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Practical Considerations for the Use of Tapentadol Prolonged Release for the Management of Severe Chronic Pain

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ABSTRACT

Purpose: Chronic pain is often challenging to address appropriately. Although patients with severe chronic pain may respond to treatment with an opioid analgesic, opioids are often associated with adverse effects that may lead patients to disrupt or discontinue therapy. In addition, opioid analgesics alone may not be effective for all types of chronic pain, including neuropathic pain. Tapentadol prolonged release (PR), a centrally acting analgesic with 2 mechanisms of action (μ -opioid receptor agonism and noradrenaline reuptake inhibition), provides strong and reliable analgesia across a range of indications, including nociceptive, neuropathic, and mixed types of chronic pain, and is associated with an improved tolerability profile relative to classic opioid analgesics. The purpose of this article was to review the recent literature on different aspects related to the clinical use of tapentadol PR.

Methods: A review was conducted of the current literature and relevant unpublished data on initiation and titration of tapentadol PR, switching from classic strong opioids, risk of withdrawal after discontinuation, long-term treatment, coadministration with other medications, and risk of abuse and diversion.

Findings: Tapentadol PR may provide clinically meaningful benefits over classic opioid analgesics, including ease of initiating and titrating tapentadol PR treatment in opioid-naïve and opioid-experienced patients, low risk of withdrawal after cessation of tapentadol PR therapy, a favorable pharmacokinetic profile (allowing for coadministration with other medications) of tapentadol PR, and low potential for tapentadol PR abuse.

Implications: The broad analgesic efficacy of tapentadol PR may simplify chronic pain management by allowing for the treatment of different types of pain

with a single analgesic. In addition, tapentadol is associated with a low risk of pharmacokinetic interactions, which permits its use in patients taking multiple medications. Furthermore, the favorable tolerability profile of tapentadol PR may result in improved patient compliance and allow for easy titration and rotation from previous strong opioids. (*Clin Ther.* 2014;■:■■■-■■■) © 2014 The Authors. Published by Elsevier HS Journals, Inc.

Key words: pain management, prolonged release, severe chronic pain, tapentadol.

INTRODUCTION

Chronic pain is a common complaint, with a mean prevalence of 27% in the general European adult population.¹ Chronic pain may have a negative effect on physical function, mental health, day-to-day activities, and interpersonal relationships, and may be associated with significant costs related to lost work days and increased health care utilization.¹⁻³ The negative effects of chronic pain on patients' overall health and well-being are compounded by poor pain control, which is relatively common for patients with chronic pain. In a 2006 survey of 4389 European patients with chronic pain, 34% had severe pain and 40% felt that their pain was not adequately controlled; furthermore, >50% of patients taking prescription medications for their chronic pain felt that

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these treatments were not effective or were only somewhat effective.³

The challenges associated with achieving adequate pain management for patients with severe chronic pain are manifold. Patients with severe chronic pain may require treatment with an opioid analgesic, which may provide effective analgesia for severe chronic pain but may be associated with adverse effects (eg, nausea, vomiting, constipation, and somnolence) that could lead to the use of inadequate doses or to the disruption or discontinuation of therapy.⁴⁻⁷ Some opioid-induced adverse effects, such as constipation, may be refractory to standard treatments and may not resolve with continued opioid treatment.^{8,9} Patients may also develop tolerance to opioid analgesics over time and may require higher doses to achieve adequate analgesia,¹⁰ which may exacerbate tolerability issues. Furthermore, the use of a single analgesic (eg, an opioid) may be insufficient to address mixed or neuropathic chronic pain because nociceptive and neuropathic types of chronic pain arise from different pain mechanisms.¹¹ The development of chronic pain in general, and neuropathic pain in particular, seems to be related to alterations in descending noradrenergic modulation mechanisms¹¹; thus, addressing mixed or neuropathic pain may require the use of combination therapy that addresses the ascending and descending pain pathways.^{12,13} The use of combination therapy with an opioid analgesic and a coanalgesic may be associated with an increased risk of adverse effects or treatment discontinuation in relation to monotherapy.^{14,15} In addition, determining the correct balance of doses of the opioid analgesic and coanalgesic to optimize efficacy and tolerability may pose a substantial challenge, and patients may be less willing to comply with treatment with multiple medications. The use of a single analgesic that could address multiple pain mechanisms while providing tolerable and effective pain control for long-term treatment may alleviate many of the problems associated with managing severe chronic pain.

Tapentadol represents a proposed new class of centrally acting analgesics with 2 mechanisms of action, μ -opioid receptor (MOR) agonism and norepinephrine reuptake inhibition (NRI),^{16,17} that contribute synergistically to its analgesic activity.^{18,19} Both mechanisms of action reside in the parent compound; thus, the analgesic activity of tapentadol is not reliant on metabolic activation, and tapentadol has a

predictable and reliable pharmacokinetic profile for clinical use.^{20,21} By combining MOR agonism and NRI in a single molecule, tapentadol may offer improvements in efficacy and tolerability compared with classic opioid analgesics.¹⁷ In preclinical studies, tapentadol was found to have a lower affinity for the MOR than was morphine.^{16,22} Despite this lower affinity for the MOR, clinical trials have reported that tapentadol provides at least comparable pain relief to other classic strong opioids (eg, oxycodone)²³⁻³⁰ because of the synergistic contribution of NRI to its analgesic activity.³¹ The lower affinity of tapentadol for the MOR compared with classic opioid analgesics may contribute to the reduction in opioid-related adverse effects observed with tapentadol compared with oxycodone.²³⁻³⁰

For patients with chronic pain who require long-term analgesic treatment, prolonged-release (PR) analgesics allow for less frequent dosing and more consistent pain management.³² The PR formulation of tapentadol, which is taken twice daily, is approved in Europe for the management of severe chronic pain in adults, which can be adequately managed only with opioid analgesics,³³ and in the United States (tapentadol extended release) for the management of moderate to severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period.³⁴ In the United States, the extended-release formulation is also indicated for pain associated with diabetic peripheral neuropathy (DPN).³⁴ Tapentadol PR, a World Health Organization (WHO) step III analgesic, is a scheduled substance in the United States and Europe.^{33,35} Since 2010, PR formulations of tapentadol have been launched in a variety of major European countries, the United States, Canada, and Australia.

Tapentadol PR has been evaluated in patients with severe or moderate to severe chronic low back pain,^{24,29,36,37} osteoarthritis knee pain,^{23,29,38} pain associated with DPN,³⁹⁻⁴¹ and cancer-related pain,⁴²⁻⁴⁴ and has been found to provide strong and reliable analgesia across a broad range of indications. Tapentadol PR has also been associated with improvements in neuropathic pain symptoms and quality of life in patients with neuropathic pain,^{37,45} which are not consistently observed with classic opioid treatments.⁴⁶⁻⁵¹ The broad effectiveness of tapentadol PR for nociceptive, neuropathic, and mixed types of chronic pain,

which is likely due to its combination of MOR agonism and NRI activities,^{18,19} may simplify chronic pain treatment by eliminating the need to isolate and treat the individual types of chronic pain with a combination of different analgesics and coanalgesics. Tapentadol PR may also facilitate chronic pain management because tapentadol is associated with a low risk of pharmacokinetic interactions,^{20,21} making it a viable option for poly-medicated patients, including elderly patients. In addition, the favorable tolerability profile of tapentadol PR^{23,24,29} relative to classical opioid analgesics may be associated with improved patient compliance, which, along with the low risk of tolerance development observed over 1 year of treatment,³⁰ may allow for stable long-term dosing and consistent analgesia. Furthermore, the relatively low risk of adverse effects associated with tapentadol PR may allow for rapid up-titration, allowing patients to achieve pain control more quickly. Thus, the integration of tapentadol PR as a first option for patients needing an opioid analgesic to control their pain, or as an alternative for patients with inadequately managed pain or intolerable adverse effects when taking another opioid, may simplify chronic pain management and improve patient outcomes. This article summarizes various aspects of the practical handling of tapentadol PR in a clinical setting, including the established titration regimen for tapentadol PR, the convenient conversion from other strong opioid analgesics to tapentadol PR, the efficacy of the available dose range for severe pain, the low potential of withdrawal after discontinuation of tapentadol PR, the use of tapentadol PR with concomitant medications, and the low potential for tapentadol PR abuse.

INITIATION, TITRATION, AND DOSING OF TAPENTADOL PR TREATMENT

Initiation, Titration, and Dosing of Tapentadol PR in the General Population With Chronic Pain

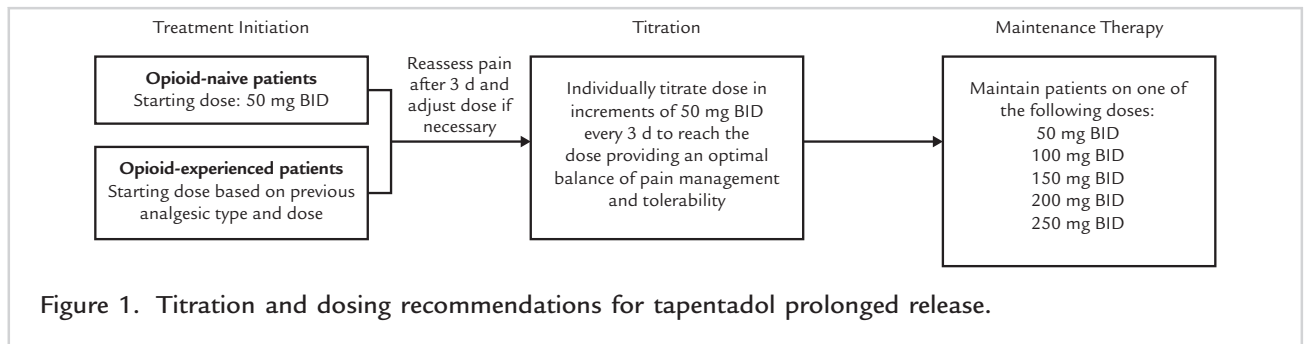
Achieving adequate pain control rapidly while minimizing intolerable adverse effects is a goal for many patients with chronic pain initiating a new analgesic regimen. For patients with severe chronic pain who are treated with an opioid analgesic, low starting doses and slow upward titration are recommended to minimize the risk of opioid-related adverse events.^{52,53} This cautious approach is warranted because opioid analgesics may be associated with potential severe adverse effects that may be exacerbated

by rapid increases in doses.⁵³ Opioid-naive patients are particularly at risk for early adverse effects (eg, nausea and vomiting) and are more vulnerable to the rare, but serious, tolerability issue of respiratory depression.^{7,54} With a slow titration schedule, however, patients may experience delays in achieving adequate analgesia. Furthermore, patients may be unable to use sufficient doses of opioid analgesics to achieve adequate pain control owing to the occurrence of intolerable adverse effects.⁴⁻⁷

Tapentadol PR has been associated with improved tolerability (specifically, lower incidences of nausea, vomiting, dizziness, and constipation) relative to the classic opioid analgesics oxycodone controlled release (CR)^{23,24,29,30} and morphine CR.⁴² In a randomized placebo- and active-controlled study of tapentadol PR for the management of moderate to severe chronic low back pain, the odds of experiencing constipation or the composite of nausea and vomiting was significantly lower with tapentadol PR than with oxycodone CR ($P < 0.001$ for both comparisons).²⁴ In that same study, the incidence of the central nervous system (CNS)-related adverse event of dizziness was significantly lower with tapentadol PR than with oxycodone CR ($P < 0.05$).⁵⁵ The rate of discontinuations due to any CNS-related adverse event was also numerically lower with tapentadol PR (6.2%) than with oxycodone CR (14.0%).²⁴ Although patients often develop tolerance to these adverse effects with continuing opioid treatment, the occurrence of nausea and vomiting early in the course of therapy may reduce patient adherence to treatment^{4,5,7} or may delay increases in analgesic doses, resulting in inadequate analgesia. Furthermore, tapentadol PR has also been associated with a reduction in the occurrence of adverse effects that typically do not resolve with continued opioid treatment (eg, constipation) relative to other opioids,^{23,24,29} which may improve quality of life for patients undergoing long-term therapy. The improved tolerability profile, particularly the improved gastrointestinal tolerability profile, of tapentadol PR may allow for relatively rapid up-titration of doses and the use of higher doses (up to 500 mg/d), which may allow patients to achieve effective pain control more rapidly.

In opioid-naive patients, the recommended starting dose of tapentadol PR is 50 mg BID (approximately every 12 hours), and that dose should be individually titrated to the dose within the range of 50 to 250 mg

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BID that provides an optimal balance of analgesic efficacy and tolerability (Figure 1).³³ For patients who are currently taking opioid analgesics, the recommended starting dose of tapentadol PR depends on the type and daily dose of the previous opioid. A titration regimen in which twice-daily doses of tapentadol PR are increased by 50 mg BID every 3 days is appropriate for most patients to achieve adequate pain control.³³ A more rapid titration schedule may be considered for patients with uncontrolled pain.^{37,38,45,56} The recommended dose range of tapentadol PR is 50 to 250 mg BID; daily doses of > 500 mg of tapentadol PR are not recommended.³³ Tapentadol PR is available in 50-, 100-, 150-, 200-, and 250-mg dose strengths.³³ A 25-mg tapentadol PR tablet formulation, currently available in Spain, may offer a future option for finer dose adjustments up to 250 mg BID in patients with a potential higher sensitivity to the analgesic effects of tapentadol PR (eg, elderly patients, patients with hepatic impairment).

The easy and reliable titration schedule and the use of doses within the recommended dose range are supported by the results of 4 key Phase III studies of tapentadol PR in patients with moderate to severe chronic low back pain,^{24,30} osteoarthritis pain,^{23,30} or pain related to DPN,^{40,57} and the results of 2 recent Phase IIIb studies of tapentadol PR in patients with severe chronic osteoarthritis knee pain³⁸ or low back pain with or without a neuropathic component.³⁷ The mean (SD) doses of tapentadol PR taken after the initial titration periods in each study are shown in Table I; mean total daily doses (TDDs) in the Phase IIIb studies^{37,38} were lower than those observed in the Phase III studies.^{23,24,30,40} This difference was possibly due to the permitted use of concomitant WHO step I analgesics or coanalgesics during study treatment (which is more representative of clinical practice) in the Phase IIIb studies,^{37,38} whereas no concomitant

analgesics were permitted in the Phase III studies other than paracetamol/acetaminophen, which was used as a rescue drug.^{23,24,30,40} At these doses, tapentadol PR was associated with effective and tolerable relief of chronic pain.^{23,24,30,37,38,40}

Efficacy data were pooled from 3 similarly designed, randomized, double-blind, Phase III studies comparing tapentadol PR (100–250 mg bid) with placebo and oxycodone hydrochloride CR (20–50 mg bid) in patients with moderate to severe, chronic low back pain (1 study²⁴) and chronic osteoarthritis pain (2 studies²³). Mean changes from baseline in pain intensity (last observation carried forward [LOCF]) over time from that pooled analysis are shown in Figure 2.²⁹ Based on the change in mean pain intensity (11-point numerical rating scale [NRS]) from baseline for the overall 12-week maintenance period (LOCF), tapentadol PR met the primary end point of showing noninferior efficacy, and even superior efficacy based on the outcome of a preplanned additional analysis, to that of oxycodone CR (least-squares mean difference for tapentadol PR vs oxycodone CR = 0.2; 95% CI, 0.01–0.40; $P = 0.037$ for superiority). Sensitivity analyses using different methods of imputation (baseline observation carried forward [BOCF], worst observation carried forward [WOCF], and modified BOCF) also indicated that tapentadol PR provided superior analgesic efficacy to oxycodone CR (Figure 3). Tapentadol PR also showed significantly greater improvements from baseline than oxycodone CR for measures of health-related quality of life, including the 36-item Short Form Health Survey physical and mental component summary scores ($P < 0.001$ for both comparisons) and all subscale scores ($P \leq 0.048$ for all comparisons) except general health ($P = 0.061$; Figure 4). Similar results were observed when efficacy data were pooled from the

Table I. Total daily doses (TDDs) of tapentadol PR in clinical studies. Data are given as mean (SD) milligrams.

Study	TDD
Phase III studies	
Low back pain study ²⁴	381.8 (117.13)*
Osteoarthritis knee pain study ²³	357.9 (112.59)*
Diabetic peripheral neuropathy study ⁴⁰	418.6 (314.17)*
1-y tolerability study ³⁰	326.7 (120.23)†
Phase IIIb studies	
Chronic low back pain with or without a neuropathic component study ³⁷	311.2 (123.85)‡
Chronic low back pain with or without a neuropathic component (after conversion from previous WHO step III therapy) study ⁴⁵	322.8 (120.73)‡
Chronic osteoarthritis knee pain study ³⁸	256.9 (111.38)‡
Chronic osteoarthritis knee pain with or without a neuropathic component (after conversion from previous WHO step III therapy) study ⁵⁶	232.7 (145.37)‡
Noninterventional study	
Severe chronic pain study ⁵⁸	203.7 (102.40)§

PR = prolonged release; WHO = World Health Organization.

*Dose during the 12-week maintenance period.

†Dose during the 52-week study.

‡Dose at week 6 (the first week after titration).

§Dose at the final study visit.

2 studies in patients with moderate to severe chronic osteoarthritis pain²³ only. Based on the change in mean pain intensity (11-point NRS) from baseline for

the overall 12-week maintenance period (LOCF), tapentadol PR showed superior analgesic efficacy to that of oxycodone CR (least-squares mean difference

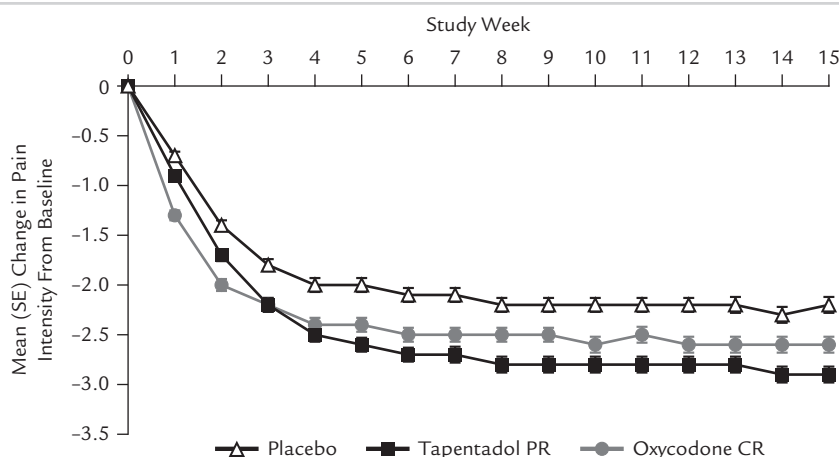
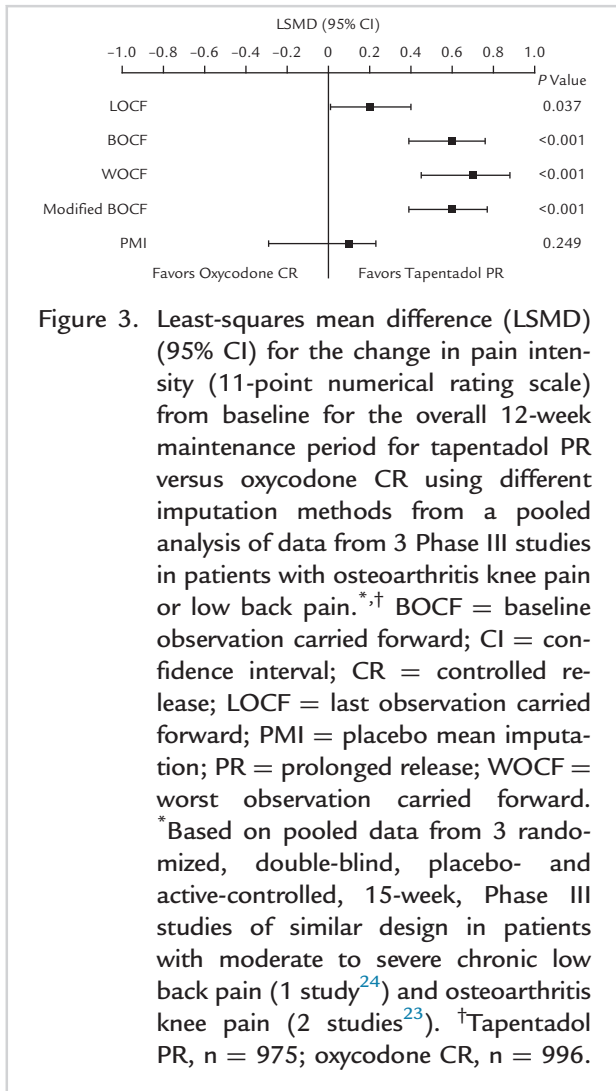


Figure 2. Mean change from baseline in mean pain intensity over time using the last observation carried forward (intention-to-treat population).²⁹ CR = controlled release; PR = prolonged release; SE = standard error. Reproduced with permission from Lange et al.⁹⁷ Copyright © 2010 Springer.



for tapentadol PR vs oxycodone CR = 0.72; 95% CI, 0.50–0.94; $P < 0.001$). For that meta-analysis, sensitivity analyses using different methods of imputation (BOCF, WOCF, and modified BOCF) also indicated that tapentadol PR provided superior analgesic efficacy to oxycodone CR (Figure 5).

Beyond these clinical trials, the administration of tapentadol PR in routine clinical practice has been evaluated in a prospective, noninterventional trial.⁵⁸ That trial included results from 3134 patients with severe chronic back pain; osteoarthritis pain; pain related to DPN, postherpetic neuralgia, stroke, or trauma; tumor-related pain; and pain related to other causes. Tapentadol PR was prescribed and titrated as recommended in the package insert. At the end of the observation period, the mean dose (203.7 mg) was

lower than that used in the Phase III studies, likely due to the permitted use of concomitant nonopioid analgesic regimens during tapentadol PR treatment (Table I).⁵⁸

Initiation and Dosing of Tapentadol PR Treatment in Special Populations

Initial doses of tapentadol PR may need to be adjusted depending on certain patient-specific factors, including age and comorbid medical conditions. In general, no dose adjustment is needed for patients with mild hepatic impairment, whereas treatment for patients with moderate hepatic impairment should be initiated at the lowest possible dose strength (tapentadol PR, 50 mg or 25 mg [if available]) and should not be administered more than once in a 24-hour period.³³ This approach is recommended because in patients with moderate hepatic impairment, elevations in serum concentrations of tapentadol have been observed compared with patients with normal hepatic function.³³ In patients with renal impairment, no alteration has been observed in tapentadol levels compared with patients with normal renal function.³³ Treatment with tapentadol PR is not recommended in patients with severe renal or hepatic impairment because it has not been studied in patients with these conditions.³³

The mean exposure (area under the curve) to tapentadol has been found to be similar for elderly patients (65–78 years old) and young patients (19–43 years old), with a 16% lower maximum concentration in elderly patients than in young patients.³³ In general, no dose adjustment is necessary for elderly patients treated with tapentadol PR. A favorable gastrointestinal tolerability profile has been reported for elderly patients (≥ 75 years of age) in a post hoc analysis of pooled data from 3 similarly designed, randomized, double-blind, Phase III studies that found significantly lower incidences of gastrointestinal treatment-emergent adverse events (TEAEs) and gastrointestinal TEAE-related discontinuations with tapentadol PR compared with oxycodone CR ($P < 0.05$ for both comparisons).⁵⁹ In this respect, tapentadol PR also offers a promising alternative to poorly tolerated treatment options in practice. Because renal or hepatic impairment is more likely for older patients, these patients should be checked for potentially related dose-limiting factors.

Tapentadol PR is currently not recommended for use in a pediatric population.³³ A pediatric development

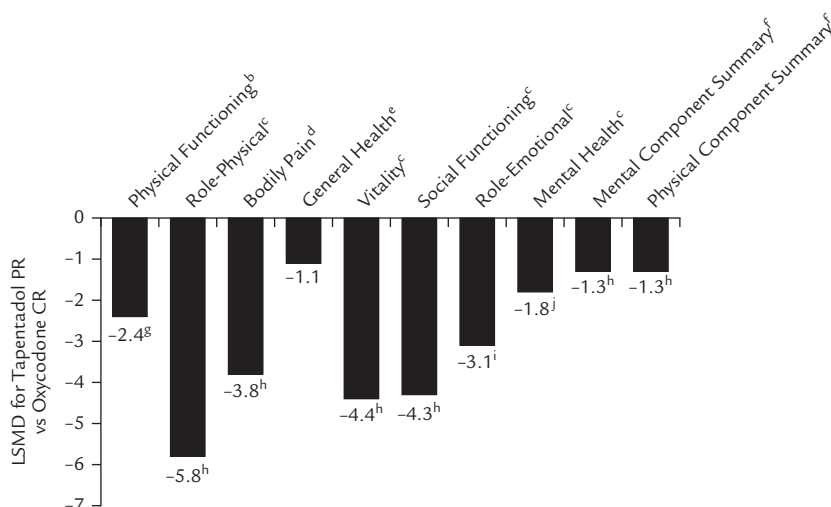


Figure 4. Least-squares mean difference (LSMD) for tapentadol PR versus oxycodone CR for the change from baseline in 36-item Short Form Health Survey subscale and summary scores (last observation carried forward). CR = controlled release; PR = prolonged release. ^aBased on pooled data from 3 randomized, double-blind, placebo- and active-controlled, 15-week, Phase III studies of similar design. ^bTapentadol PR, n = 976; oxycodone CR, n = 996. ^cTapentadol PR, n = 978; oxycodone CR, n = 997. ^dTapentadol PR, n = 977; oxycodone CR, n = 997. ^eTapentadol PR, n = 978; oxycodone CR, n = 995. ^fTapentadol PR, n = 978; oxycodone CR, n = 998. ^g $P = 0.008$. ^h $P < 0.001$. ⁱ $P = 0.048$. ^j $P = 0.010$.

program for tapentadol is ongoing at the time of this publication.

In summary, the favorable tolerability profile for tapentadol PR relative to other classic opioid analgesics allows for a simple titration schedule with relatively rapid up-titration so that patients do not need to remain at a low dose for an extended period. The recommended dosing regimen and rapid titration schedule for tapentadol PR (Figure 1) have been successfully used in clinical studies^{23,24,30,40} and in a noninterventional trial.^{58,60} This titration schedule may facilitate earlier establishment of pain control for patients with chronic pain, and the recommended dose range (up to 500 mg/d) has been sufficient to control severe to very severe pain.

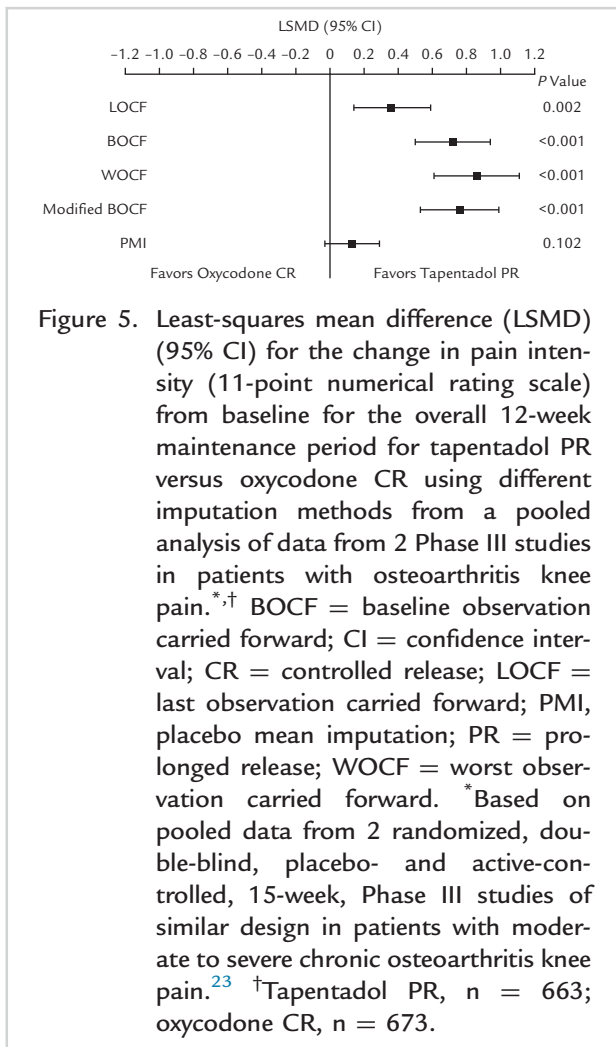
CONVERSION/SWITCHING FROM CLASSIC STRONG OPIOIDS

Patients may need to switch opioid analgesics if their pain does not respond to increasing doses of their current opioid, if increasing doses of their current opioid are associated with unmanageable adverse effects, or if opioid switching may be associated with

other potential benefits (eg, improved pharmacokinetic profile, improved ease of administration).⁶¹ Opioid switching between opioid analgesics with similar mechanisms of action may not yield long-term improvements in tolerability or efficacy.^{62–64} Given its improved tolerability profile relative to the classic opioid analgesics oxycodone CR^{23,24,29,30,40} and morphine CR⁴² and its proposed lower cross-tolerance for analgesia due to a unique mechanism of action, tapentadol PR may offer a better option than classic opioid analgesics when converting patients from a previous strong opioid to a new analgesic.

When switching from a previous strong opioid analgesic to tapentadol, the type and dose of the previous opioid analgesic should be considered in selecting a starting dose of tapentadol PR, which may be higher than that required for opioid-naive patients.³³ Recommended starting doses of tapentadol PR based on previous opioid doses are summarized in Tables II and III. A dose reduction is typically recommended when switching from one opioid to another.^{65,66} When switching opioids, it may be

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difficult to find the ideal dose of the new opioid analgesic in terms of balancing the potential for providing too high of a dose, which may exacerbate potential opioid-related adverse effects, and underdosing, which may increase the risk of pain peaks or withdrawal symptoms. For tapentadol PR, which exerts less opioid receptor activation than conventional opioids owing to its MOR and NRI mechanisms of action, it may be considered to not reduce the dose by >30% of the calculated equianalgesic dose of the previous opioid (if that dose is within the therapeutic dose range of tapentadol PR) because this may minimize the risk of withdrawal symptoms related to discontinuation of the previous opioid. Generally, titration after conversion from previous strong opioid analgesics should follow the same schedule described in Section 2. Because of tapentadol's favorable tolerability profile, it may be

possible to titrate tapentadol PR to doses above the equianalgesic doses of previous opioids, thereby offering the potential for added analgesia.

The successful rotation of patients from previous strong (WHO step III) opioids to tapentadol PR has been reported in 2 recent Phase IIIb studies^{45,56} in patients with severe chronic low back pain or osteoarthritis pain who had responded to WHO step III opioids but showed poor tolerability. The starting doses in these 2 studies^{45,56} were based on the morphine equivalent doses of all previous opioids used (Table II). In the low back pain study,⁴⁵ approximately two-thirds of patients achieved comparable analgesia as with their previous WHO step III analgesic on that starting dose and required no dose increase, and >80% of patients in the osteoarthritis study⁵⁶ achieved comparable analgesia as with their previous opioid on the starting dose. After titration, most patients in both studies (low back pain study, 80.9%⁴⁵; osteoarthritis pain study, 94.3%⁵⁶) achieved at least comparable or better pain control with tapentadol PR as with their previous WHO step III analgesic. In the low back pain study,⁴⁵ tapentadol PR showed improvements in efficacy and neuropathic pain symptoms compared with the previous WHO step III opioid, with significant improvements from baseline (when patients were receiving previous WHO step III therapy) to weeks 6 and 12 of the study (on tapentadol PR) in mean pain intensity and neuropathic

Table II. Dosage conversions for the start of therapy to achieve an equianalgesic dose when switching from strong opioids: dosing conversions used in Phase IIIb conversion studies. Reproduced with permission.⁵⁶

Mean MED (mg/d) [*]	Starting Dose of Tapentadol PR per Day
≤ 100	50 mg BID [†]
101-160	100 mg BID [†]
> 160	150 mg BID [†]

MED = morphine-equivalent dose; PR = prolonged release.

^{*}Includes all formulations of all strong opioids taken.

[†]Approximately every 12 hours.

Table III. Dosage conversions for the start of therapy to achieve an equianalgesic dose when switching from strong opioids: European dosing recommendations.

Opioid	Starting Dose of Tapentadol PR (mg/d)				
	50 BID	100 BID	150 BID	200 BID	250 BID
Oxycodone, oral (mg/d)*	39	40–59	60–79	80–99	At higher dosages (depending on previous opioid daily dose), one might consider starting with the maintenance dose of 250 mg/d BID. Tapentadol PR total daily doses > 500 mg have not been studied and are, therefore, not recommended.
Morphine, oral (mg/d)	79	80–119	120–159	160–199	
Hydromorphone, oral (mg/d)	11	12–15	16–19	20–27	
Fentanyl, transdermal (µg/h)	37.4	37.5–49.9	50–74	75–86	
Buprenorphine, transdermal (µg/h)	34	35–52.4	52.5–69	70–87.4	

CR = controlled release; PR = prolonged release.

*The dose conversion ratio for tapentadol PR versus oxycodone CR was derived from clinical Phase III studies (tapentadol: oxycodone ~5.1) and is in line with equianalgesic information from a Phase IIIb trial.⁵⁶

pain symptoms ($P < 0.05$ for all comparisons). Equianalgesic ratios of tapentadol PR and WHO step III opioids in the Phase IIIb study in patients with severe chronic low back pain are summarized in [Table IV](#).⁴⁵ Although the number of patients used to determine each of these equianalgesic ratios was relatively small, the equianalgesic ratio determined for tapentadol PR to oxycodone CR in this Phase IIIb study⁴⁵ was in line with that observed in a pooled analysis of data from randomized, double-blind, placebo- and active-controlled, Phase III studies comparing tapentadol PR and oxycodone CR,²⁹ and was confirmed in a second Phase IIIb study of similar design.⁵⁶ In both studies,^{45,67} the prevalence of TEAEs that were reported as the reason for switching from previous WHO step III therapy (most commonly constipation and nausea) decreased with tapentadol treatment ([Figure 6](#)). Approximately 6% of patients in the osteoarthritis study⁴⁵ and 20% of patients in the low back pain study⁴ experienced drug withdrawal syndrome, largely on switching from their previous strong opioid to tapentadol PR. Withdrawal symptoms on opioid switching are relatively common, and the rates of withdrawal observed on switching from a previous WHO step III opioid to tapentadol PR in these 2 studies^{45,67} are notably lower than those observed

in a study of patients with chronic nonmalignant pain who were switched from one strong opioid to another.⁶⁸ In that study,⁶⁸ the rate of withdrawal was 32% for patients switching from one PR opioid to another and 44% for patients switching from an immediate-release (IR) opioid to a PR opioid.⁶⁸ Withdrawal symptoms occurring on opioid switching may be addressed by coadministration of another opioid analgesic, preferably the IR formulation of the previous opioid.⁶³ For concomitant use of IR opioids with tapentadol PR for breakthrough pain, please refer to the “Concomitant Analgesics and Coanalgesics” subsection later herein.

Findings from the previously described noninterventional trial⁵⁸ provided further evidence for the successful rotation of patients directly from a previous strong opioid analgesic to tapentadol PR. At the time of this trial, a refined conversion table, based on the results of Phase IIIb studies and early practical postlaunch experience, was used. In this non-interventional trial,⁵⁸ 1331 patients had previously received a WHO step III analgesic; the most common reasons that patients switched to tapentadol PR from their previous strong opioid analgesic were a lack of efficacy, poor quality of life, and poor tolerability. The mean (SD) dose of tapentadol PR used by this subset of patients at the end of the study was 227.8 (108.8) mg.

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Table IV. Equianalgesic ratios of tapentadol to WHO step III opioids. Adapted with permission.^{45,*}

WHO Step III Opioid [†]	No.	PR Formulations [‡]	PR and IR Formulations [§]
Buprenorphine	24	170:1	210:1
Fentanyl	22	224:1	251:1
Hydromorphone	8	8.3:1	10.5:1
Morphine	14	2.9:1	3.0:1
Oxycodone	35 [¶]	4.3:1	5.3:1

IR = immediate release; PR = prolonged release; WHO = World Health Organization.

*Based on data from a Phase III study in which patients with severe chronic low back pain with or without a neuropathic component switched directly from previous strong (WHO step III) opioid therapy to tapentadol PR use.⁴⁵

[†]Buprenorphine was administered transdermally or as an IR formulation (sublingually); fentanyl was administered transdermally; all other WHO step III opioids were administered orally.

[‡]Equianalgesic dose ratios calculated for tapentadol PR to PR formulations of WHO step III opioids.

[§]Equianalgesic dose ratios calculated for tapentadol PR plus tapentadol IR to PR plus IR formulations of WHO step III opioids.

^{||}PR formulations, n = 21.

[¶]PR formulations, n = 34.

Most patients (>80%) continued tapentadol PR treatment after the end of the 3-month observation period, and ~88% of patients achieved their treatment goal with tapentadol PR. Based on the results of this trial⁵⁸ and further refined practice-related experience, a further refined conversion table was developed in Europe (Table III).

In summary, the efficacy and tolerability profile of tapentadol PR make it a favorable option for patients who need to be switched from a previous strong opioid analgesic owing to poor tolerability or a lack of efficacy at the current doses. Evidence from Phase IIIb studies^{45,67} and a noninterventional trial support the ease of successfully switching patients directly from a previous strong opioid analgesic to tapentadol PR, even for those who had achieved adequate analgesia (but experienced poor tolerability) on their previous opioid.

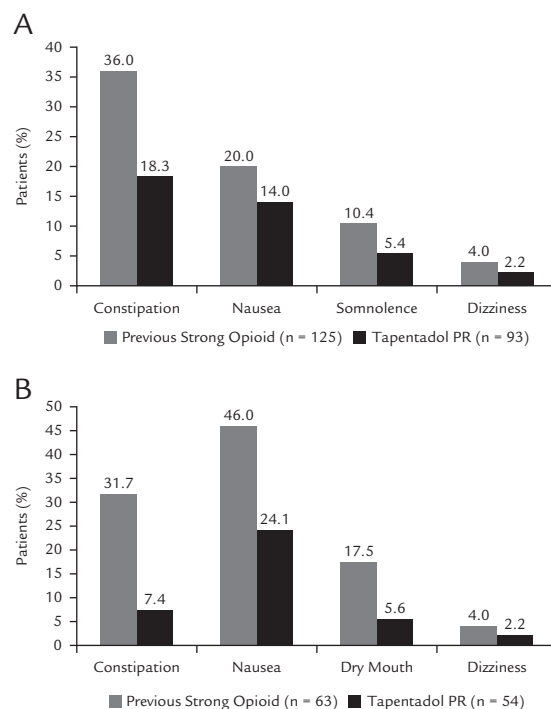


Figure 6. Reduction in the prevalence of gastrointestinal and nervous system adverse events reported as the reason for switching from strong opioid therapy to tapentadol PR therapy in patients with (A) severe chronic low back pain with or without a neuropathic component⁴⁵ and (B) severe chronic osteoarthritis knee pain.⁶⁷ The prevalence of these adverse effects for previous strong opioids was summarized during the week before starting tapentadol PR treatment, when patients were still on their previous opioid regimen, and the prevalence of these adverse effects for tapentadol PR was summarized during the last week of a 12-week treatment period with tapentadol PR. PR = prolonged release.

STOPPING TAPENTADOL PR TREATMENT

Patients taking opioid analgesics for chronic non-cancer pain may experience withdrawal as a symptom of physical dependence after cessation of therapy.^{69,70} Withdrawal symptoms may represent a significant problem for patients who need to discontinue their opioid treatment. As an analgesic with MOR agonist activity, tapentadol PR may be associated with the

potential for withdrawal symptoms after abrupt discontinuation.³³

To determine the extent of any possible opioid withdrawal after cessation of tapentadol PR treatment, the occurrence of withdrawal after abrupt discontinuation of tapentadol PR has been evaluated in a 1-year, open-label, Phase III tolerability study³⁰; in a 1-year, open-label extension study including patients who had previously taken tapentadol PR for 1 year during the tolerability study⁷¹; and in a pooled analysis of 9 randomized, multiple-dose Phase II or III studies in patients with chronic osteoarthritis pain, low back pain, or pain related to DPN of up to 1 year.⁷² The Clinical Opiate Withdrawal Scale in the 1-year tolerability study³⁰ and open-label extension study⁷¹ found that most patients ($\geq 88\%$) who were treated with tapentadol PR for ≤ 2 years experienced no opioid withdrawal after abrupt discontinuation of treatment and that all occurrences of withdrawal were of mild to moderate intensity. Clinical Opiate Withdrawal Scale results from the pooled analysis⁷² found that most patients (85% [972 of 1145]) experienced no opioid withdrawal and that all occurrences of opioid withdrawal were of mild to moderate intensity after discontinuation of tapentadol PR (mean TDD, ~ 260 mg).

In summary, these results indicate that withdrawal after discontinuation of tapentadol PR treatment is minimal on abrupt cessation. Nevertheless, to minimize the possibility that respective symptoms will occur, tapentadol PR doses may be tapered gradually rather than being stopped abruptly.³³

LONG-TERM TREATMENT WITH TAPENTADOL PR

Patients with chronic pain often require long-term analgesic treatment.⁷³ The use of opioid analgesics to manage chronic noncancer pain is increasing⁷⁴; however, evidence supporting the long-term efficacy and tolerability of these agents is frequently lacking.⁷³ In addition to the generally favorable efficacy and tolerability profile reported for tapentadol PR in patients with chronic pain for approximately 3 to 4 months,^{23,24,29,36–44} tapentadol PR has been found to be effective and well tolerated for up to 2 years in patients with chronic osteoarthritis knee pain or low back pain.^{30,71,75}

Findings from the previously mentioned 1-year, open-label, Phase III tolerability study of tapentadol

PR versus oxycodone CR³⁰ and the 1-year, open-label extension study support the well-tolerated and effective use of tapentadol PR for up to 2 years. Among patients who received tapentadol PR during the 1-year tolerability study³⁰ and continued treatment in the 1-year extension study,⁷⁶ mean pain intensity (11-point NRS; LOCF) decreased from a baseline score of 7.6 to ~ 3.4 within 4 weeks of treatment and then remained relatively constant during the remaining up to 2 years of treatment (Figure 7). After the initial titration period, mean TDDs of tapentadol PR remained relatively stable, as did mean pain intensity scores, for up to 2 years of treatment, indicating that tapentadol PR treatment was not associated with acquired tolerance.^{30,76} During the initial 1-year tolerability study,³⁰ mean TDDs of oxycodone CR remained relatively stable after the titration period, as did mean pain intensity scores. For the overall population in the initial tolerability study,³⁰ tapentadol PR treatment was associated with clinically meaningful improvements^{77,78} in measures of health-related quality of life during 1 year of treatment; these improvements were maintained during the second year of treatment for patients who continued tapentadol PR treatment in the extension study.⁷⁶ Tapentadol PR was well tolerated, with a particularly favorable gastrointestinal tolerability profile, during up to 2 years of treatment.^{30,76} During the initial 1-year tolerability study,³⁰ 22.1% of patients in the tapentadol extended-release group and 36.8% of patients in the oxycodone CR group experienced TEAEs leading to study discontinuation. The overall incidence of gastrointestinal TEAEs leading to discontinuation was lower in the tapentadol PR group (8.6%) than in the oxycodone CR group (21.5%), as were the incidences of the individual gastrointestinal TEAEs of nausea (3.4% vs 12.1%), constipation (1.6% vs 7.2%), and vomiting (2.6% vs 6.7%).³⁰ For the overall population in the initial tolerability study,³⁰ the incidences of the following gastrointestinal adverse events were lower with tapentadol PR than with the active comparator, oxycodone CR: nausea (18% vs 33%), vomiting (7% vs 14%), and constipation (23% vs 39%). The incidences of the most common TEAEs (incidence $\geq 5\%$) reported by patients who received up to 2 years of tapentadol PR treatment are summarized in Table V.

In summary, these results indicate that tapentadol PR is well tolerated and effective during up to 2 years

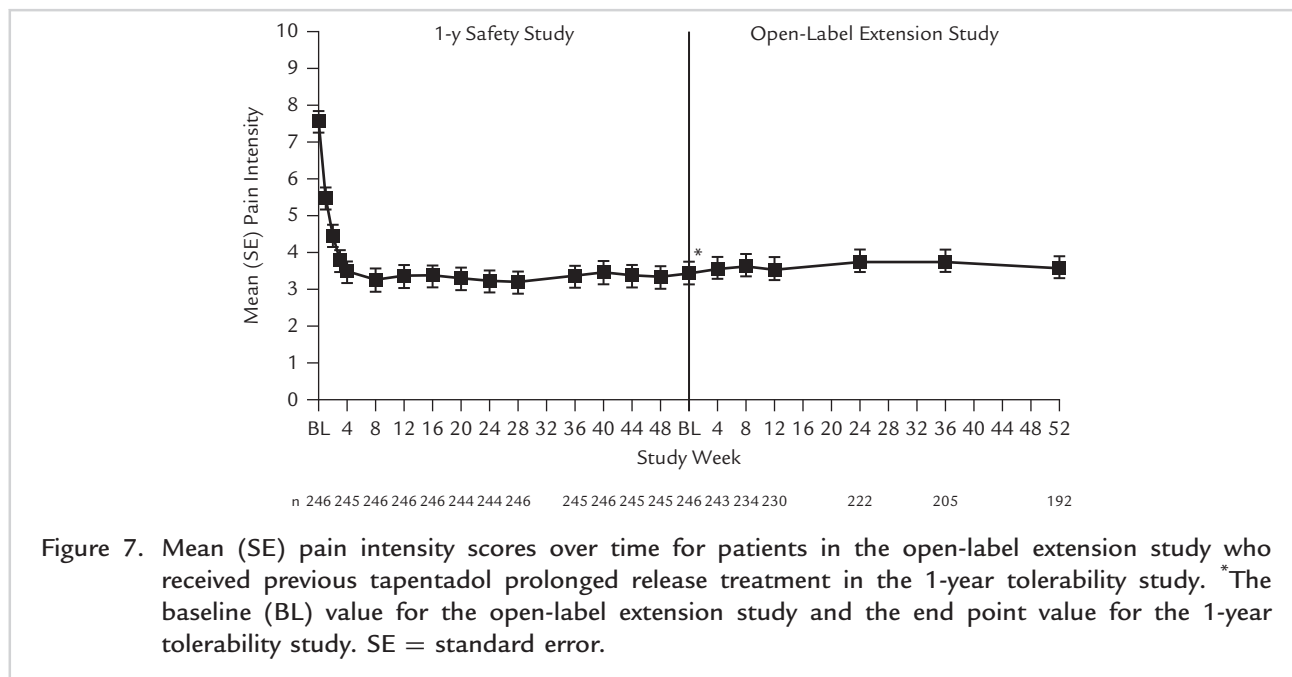


Figure 7. Mean (SE) pain intensity scores over time for patients in the open-label extension study who received previous tapentadol prolonged release treatment in the 1-year tolerability study. *The baseline (BL) value for the open-label extension study and the end point value for the 1-year tolerability study. SE = standard error.

of treatment in patients with chronic pain,^{30,76} with no development of acquired tolerance to the analgesic effects of tapentadol over time (based on evaluations of mean pain intensity and mean TDDs over time).

USE OF TAPENTADOL IR IN ADDITION TO TAPENTADOL PR FOR ACUTE PAIN EPISODES

Tapentadol IR is indicated for the relief of moderate to severe acute pain in adults, which can be adequately managed only with opioid analgesics.⁷⁹ Tapentadol IR has been used on top of tapentadol PR treatment for acute pain episodes or for the relief of withdrawal symptoms after direct conversion from previous strong opioid analgesics in several Phase IIIb studies.^{37,38,45,56} The results of these studies suggest the effectiveness and tolerability of tapentadol IR on top of tapentadol PR in patients with low back pain with or without a neuropathic pain component^{37,45} and in those with osteoarthritis knee pain.^{38,56}

In 4 open-label, Phase IIIb studies in patients with severe low back pain or osteoarthritis knee pain,^{37,38,38,45} tapentadol IR (50 mg, twice daily or less; ≥ 4 hours apart) was permitted for acute pain episodes or for the relief of withdrawal symptoms occurring after the discontinuation of previous opioid analgesics; the total tapentadol doses (including PR and IR formulations) could not exceed 500 mg/d.^{37,38,45,56} After the tapentadol PR doses had stabilized, most

patients (~55% to ~89%) did not require additional analgesia with tapentadol IR, and the mean daily doses of tapentadol IR used were relatively low (6.7–24.6 mg).^{37,38,45,56} In all 4 studies,^{37,38,45,56} tapentadol treatment, which included a combination of tapentadol PR and IR, was well tolerated and effective. The data collected on the use of tapentadol IR for the treatment or prevention of withdrawal symptoms after discontinuation of previous opioids in these trials^{37,38,45,56} were not sufficient to allow for a detailed analysis.

In summary, these results suggest that the use of tapentadol IR on top of tapentadol PR could be a feasible option for addressing particularly acute pain episodes.^{37,38,45,56} Both the IR and PR formulations of tapentadol may not be available in all countries. In those cases, it may be possible to use other IR opioids (eg, morphine, oxycodone) for the management of acute pain episodes or withdrawal symptoms based on the positive results observed with tapentadol IR on top of tapentadol PR.

USE OF CONCOMITANT MEDICATIONS WITH TAPENTADOL PR

Pharmacokinetic Interactions

Patients with severe chronic pain may have comorbid conditions that necessitate the use of concomitant medications. Tapentadol is largely metabolized by

Table V. TEAEs reported by $\geq 5\%$ of patients who received up to 2 years of treatment with tapentadol PR (tolerability population [n = 249]).^{76,*}

System Organ Class TEAEs, No. (%)	Tapentadol PR (n = 249)
Gastrointestinal disorders	162 (65.1)
Constipation	73 (29.3)
Nausea	51 (20.5)
Dry mouth	35 (14.1)
Diarrhea	34 (13.7)
Vomiting	26 (10.4)
Infections and infestations	149 (59.8)
Nasopharyngitis	35 (14.1)
Influenza	32 (12.9)
Upper respiratory tract infection	30 (12.0)
Sinusitis	24 (9.6)
Urinary tract infection	24 (9.6)
Bronchitis	17 (6.8)
Viral gastroenteritis	16 (6.4)
Nervous system disorders	132 (53.0)
Headache	51 (20.5)
Dizziness	39 (15.7)
Somnolence	34 (13.7)
Musculoskeletal and connective tissue disorders	82 (32.9)
Arthralgia	23 (9.2)
Muscle spasms	13 (5.2)
Injury, poisoning, and procedural complications	81 (32.5)
Contusion	14 (5.6)
Psychiatric disorders	75 (30.1)
Insomnia	35 (14.1)
Anxiety	20 (8.0)
Depression	14 (5.6)
General disorders and administration site conditions	64 (25.7)
Fatigue	24 (9.6)
Respiratory, thoracic, and mediastinal disorders	50 (20.1)
Pharyngolaryngeal pain	13 (5.2)
Vascular disorders	41 (16.5)
Hypertension	27 (10.8)

PR = prolonged release; TEAE = treatment-emergent adverse event.

*Incidences are based on the number of patients experiencing ≥ 1 adverse event, not on the number of events.

phase 2 glucuronidation, a high-capacity/low-affinity system that would not be inhibited at clinically relevant concentrations, suggesting a low potential for interactions related to phase 2 metabolism.³³ Furthermore, tapentadol does not inhibit or induce cytochrome P450 enzymes,²⁰ and tapentadol shows low plasma protein binding ($\sim 20\%$).³³ Therefore, the occurrence of pharmacokinetic drug-drug interactions related to the cytochrome P450 system or displacement from protein binding is unlikely.³³ Tapentadol has no active metabolites and is not a prodrug that is activated by metabolism,¹⁶ resulting in a reliable pharmacokinetic profile and an analgesic profile that is not altered by metabolic factors. Accordingly, 2 randomized, open-label, drug-drug interaction studies reported that when tapentadol was administered concomitantly with the commonly used nonopioid analgesics paracetamol, acetylsalicylic acid, and naproxen, no clinically relevant changes were observed in its pharmacokinetic properties.⁸⁰ Results of other studies suggest no evidence of clinically relevant changes in the pharmacokinetic properties of tapentadol administered with metoclopramide, probenecid, or omeprazole.^{81–83}

Pharmacodynamic Interactions

As for all combinations of centrally acting drugs, certain precautions are recommended when dosing tapentadol PR with other CNS-active medications. The concomitant use of CNS-depressant drugs, including benzodiazepines, antipsychotics, H1 antihistamines, opioids, and alcohol, may, in general, result in an increase in sedative effects, respiratory depression, or impaired vigilance.³³ Despite an improved CNS tolerability profile, such pharmacodynamic interactions may also occur with tapentadol, and care should be taken. In a pooled analysis of data from 11 randomized placebo-controlled trials⁸⁴ that evaluated the tolerability of tapentadol used concomitantly with a selective serotonin reuptake inhibitor or serotonin norepinephrine reuptake inhibitor, the TEAEs observed were in line with those expected with tapentadol treatment based on the population studied and the labeling,^{33,79} and no clinically relevant drug-drug interactions were identified.⁸⁴ For further updated details, reference should be made to the summary of product characteristics for tapentadol PR.³³

Concomitant Analgesics and Coanalgesics

The use of tapentadol PR concomitantly with analgesics and coanalgesics has been evaluated in a

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variety of studies.^{36–38,42,45,56} The concomitant use of WHO step I analgesics and coanalgesics was permitted in the 4 previously described open-label, Phase IIIb studies of tapentadol PR in patients with low back pain with or without a neuropathic pain component^{37,45} or with osteoarthritis knee pain.^{38,56} Across all 4 studies,^{37,38,45,56} concomitant coanalgesics were taken by 14.3% to 54.4% of patients and concomitant WHO step I analgesics were taken by 55.6% to 64.5% of patients. Despite the relatively high percentages of patients taking WHO step I analgesics or coanalgesics, the tolerability profile observed in these studies^{37,38,45,56} for tapentadol PR was generally better than that observed in randomized, controlled, Phase III studies^{23,24,40} that did not allow additional analgesics or coanalgesics, indicating that the concomitant use of WHO step I analgesics or coanalgesics did not have a negative effect on the tolerability of tapentadol PR but also reflecting the lower mean doses of tapentadol PR used in Phase IIIb studies. In addition, morphine IR^{42,85,86} and oxycodone IR⁸⁶ were permitted for the treatment of breakthrough pain concomitantly with tapentadol PR in Phase III studies in patients with moderate to severe chronic malignant tumor-related pain. In those studies,^{42,85,86} tapentadol PR used concomitantly with morphine IR and oxycodone IR was well tolerated. Although only the concomitant use of morphine IR and oxycodone IR for breakthrough pain has been evaluated, these findings suggest that other IR opioids could be safely used as well.

In a randomized, double-blind, Phase IIIb study in patients with severe low back pain with a neuropathic component,³⁶ the analgesic efficacy of a combination of tapentadol PR (300 mg/d) and pregabalin (300 mg/d) was comparable with that of tapentadol PR (500 mg/d), and the incidence of the composite of dizziness and/or somnolence was significantly lower with tapentadol PR monotherapy (16.9%) than with the combination of tapentadol PR and pregabalin (27.0%; $P = 0.0302$). Still, incidences of the most common TEAEs in the combination arm were relatively low compared with the rates of adverse effects observed in historical trials of combinations of opioids and coanalgesics.^{14,15} Furthermore, the rate of adverse event-related discontinuations remained comparable in both treatment groups (tapentadol PR monotherapy, 7.8%; tapentadol PR plus pregabalin combination therapy, 7.5%). Taken together, these results

suggest that combination therapy with tapentadol PR and pregabalin was well tolerated and effective and that tapentadol may be a more favorable and complementary combination partner than pure strong opioid agonists.³⁶

Findings from the previously described prospective noninterventional trial⁶⁰ in patients with severe chronic pain who were receiving tapentadol PR during routine treatment by a general practitioner or internist provided further support for the tolerable use of concomitant analgesics with tapentadol PR. In that study,⁶⁰ concomitant analgesics were taken with tapentadol PR by 48.4% of patients (strong opioids, 3.6%; weak opioids, 6.4%; nonopioids, 44.7%) at the final visit. Treatment was well tolerated, with adverse drug reactions reported for only 7% of patients.⁶⁰

In summary, the results of these studies^{36–38,45,56,60,80,84} suggest that tapentadol PR has a low potential for pharmacokinetic drug-drug interactions. Pharmacokinetic drug-drug interactions mediated by cytochrome P450 pathways²⁰ or plasma protein binding are unlikely to occur with tapentadol PR.³³ There is a potential for pharmacodynamic interactions with CNS-active drugs (see the summary of product characteristics for full information).³³ When tapentadol PR has been administered with centrally acting analgesics and coanalgesics,^{37,38,45,56} selective serotonin reuptake inhibitor- or serotonin norepinephrine reuptake inhibitor-type antidepressants, or anticonvulsants,^{33,36,79,84} the tolerability profile has been found to be comparable with that of tapentadol PR alone, in line with the subpopulation studied. In addition, a combination of tapentadol PR and pregabalin³⁶ was found to have a better tolerability profile compared with historical trials of other opioid analgesics and coanalgesics.^{14,15} Taken as a whole, these results indicate that tapentadol PR may be safely coadministered with many other medications.

ABUSE AND DIVERSION

Abuse and diversion are major concerns for physicians prescribing long-term opioid analgesics for the management of chronic noncancer pain.^{87–89} An abuse liability trial in opioid-experienced patients versus oral hydromorphone that was early in the clinical development of tapentadol reported a similar liking potential for oral tapentadol. In the United States and Europe,

tapentadol is considered a scheduled substance^{33,35}; in the United States, the Food and Drug Administration has implemented a Risk Evaluation and Mitigation Strategy for controlled substances to improve prescribing practices and reduce drug diversion.⁹⁰ A tamper-resistant formulation of tapentadol PR (which is resistant to crushing and forms a gel when combined with small volumes of liquid) is available in the United States.⁹¹

Although caution is warranted when prescribing tapentadol PR to patients for whom there is a concern about an elevated risk of drug misuse, abuse, addiction, or diversion,³³ results of recent studies indicate a low level of abuse for tapentadol in practice. In a study⁹² that evaluated the rates of abuse and diversion of tapentadol IR after its introduction to the US market using data from a US surveillance system (the Researched Abuse, Diversion, and Addiction-Related Surveillance [RADARS] system⁹³), rates of tapentadol IR abuse and diversion were low during the first 24 months after its introduction (Figure 8).⁹² Drug diversion rates were found to be low when either population and unique recipients of dispensed drug denominators were used.⁹² During the first 2 years after its introduction, no tapentadol IR diversion was reported during a 9-month period (from the third quarter of 2009 to the second quarter of 2010).⁹² The diversion rate per 1000 unique recipients of dispensed drug for tapentadol IR was low (substantially lower than that for oxycodone or hydrocodone) throughout the 2-year evaluation period despite the increase in the number of unique tapentadol IR recipients during that time frame.⁹² Data from that same surveillance system were used to evaluate the street value of selected prescription opioids, including tapentadol, during the fourth quarter of 2012; very few street price reports were available for tapentadol during the quarter surveillance period, indicating limited availability of tapentadol in the illicit market. In that study,⁹⁴ opioids with a single mechanism of action had higher street values than drugs with >1 mechanism of action, including tapentadol.⁹⁴ In a separate study⁹⁵ evaluating the rate of abuse of tapentadol IR among US college students during the 2 years after its launch in 2009, the rate of nonmedical use of tapentadol IR was low (7 times lower than that of oxycodone and 9 times lower than that of hydrocodone) and declined during the 2-year period despite increasing pharmacy sales. The low rate of

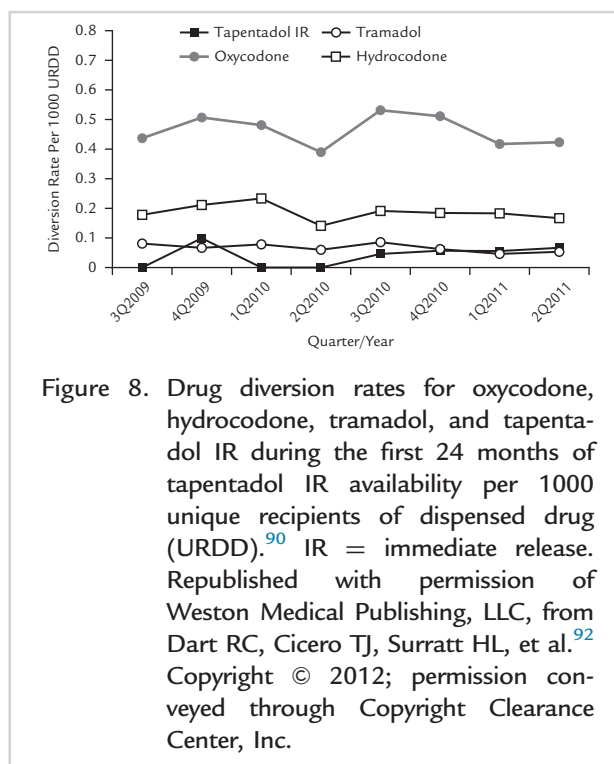


Figure 8. Drug diversion rates for oxycodone, hydrocodone, tramadol, and tapentadol IR during the first 24 months of tapentadol IR availability per 1000 unique recipients of dispensed drug (URDD).⁹⁰ IR = immediate release. Republished with permission of Weston Medical Publishing, LLC, from Dart RC, Cicero TJ, Surratt HL, et al.⁹² Copyright © 2012; permission conveyed through Copyright Clearance Center, Inc.

tapentadol misuse was also observed in a recent retrospective cohort study,⁹⁶ which found that the risk of opioid doctor shopping was >3 times more likely for patients treated with oxycodone than for those treated with tapentadol.⁹⁶

These findings from early clinical experience with tapentadol suggest that it is associated with low rates of abuse and diversion in practice. The potential for abuse and addiction with tapentadol PR should be considered, however, for patients for whom there is a concern about an increased risk of misuse, abuse, addiction, or diversion.³³ Further data on abuse and diversion of tapentadol need to be collected and analyzed. If the currently observed profile is maintained, tapentadol may offer a safer option in this respect for patients requiring strong analgesic therapy for their chronic pain.

SUMMARY AND CONCLUSIONS

Tapentadol PR, which represents a proposed new class of centrally acting analgesic with 2 mechanisms of action, MOR agonism and NRI,^{16,17} has been in practical use for ≥ 3 years in various countries. Tapentadol PR, which has been associated with improvements in pain and quality of life for patients

with and without a neuropathic component to their chronic pain, may provide clinically meaningful benefits over classic opioid analgesics for the long-term management of severe chronic pain. Furthermore, tapentadol PR treatment has been associated with improvements in neuropathic pain symptoms for patients with neuropathic pain only.^{37,45} Tapentadol PR also has an improved tolerability profile, particularly gastrointestinal tolerability, compared with other classic opioid analgesics,^{23,24,29,30,40,42} which may improve patient adherence to treatment and, consequently, result in sustained pain relief. These advantages regarding tolerability and efficacy over other opioid analgesics suggest that tapentadol PR may provide a preferred option for managing chronic pain in patients in a clinical setting.

Tapentadol PR generally provides effective and well-tolerated analgesia for the management of chronic pain across a broad range of analgesic indications.^{23,24,29,30,37,38,40,45,56,57} Evidence from practice-related surveillance systems suggests a low rate of abuse in clinical practice.^{92,95} The favorable efficacy and tolerability profiles of tapentadol PR and the low risk of pharmacokinetic drug-drug interactions, with fewer treatment discontinuations, may simplify use in clinical practice. Full details regarding the prescription and administration of tapentadol PR are available in the summary of product characteristics.³³

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CONFLICTS OF INTEREST

Dr. Sánchez del Águila was a speaker at a Grünenthal-sponsored satellite symposium focusing on tapentadol at the International Association for the Study of Pain (IASP) Congress in 2012, and Dr. Sánchez del Águila participated in an International Education Workshop on managing severe chronic low back pain at the European Federation of IASP Chapters Congress in 2013. Dr. Sánchez del Águila has also participated in the international launch of tapentadol, the 2012 Andalusian Pain Society tapentadol symposium, and the 2013 Spanish Pain Society tapentadol symposium. M. Schenk is a consultant for Grünenthal, Mundipharma, MSD, Pfizer,

and Teva. K.-U. Kern is a consultant or presenter for Astellas, Berlin Chemie, Boehringer Ingelheim, BetaPharma, Grünenthal, Lilly, Medi Bayreuth, and Mundipharma and received LIIRA grant support for clinical research from Pfizer. T. Drost and I. Steigerwald are employees of Grünenthal GmbH. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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