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REVIEW

Tapentadol: an effective option for the treatment of back pain

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Abstract: Back pain, including low back pain and neck pain, is the leading cause of disability worldwide. This type of pain is challenging to treat, since it presents both a nociceptive and a neuropathic component. The latter also contributes to the evolution of pain toward chronification. Treatment selection should therefore consider the ability to prevent this event. Tapentadol is characterized by a unique and innovative peculiar mechanism of action that makes it the first representative of a new class of central strong analgesics referred to as MOR-NRI. This molecule acts both on the nociceptive and neuropathic components of pain, and it can therefore be effective in the treatment of a mixed pain condition such as back pain. This narrative review discusses the rationale for the use of tapentadol in both low back pain and neck pain and presents available clinical data. Overall, data show that tapentadol prolonged release is a well-grounded treatment for chronic back pain, sustained by a strong mechanistic rationale and robust evidence. Given also the availability of long-term efficacy and safety data, we believe that this molecule should be considered as an elective therapy for chronic back pain.

Keywords: tapentadol, low back pain, neck pain

Introduction

Low back pain (LBP) is one of the most frequent chronic pain conditions worldwide, with a lifetime prevalence >70% in western countries and a heavy burden for the healthcare system.[1–3] Indeed, LBP is now considered the leading cause of disability worldwide. Remarkably, more than two out of three patients experiencing acute LBP attacks ultimately develop chronic LBP.[4] Moreover, chronic LBP is frequently associated with comorbid conditions, including depression, panic and anxiety disorders, and sleep disturbances.[5]

Although sometimes neglected when compared with LBP, neck pain is also a common disabling disease.[6] Indeed, the prevalence of neck pain can be as high as 23%.[7] Therefore, the economic burden of neck pain is also high, mostly due to increased need of medical visits, physiotherapy, pharmacological and surgical treatments, working days lost, and compensation expenditure.[8]

Noteworthy, chronic LBP or neck pain – collectively, back pain – results from chronification processes occurring over time and involving plastic alterations of the involved structures.[9–11] Back pain presents in the wide majority of cases (>90%) as a neuropathic component.[9,12] Proper selection of treatment is therefore of paramount importance. In this setting, routine use of classical opioids is not recommended, since benefits are small and substantial risks exist, including overdose and addiction potential, and poorer long-term outcomes than without use.[13]

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Tapentadol is a dual μ-opioid receptor (MOR) agonist and noradrenaline reuptake inhibitor (NRI), which was rationally designed, and represents the first and unique member of a new class of analgesic agents, MOR-NRI.[14] Remarkably, the "μ-load" of tapentadol is ≤40% relative to classical MOR agonists. This reduced μ-load results from the combination and synergistic interaction of the two mechanisms of analgesic action. Due to this, lower opioid activity is needed to reach comparable analgesia and therefore a more favorable tolerability profile is achieved, in terms of gastrointestinal, respiratory, and endocrinological adverse events.[15,16] Moreover, tapentadol shows minimal serotoninergic activity, with potential safety advantages over the long term in terms of risk of emesis.[17]

This narrative review discusses the rationale for the use of tapentadol in both LBP and neck pain and presents available clinical data.

Tapentadol in the treatment of LBP

Rationale of use

Chronic LBP is a heterogeneous condition, where both nociceptive and neuropathic pain mechanisms may be involved.[5] In particular, nociceptive pain results from the activation of nociceptors as a response to tissue injury and biomechanical stress. On the other hand, the neuropathic component arises from injury affecting the nerve roots that innervate the spine and lower limbs, and pathological invasive innervation of the damaged lumbar discs. This latter component has often been underestimated when selecting appropriate treatment for LBP.[5]

Indeed, several practice guidelines for the management of chronic LBP have been published.[18–21] In most cases, they advise a multimodal approach for the management of chronic LBP, combining pharmacological therapies with nonpharmacological approaches. However, these guidelines typically do not include specific recommendations for the treatment of the neuropathic components of this type of pain. Moreover, available guidelines for the treatment of neuropathic pain are usually focused on disease other than LBP, such as postherpetic neuralgia or painful diabetic neuropathy.[22–25]

Noteworthy, studies of LBP are typically short term (<3 months duration), and evidence of effectiveness and safety associated with long-term treatment is currently limited.[5,26] In addition, few head-to-head trials comparing different treatments and combination strategies have been published, and therefore, direct comparisons of drug efficacy and tolerability are not possible.

Tapentadol prolonged release (PR) has been proven to provide a strong analgesic effect, due to its synergic MOR and NRI action.[9,10,27,28] Remarkably, the different pharmacological effects of tapentadol are not synergic in terms of adverse effects.[29] Noteworthy, these benefits are paralleled by improvements in quality of life (QoL).[30] Therefore, tapentadol PR may be considered a particularly suitable option in patients with chronic LBP, given the important neuropathic component of this condition. The efficacy of tapentadol in this setting is also supported by the results of a Cochrane Review – although published in 2015, it also includes studies on osteoarthritis – which shows that tapentadol PR is associated with a reduction in pain intensity compared with placebo and oxycodone and presents improved safety compared with oxycodone.[31] However, the authors of this review pointed out that some methodological flaws were present in the studies considered, therefore reducing the quality of the results.

Clinical data

The efficacy and safety of tapentadol PR were extensively tested in patients with LBP, both in an experimental and in a "field-practice" settings, and in comparative studies (Table 1).

In the pivotal trial of tapentadol in LBP, with a randomized, double-blind, placebo-controlled design, ~1,000 patients were assigned to tapentadol PR 100–250 mg twice daily, oxycodone controlled release (CR) 20–50 mg twice daily or placebo over 15 weeks (3-week titration period, 12-week maintenance period).[32] Overall, both tapentadol PR and oxycodone significantly reduced average pain intensity, as assessed by the numerical rating scale (NRS), vs placebo at week 12 and throughout the maintenance period; however, tapentadol was associated with a lower incidence of treatment-emergent adverse events (TEAEs). Indeed, the incidence of gastrointestinal TEAEs, including constipation, nausea, and vomiting, was 43.7% with tapentadol and 61.9% with oxycodone CR. Moreover, the odds of experiencing constipation or the composite of nausea and/or vomiting were lower with tapentadol PR than with oxycodone CR ($P<0.001$).

In another Phase IIIb study, with an open-label design and without a control group, Gálvez et al evaluated the effectiveness and tolerability of tapentadol PR in the management of severe chronic LBP in patients with poor tolerance to opioids.[33] Equi-analgesic ratios for tapentadol to strong opioids were calculated, and patients switched directly to tapentadol. Patients received tapentadol PR 50–250 mg twice daily over a 5-week titration and a 7-week maintenance

Table 1 Key elements from clinical trials on tapentadol PR in the treatment of OA-related pain in the nonsurgical setting

Study (year)	Design	Patients enrolled	Tapentadol PR median modal daily dose[a]	Duration study treatment	Efficacy on pain (primary endpoint)	Safety
Buynak et al (2010)[32]	Prospective, randomized, double-blind, active- (oxycodone CR 20–50 mg bid) and placebo-controlled Phase III study	981 patients with moderate-to-severe LBP	TDD: 313.2±116.7 mg Allowed dose range: 100–250 mg bid	3-week titration + 12-week maintenance	LSMD (95% CI) in pain intensity (NRS-3) at week 12 vs baseline tapentadol PR vs placebo: –0.8 (–1.22, –0.47); $P<0.001$ oxycodone CR vs placebo: –0.9 (–1.24, –0.49); $P<0.001$ 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% Gastrointestinal TEAE tapentadol PR: 43.7% oxycodone CR: 61.9% placebo: 26.3%
Gálvez et al (2013)[33]	Open label, multicenter, Phase IIIb study	125 patients with chronic LBP and low tolerance to WHO step III opioids	TDD (week 6): 322.8±120.73 mg Allowed dose range: 50–250 mg bid tapentadol IR TDD (week 6): 24.6±32.96 mg Allowed dose: 50 mg (≤ bid; ≥4 hours apart)	5-week titration + 7-week maintenance	Response rate week 6: 80.9%; $P<0.0001$ vs null Hp Mean ± SD change in pain intensity (NRS-3) vs baseline Week 6: –0.9±1.89; $P<0.0001$ Week 12: –1.3±2.10; $P<0.0001$	Patients with at least one TEAE: 68.0% (78.6% mild-to-moderate) Gastrointestinal TEAEs: 46%
Baron et al (2015)[34]	Randomized, double-blind, active- (tapentadol PR + pregabalin) controlled, multicenter, Phase IIIb study	445 patients with chronic LBP with a neuropathic component; average pain intensity (NRS-3) ≥4 and ≥1 point decrease in pain intensity after titration	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% Composite of dizziness and/ or somnolence tapentadol PR: 16.9% tapentadol PR + pregabalin: 27.0% ($P=0.0302$)
Baron et al (2015)[35]	Open label, continuation arm of randomized Phase IIIb study[32]	59 patients with chronic LBP with a neuropathic component; average pain intensity <4	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%
Baron et al (2016)[36]	Randomized, open-label, active (oxycodone/naloxone PR 10 mg/5 mg – 40 mg/20 mg) controlled, Phase IIIb/IV study	258 opioid-naïve patients with severe chronic LBP with a neuropathic component	Allowed dose range: 50–250 mg bid	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 97.5% RCI for tapentadol PR minus oxycodone/naloxone PR: –1.820,–0.184; $P<0.001$ for non-inferiority	Patients with at least one TEAE tapentadol PR: 76.9% oxycodone/naloxone PR: 83.6% Gastrointestinal TEAEs tapentadol PR: 44.6% oxycodone/naloxone PR: 51.6%

(*Continued*)

Table 1 (*Continued*)

Study (year)	Design	Patients enrolled	Tapentadol PR median modal daily dose[a]	Duration study treatment	Efficacy on pain (primary endpoint)	Safety
Ueberall et al (2016)[37]	Observation cohort study of real-world data	579 patients with chronic LBP included in the German Pain Registry	TDD: 318.9±63.9 mg/day Dose range: 150–450 mg/day	12 weeks	Oxycodone PR vs tapentadol PR Primary endpoint response[a]: 39.8% vs 25.6%; *P*=0.014	
					≥30% RR pain intensity: 85.2% vs 83.5%; *P*=NS Pain-related disability: 78.1% vs 66.9%; *P*=0.043 QoL: 76.6% vs 63.9%; *P*=0.026	Normal bowel function: 68.0% vs 72.2%; *P*=NS No CNS side effects: 91.4% vs 89.5%; *P*=NS No TEAE-related discontinuation: 93.0% vs 92.5%; *P*=NS
Guillén-Astete et al (2017)[39]	Retrospective observational study	732 patients attending ED due to LBP (91 treated with tapentadol)	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); $P<10^{-4}$	–
Notaro (2017)[40]	Prospective, observational, monocentric study	27 patients with chronic severe LBP (NRS ≥5)	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 tolerated in 30% of patients
Finco et al (2018)[41]	Long-term prospective, single-center, observational study	27 patents with refractory chronic moderate-to-severe LBP	Median dose: 300 mg/day	3-week titration 30 months mean FU	Pain intensity Reduction >40% in all the patients; $P=6.71\times10^{-19}$ 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); $P=2.34\times10^{-19}$ Mental component: from 30.5 (31.8–26.6) to 50.1 (52.6–45.8); $P=1.03\times10^{-15}$ PGIC score "definite" or "considerable Improvement" at 12 months: 92.6%	Patients with at least one AE: 70.4% Most common AEs Mild drowsiness: 37% Nausea: 26% Moderate constipation: 22%

Notes: [a]Composite endpoint of three efficacy components (≥30% improvement of pain, pain-related disability, QoL) and three safety components (normal bowel function, no CNS side effects, no TEAE-related discontinuation). *Median modal daily dose = most frequently used daily dose.

Abbreviations: AE, adverse event; ED, emergency department; baseline, bsl; 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; LBP, low back pain; TEAE, treatment-emergent adverse event; OA, osteoarthritis; NRS, numerical rating scale; TDD, total daily dose; PR, prolonged release; FU, follow-up; bid, twice daily; LS, least square; NS, not significant.

period. Responder rate (ie, reduced intensity of pain by NRS) at week 6 was 80.9% ($P<0.0001$ vs the null responder hypothesis rate, <60%), resulting in a positive trial despite premature termination. Moreover, reduced intensity of pain was maintained up to week 12. The prevalence of adverse events was reported as the reason for switching to tapentadol – in most cases constipation and nausea – decreased over time. Overall, these data show that tapentadol PR provided at least comparable analgesia and improved tolerability vs strong opioids in patients with severe, chronic LBP. In 2015, Baron et al published the results of a randomized, double-blind study comparing the effectiveness and tolerability of tapentadol PR monotherapy vs tapentadol PR/pregabalin combination therapy for severe chronic LBP with a neuropathic component.[34] All patients had painDETECT "unclear" or "positive" ratings and average pain intensity at baseline of ≥6 on an NRS. Patients were then titrated to tapentadol PR 300 mg/day over 3 weeks, and those with ≥1-point decrease in pain intensity and average pain intensity ≥4 were assigned to tapentadol PR (500 mg/day) or tapentadol PR (300 mg/day)/pregabalin (300 mg/day) for an 8-week comparative period. In the per-protocol population, which consisted of 288 patients, the effectiveness of tapentadol PR was comparable to tapentadol PR/pregabalin; similarly, neuropathic pain and QoL measures improved in both the groups. Tolerability was good, but the incidence of the composite of dizziness and/or somnolence was lower with tapentadol PR (16.9%) compared with tapentadol PR/pregabalin (27.0%; $P=0.0302$). According to these data, tapentadol PR monotherapy may be considered a favorable treatment option for severe LBP with a neuropathic component. In the extension phase of this trial, a subpopulation with pain intensity <4 continued receiving tapentadol PR 300 mg/day during an 8-week, open-label continuation arm.[35] Overall, greater improvements in all measures were observed for this selected population. In another randomized, controlled, open-label, Phase IIIb/IV study by the same group, the effectiveness of tapentadol PR was compared with that of oxycodone/naloxone PR in opioid-naive patients with severe chronic LBP and a neuropathic pain component.[36] Patients were randomly assigned to tapentadol PR 50 mg twice daily or oxycodone/naloxone PR 10 mg/5 mg. After a 21-day titration, maximum allowed twice-daily doses were 250 mg for tapentadol and 40 mg/20 mg for oxycodone/naloxone. Target doses were then continued for 9 weeks. The primary effectiveness endpoint was the change in NRS-3 from baseline to final evaluation; the exact repeated confidence interval for tapentadol PR minus oxycodone/naloxone PR was used to establish noninferiority (upper limit <1.3) and superiority (confirmatory analyses). For the primary effectiveness endpoint (change in pain intensity from baseline to final evaluation), tapentadol PR was superior over oxycodone/naloxone ($P<0.003$).[36] Pain intensity at baseline was 7.6 in both groups; at final evaluation, it was 4.8 with oxycodone/naloxone (mean change vs baseline, –2.7) and 3.9 with tapentadol PR (mean change vs baseline, –3.7).[36] Moreover, improvements in painDETECT and Neuropathic Pain Symptom Inventory scores were greater with tapentadol PR, and this molecule was associated with a more favorable tolerability profile. On these bases, the authors concluded that tapentadol PR may be considered a first-line option for managing severe chronic LBP with a neuropathic pain component.

Several studies have also investigated the effectiveness of tapentadol PR for the treatment of LBP in the "field-practice" setting, although with all the inherent limitations of any observational analysis. Ueberall et al analyzed randomly selected data of the German Pain Registry, collected over a 12-week period, of adult patients treated with either tapentadol PR (n=133) or oxycodone/naloxone (n=128).[37] The primary endpoint was a composite of ≥30% improvement of pain, pain-related disability, and QoL and three tolerability components (normal bowel function, absence of either central nervous system side effects, and TEAE-related treatment discontinuation during the observation period). Overall, the two treatments were comparable in terms of effectiveness and safety. However, this study was judged to be affected by major methodological bias,[38] and therefore, its results should be considered with caution. A retrospective observational study was conducted by Guellen-Astete et al, who evaluated patients attending the emergency department (ED) due to LBP over a period of 24 months.[39] Among 732 patients referring to the ED, 91 were treated with tapentadol. In the first month after the first assessment, reassessments were less frequently observed in the tapentadol group, reaching statistical significance from day 8 onwards. Patients on tapentadol also had a better clinical evolution of pain compared with those who did not receive this analgesic drug. In another 6-month "field-practice" monocentric experience, with a prospective design, Notaro evaluated 27 patients treated with tapentadol PR for chronic (>1 year in about 90% of patients) severe LBP.[40] All patients had received previous analgesic therapy; treatment with tapentadol PR was started at 100 mg/day and could be increased up to 500 mg/day. Tapentadol PR promptly reduced the average intensity of pain at rest (–44% at 9 days) and pain on movement (–27% at 3 days; $P<0.01$ for both comparisons). Moreover, the neuropathic component of pain, QoL,

and health status improved. No relevant safety signals were reported. In a long-term prospective experience, Finco et al investigated the effectiveness, safety, and tolerability of oral formulation of tapentadol PR in 27 patients with refractory chronic LBP over a long-term follow-up (up to 51 months).[41] All the patients reported a significant improvement of pain intensity and QoL at last follow-up, and, remarkably, no relevant safety concerns were reported. Overall, these results further confirm the long-term effectiveness, safety, and tolerability of oral tapentadol PR for the treatment of chronic LBP.

The identification of predictive factors of response would improve treatment selection and reduce healthcare costs. In a retrospective analysis of an open-label study, 46 baseline characteristics of the 122 evaluated patients were included in statistical prediction modeling.[42] Overall, demographic data were not relevant for response prediction. The most important predictive factors were QoL and functionality. Neuropathic symptoms (high painDETECT score) had a positive predictive validity, while painful attacks and classical yellow flags (depression, anxiety) were negative predictors of response.

A remarkable new field of investigation is represented by the association of nutraceuticals and tapentadol in the treatment of LBP.[43] In a pilot Italian study, the addition of ultra-micronized palmitoylethanolamide to tapentadol led to a major reduction in pain intensity, with a good QoL and without any serious adverse event.[43]

Tapentadol in the treatment of neck pain

Neck pain may be caused by several different conditions that compress, irritate, and eventually destroy sensitive structures, including the annulus fibrosus, posterior longitudinal ligament, and the capsule of the zygapophyseal joints.[44] Remarkably, relapses and establishment of chronic pain are frequent among patients with neck pain and cervical radiculopathy, leading to major impairments in QoL, activity limitation, and disability. Central sensitization is thought to play a major role in the progression to chronic neck pain.[9] However, only few studies are available on the efficacy of different pharmacological treatments for neck pain, and the only published recommendations on the pharmacological approach for this disease is based on expert opinion.[6]

On these bases, tapentadol PR has been tested in the management of chronic neck pain, given its dual action on the nociceptive and neuropathic components of pain.[6] In a small observational study, Billeci et al evaluated 54 patients with moderate-to-severe (mean NRS 8.1) chronic neck pain receiving tapentadol PR 100 mg/day; dosage could be adjusted according to clinical needs. Over a 12-week period, the dosage of tapentadol PR increased up to 204.5±102.8 mg/day. Mean pain intensity at movement decreased over time (mean change at final evaluation vs baseline, –5.9).[6] At baseline, 70% of patients presented a positive neuropathic component, and this percentage decreased to 23% at 12 weeks; a 35% decrease was evident already at week 2.[6] Tapentadol PR was also associated with an improvement in the Neck Disability Index scores (from 55.6±18.6 at baseline to 19.7±20.9 at 12 weeks; $P<0.01$), and with increased range of motion in all three planes, particularly in lateral flexion. QoL significantly improved, and ~90% of patients rated their overall condition as much/very much improved. No patients discontinued tapentadol due to side effects and the use of other analgesics diminished during the observed period. Overall, these findings suggest that tapentadol PR is effective and well tolerated in patients with moderate-to-severe chronic neck pain and is associated with a relevant improvement of movement functionality and QoL.

Conclusion

Back pain, including LBP and neck pain, is the leading cause of disability worldwide. This type of pain is challenging to treat, since it presents, in the wide majority of cases, as a mixed pain characterized by a nociceptive and a neuropathic component. The latter also contributes to the chronification. Treatment selection should therefore consider the ability to prevent pain chronification by acting on the noradrenergic axis.

The pharmacological profile of tapentadol, combining synergistically MOR agonism and NRI in one molecule, appears to be unique, and therefore, this molecule has been proposed to be the first-in-class for a new class of centrally acting analgesics, namely MOR-NRI.[14] Experimental evidence that NRI is a key mechanism that can be predominant in chronic LBP reinforces the concept that tapentadol is different from classical opioids and may therefore be an a priori choice for the treatment of chronic, neuropathic, and mixed pain.[15,45,46]

Clinical data on the efficacy of tapentadol PR in back pain are quite solid and do confirm its strong pharmacological rationale of use. Moreover, tapentadol PR is well-tolerated, and it is associated with a negligible incidence of adverse events associated with opioid therapy (eg, constipation and gastrointestinal events) and effects on hormonal axes.[47] This favorable safety profile is of utmost importance, given the frequent need of long-term treatment in patients with back pain. To this end, it is worth mentioning that tapentadol has a low potential of abuse and can be easily titrated and tapered in clinical practice;[48,49]

dedicated studies should further investigate the titration/tapering and exit strategies with tapentadol PR.

In conclusion, tapentadol PR is a well-grounded treatment for chronic back pain, sustained by a strong mechanistic rationale and robust evidence. Given also the availability of long-term efficacy and safety data, we believe that this molecule should be considered as the elective therapy for chronic back pain.

Key points

- Back pain, including LBP and neck pain, is the leading cause of disability worldwide.
- This pain is challenging to treat, since it usually presents as a mixed pain characterized by a nociceptive and a neuropathic component. The latter also contributes to chronification.
- Treatment selection should therefore consider the ability to prevent chronification by acting on the noradrenergic axis.
- Tapentadol is characterized by a unique peculiar mechanism of action, and it is the only member of the MOR-NRI class of analgesic. This molecule acts on both the nociceptive and neuropathic components of pain, and it can be therefore effective in the treatment of back pain.
- Clinical data on the efficacy of tapentadol PR in back pain are quite solid and do confirm its strong pharmacological rationale of use.
- Tapentadol PR is well tolerated, and it is associated with a negligible incidence of adverse events associated with opioid therapy (eg, constipation and gastrointestinal events). This favorable safety profile is of utmost importance, given the frequent need of long-term treatment in patients with back pain.

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