pooled analysis of two randomized, double-blind, active-(oxycodone CR 20-50 mg bid) and place-bo-controlled studies	2010 patients	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	

bid: twice daily; CR: controlled release; IR: Immediate release; OA: osteoarthritis; TEAE: treatment-emergent adverse event; TDD: total daily dose; bid: twice a day; CI: confidence interval; VAS: Visual analog scale, WOMAC: Western Ontario and Mc Master University osteoarthritis index

CR and placebo. These findings were further confirmed by those of another pooled analysis of two double-blind, randomized, placebo- and oxycodone CR-controlled studies of 2010 patients with moderate-to-severe OA knee pain[35]. At the analysis of PGIC, more patients on tapentadol PR (57.3%) rated their overall health status at the end of treatment as "very much improved" or "much improved", compared with oxycodone CR (44.7%) and placebo patients (39.5%; $p<0.001$). A significant advantage for tapentadol PR was also observed in terms of physical and mental SF-36 dimensions, as well as for EQ-5D health status and WOMAC score. A dedicated trial by Baron et al[24] led to similar results.

Implications for Clinical Practice

Musculoskeletal pain, encompassing back pain and OA pain, represents the most frequent source of chronic pain in western countries, and it is particularly frequent in older adults. In these conditions, central sensitization, reduction of descending inhibition, descending excitation and cortical atrophies are observed, contributing to the transition to chronic state and enhanced severity of pain. Remarkably, back pain and OA pain present, in the wide majority of cases, both a nociceptive and a neuropathic component of pain. Treatment selection should, therefore, properly consider the ability of a drug to act on both components, reducing the possibility of plastic changes in the central nervous system, and consequently promoting physical rehabilitation.

The pharmacological profile of tapentadol, combining synergistically MOR agonism and NRI in one single molecule with a concomitant reduction in the burden of adverse events, is unique to date and makes this drug particularly suitable for the treatment of back pain and OA-associated pain, especially when a neuropathic component is present.

Clinical data on the efficacy and safety of tapentadol PR in these settings are quite robust and were obtained both in the trial setting and the 'field-practice' scenario. Remarkably, tapentadol PR was well tolerated in all studies, and it is associated with a negligible incidence of AEs frequently associated with opioid therapy, such as constipation and other gastrointestinal AEs: this favorable safety profile is particularly important, given the need of long-term treatment in patients with back pain or OA-associated pain. Tapentadol PR has extensively demonstrated its ability to improve patients' QoL and promote functional recovery. All these advantages have been shown regardless of patient's characteristics – including age, gender, weight, severity of baseline pain, prevalence of the neuropathic component – thus confirming that tapentadol PR can be an effective therapeutic option in all patients. In this line, tapentadol does represent a major step ahead of the optimal balance of efficacy and tolerability which has been proposed to be the key feature of the 'ideal' analgesic.

In conclusion, tapentadol PR represents a well-grounded treatment for chronic back pain and OA-associated pain, supported by a strong mechanistic rationale and strong evidence in clinical studies. Given also the availability of long-term efficacy and safety data, tapentadol PR should be considered as a suitable front-line therapy for these conditions.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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