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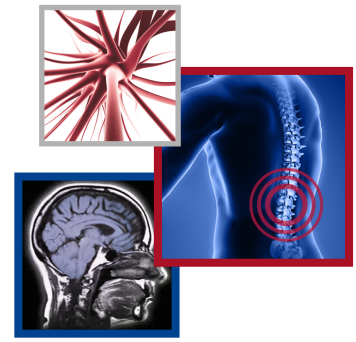

Quality of life and functional outcomes with tapentadol prolonged release in chronic musculoskeletal pain: *post hoc* analysis

Cesar Margarit Ferri[1], Silvia Natoli[2], Paz Sanz-Ayan[3], Alberto Magni[4], Carlos Guerrero[5], Argelia Lara-Solares[6], Hiltrud Liedgens*[,7], Guido Thömmes[8] & Ravi Karra[9]

[1]Hospital General Universitario de Alicante, Alicante, Spain
[2]University of Rome Tor Vergata, Department of Clinical Science & Translational Medicine & Unit of Pain Therapy, Polyclinic of Tor Vergata, Rome, Italy
[3]Hospital Universitario 12 de Octubre; Department of Rehabilitation, Hospital Universitario 12 de Octubre, Madrid, Spain
[4]Italian College of General Practitioners & Primary Care, Florence, Italy
[5]Hospital Universitario Fundación Santa Fe, Bogotá, Universidad de los Andes, Colombia
[6]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico
[7]Global Market Access, Grünenthal GmbH, Aachen, Germany
[8]R&D – Development – Data Sciences, Grünenthal GmbH, Aachen, Germany
[9]Global Medical Affairs, Grünenthal GmbH, Aachen, German
*Author for correspondence: Tel.: +49 241 569 2679; Hiltrud.Liedgens@grunenthal.com

Aims: To investigate quality of life (QOL) and functionality changes in chronic pain during tapentadol prolonged release (PR) treatment. **Patients & methods:** *Post hoc* analysis of data from three Phase III trials in patients with osteoarthritis knee pain or low back pain. QOL and functionality changes were assessed by SF-36 scores. **Results:** All SF-36 subdomain scores improved progressively to week 3 of tapentadol titration and were sustained during 12-week maintenance treatment. Improvements in SF-36 scores were similar between tapentadol dose groups (e.g., 200–<300 mg vs ≥500 mg), with no greater effect from higher doses. QOL and functionality improvements were consistently greater with tapentadol PR than oxycodone controlled release. **Conclusion:** Tapentadol PR provides consistent, clinically relevant improvements in QOL and functionality in chronic pain.

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Keywords: functionality • functional outcomes • health-related quality of life • mental health outcomes • oxycodone • physical health outcomes • SF-36 • tapentadol PR

Pain conditions are consistently among the most common disorders worldwide [1,2]. Chronic back pain in particular is among the most frequent types of chronic pain [3] and the leading global cause of disability [4]. Approximately 65–85% of adults will experience low back pain (LBP) at some point in their lives, two thirds of whom may develop chronic LBP (cLBP) [2,5–7]. The annual worldwide prevalence of cLBP has been reported at approximately 12% [8], with a wide cross-national range between 1.4 and 20% [9]. In the USA, cLBP has a prevalence of 13.1%, rising with age to 27.4% in 50–59 year olds [10]. In Europe, estimates suggest a prevalence of approximately 40% [11].

Osteoarthritis represents another highly prevalent and disabling chronic pain condition, affecting an estimated 26 million people in the USA [12] and over 40 million people in Europe [13]. The lifetime risk of developing knee osteoarthritis, in particular, is estimated at 45% [14]. As populations increasingly age, the prevalence of both cLBP and osteoarthritis are predicted to rise further in future [15]. The high prevalence of chronic pain disorders [16–18] translates to a substantial medical and health economic burden [19,20]. The societal costs for cLBP in Western countries are estimated to be 1–2% of the gross national product, with the majority of costs (80–90%) caused by productivity loss and disability [21–23]. LBP is responsible for loss in productive work time in 3.2% of US adults, representing an average of 5.5 h per week for affected workers [24]. Contributors to sickness absence in these workers are complex and include factors such as mental health, comorbidities and negative beliefs about LBP [25].

Medical advice on chronic pain must be tailored to the patient's age, lifestyle and occupational status and must include customized advice on the options, safety and efficacy of pain management, as well as nonpharmacological

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management, including exercise, self-management and the support services available for LBP [26]. The WHO provides step ladder recommendations for the selection of analgesics in pain management that were originally developed for the treatment of cancer pain in 1986. In this system, nonopioid analgesics (Step I) are used initially, with escalation to weak opioids, alone or in combination with nonopioid drugs (Step II) and then escalation to strong opioid analgesics (Step III) if the pain is not properly controlled [27,28].

Tapentadol is an atypical opioid [29] with a dual mechanism of action that combines mu-opioid receptor (MOR) agonism and noradrenaline reuptake inhibition (NRI) [30–33]. This combination of MOR agonism and NRI activity is considered [34,35] to underlie the broad range of effectiveness of tapentadol demonstrated in trials on chronic neuropathic, nociceptive, postoperative, diabetic, pediatric, cancer and mixed types of pain [36–42]. In Europe, the USA and elsewhere, tapentadol prolonged release (PR) is indicated for the management of severe chronic pain in adults that can only be adequately managed with opioid analgesics [43,44].

In the period from 2009 to 2019, tapentadol was estimated to have been prescribed to 11.8 million patients worldwide (source: IQVIA MIDAS Consumption 12/2019). The calculation of patient treatment days was done by taking the total volume (standard units) of tapentadol sold (sources: IQVIA MIDAS Consumption 12/2019) and dividing by the defined daily intake, which means: two tablets for the prolonged-release formulation (reference: Palexia® PR SmPC, July 2016) and four tablets/intakes for the immediate-release solid and liquid formulations (references: Palexia IR SmPC, September 2014; Palexia OS SmPC, October 2014). The calculation of patients treated was done by taking the patient treatment days and dividing by the average treatment duration of assumed 100 days for all strengths except Palexia PR 25 mg strength, where 75 days were considered (reference: Prescriber & Patient Tracking Market Research, 2012/2013).

Quality of life (QOL) and functional outcomes are increasingly recognized to be major parameters in the evaluation of pain management, which entails that an analgesic must be able to provide effective control of pain and improvements in QOL and functionality or functional status. Functionality or functional status is defined as the ability to ambulate, function cognitively, return to work, complete activities of daily living and sleep [45–50]. Among the multiple instruments used to assess QOL and functionality in clinical trials, the 36-item Short-Form Health Survey (SF-36) is perhaps the most widely used [51].

While the importance of achieving improved outcomes is recognized, notably in the studies on tapentadol [52–55], there remains limited clinical trial evidence for many analgesics to confirm that improvements in QOL and functionality occur [56].

Tapentadol PR was compared with oxycodone controlled release (CR) in three pivotal, randomized, double-blind, placebo-controlled Phase III studies with similar designs in patients with chronic osteoarthritis or LBP (NCT00421928, NCT00486811, NCT00449176) [37,57]. While these studies focused on efficacy and safety, they also included QOL and functionality assessments using the SF-36 [37,57] as a secondary objective.

With the increasing emphasis on how QOL and functionality are impacted by chronic pain and its management and the inclusion of functioning as a parameter in chronic pain in ICD-11 [58], it is pertinent to analyze the existing study evidence in depth. Here, we present a *post hoc* analysis of pooled SF-36 data from these three clinical studies on tapentadol PR versus oxycodone CR. The main objectives of this analysis were to compare and contrast the outcomes of SF-36 domains in terms of QOL and functionality between patients treated with tapentadol PR and oxycodone CR. The analysis addresses individual subdomain benefits, their correlations with dose and outcomes, times to improvement and the profiles of patients who switched from different prior pain medications using the WHO step ladder.

Methods

Data sources

The data sources on SF-36 score changes were three randomized, double-blind, placebo-controlled Phase III studies of tapentadol PR (therapeutic range: 100–250 mg twice daily [bid]) versus oxycodone CR (20–50 mg bid), performed in centers in Australia, Canada, New Zealand and the USA [37,54,57]. The studies used similar study designs, including screening and washout periods, randomization and a 3-week dose titration followed by a 12-week maintenance period. Baseline and demographic characteristics including age, gender, race and pain intensity score were similar across the studies [59].

Dose titration of tapentadol PR consisted of 50 mg bid for the first 3 days, 100 mg bid for the next 4 days and subsequent adjustment to a maximum of 250 mg bid during the titration period. Dose titration of oxycodone CR was 10 mg bid, 20 mg bid and up to 50 mg bid, respectively. Patients attempted to maintain steady doses during

the maintenance period, but could adjust their dose under supervision of a physician within the therapeutic ranges of 100–250 mg bid tapentadol PR (i.e., the minimum and maximum recommended total daily doses of 200 and 500 mg, respectively) or 20–50 mg bid oxycodone CR to achieve the optimal balance of efficacy and tolerability.

The SF-36 health survey was administered at weeks 4, 8 and 12 of maintenance therapy and at the end of the maintenance period if earlier than week 12. The SF-36 included 36 items organized in eight subdomains (physical functioning [10 items], role-physical [four items], bodily pain [two items], general health [five items], vitality [four items], social functioning [two items], role-emotional [three items] and mental health [five items]), scored by patients and transformed on a scale from 0 to 100 (0 being 'poor health' to 100 being 'good health') and aggregated into two summary scales of physical and mental component summaries [51].

Additional details on the design of the trials can be found in the original study publications [37,57]. All safety data were previously published [37,57] and are not the subject of this paper.

Study populations

Patients included in the studies were either men or nonpregnant women who had a clinical diagnosis of osteoarthritis knee pain or nonmalignant LBP for a duration of at least 3 months and were not satisfied with their current analgesic therapy, including opioids. For inclusion in all studies, the average pain intensity score at baseline was required to be ≥5 on an 11-point numerical rating scale (0: 'no pain' to 10: 'pain as bad as you can imagine').

Exclusion criteria included a history of alcohol or drug abuse, significant liver insufficiency, chronic hepatitis B or C, HIV, malignancy within 2 years of screening (except successfully treated basal cell carcinoma), hypersensitivity or contraindication to oxycodone or acetaminophen, seizure disorder, stroke, transient ischemic attack, brain neoplasm, traumatic brain injury, uncontrolled hypertension, severely impaired renal function or any other significant disease that could affect the efficacy or safety assessments. Patients who required surgery at the reference joint in the osteoarthritis studies or the low back area in the LBP study within 3 months of screening or during the studies were also excluded.

Concurrent medications including neuroleptics, monoamine oxidase inhibitors, serotonin norepinephrine re-uptake inhibitors, tricyclic antidepressants, anticonvulsants and antiparkinsonian drugs were prohibited within 14 days of screening and during the studies. Corticosteroids were prohibited within 4 weeks–6 months of screening (depending on the route of administration) and during the studies. All analgesics, except the study drugs and the rescue medication (acetaminophen ≤1000 mg/day), were prohibited during the treatment periods in all studies.

Statistical methods

The population analyzed included all patients in the intent to treat (ITT) set and the subset of the ITT set who entered the maintenance period (mITT). Descriptive statistics of the weekly total daily dose of tapentadol PR were created each week for all patients in the ITT set who entered the mITT. The weekly total daily dose (i.e., the average of the total daily dose over the 7 days of each week) was calculated for each patient over the 15-week trial period (3 weeks' titration followed by 12 weeks' maintenance). Dose data were presented for all the tapentadol doses combined and for the 200 to <300 mg, 300 to <400 mg, 400 to <500 mg and ≥500 mg total daily maintenance-dose groups during the maintenance period.

Mean (least squares [LS] mean) change from baseline in the SF-36 subdomain scores and mean total daily doses of tapentadol PR over time were plotted for all tapentadol doses combined and for 200 to <300 mg, 300 to <400 mg, 400 to <500 mg and ≥500 mg total daily-dose groups separately in the mITT population. These modal dose groups were defined in the three individual trials and they represent the dose range that was most often used (in terms of total daily dose) by the patient during the 12-week maintenance period. All SF-36 subdomain scores were normalized and had the same range from 0 to 100.

SF-36 subdomain scores in the tapentadol PR and oxycodone CR groups were compared by time point in the ITT population. Last observation carried forward imputation for SF-36 scores was performed to provide complete observations at weeks 4, 8 and 12. LS means by time point were calculated from an analysis of covariance of change from baseline in SF-36 subdomain scores at the specified week, with factors treatment group and pooled site and covariate baseline score. In addition, SF-36 subdomain scores in the tapentadol PR and oxycodone CR groups were compared by time point and by prior pain medication subgroup defined by WHO Step I, II or III. No adjustment for multiple comparison was made. WHO step classes were created by manual review and classification of prior pain medications. Subsequently, each patient was assigned to the highest class of prior pain medication taken. Descriptive statistics were provided on baseline characteristics by WHO step subgroups, treatment group and

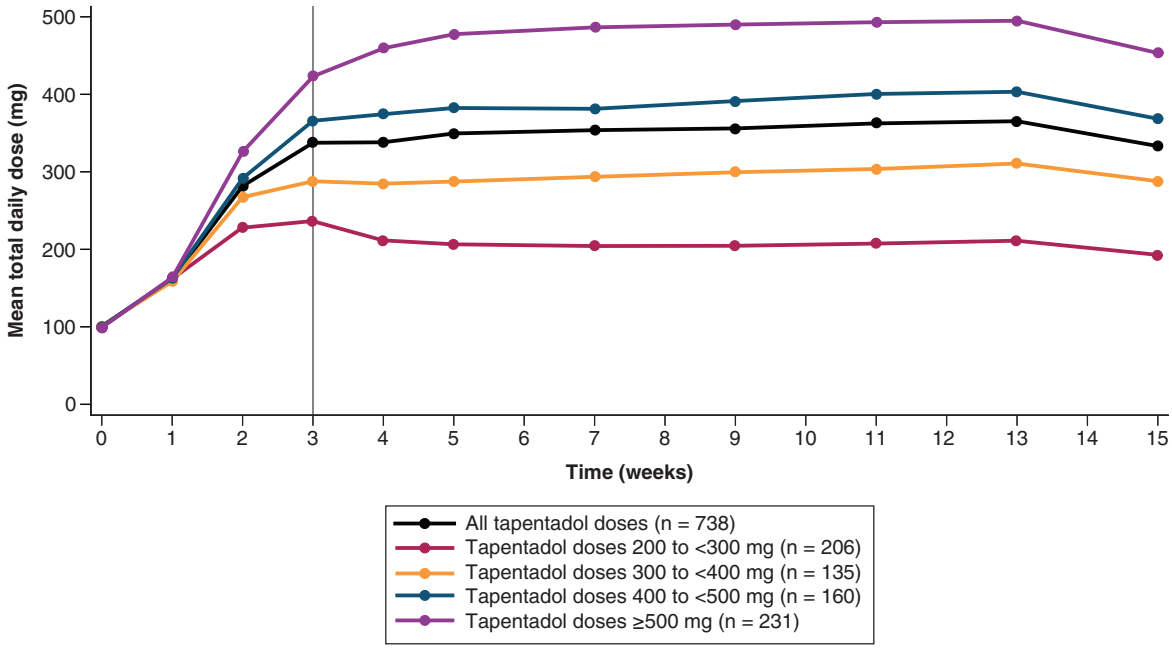

Figure 1. Mean total daily doses over time of tapentadol prolonged release in the 200–<300 mg, 300–<400 mg, 400–<500 mg and ≥500 mg maintenance-dose groups for pooled studies (intent to treat set set who entered maintenance period). Treatment period of 15 weeks comprising a 3-week titration period and a 12-week maintenance period. Starting dose was 100 mg tapentadol PR in all patients. Analysis of patients in the ITT who entered the maintenance period.
ITT: Intent to treat set; mITT: ITT set who entered maintenance period; PR: Prolonged release.

overall for the pooled trials. Baseline characteristics included subject demographics, time since diagnosis, analgesic treatment within 3 months prior to screening (opioid and nonopioid intake), reasons for dissatisfaction with current treatment, medical history, physical examination and baseline scores of pain numerical rating scale and SF-36.

Results

Tapentadol PR maintenance-dose groups

Pooling of the 3 studies provided 2968 patients in the efficacy (ITT) population, including 978, 999 and 991 patients, respectively, in the tapentadol PR, oxycodone CR and placebo groups. Baseline and demographic characteristics were similar across the three treatment groups [54]. A total of 206, 135, 160 and 231 tapentadol-treated patients were categorized in the 200–<300 mg, 300–<400 mg, 400– <500 mg and ≥500 mg total daily-dose groups, respectively. Two hundred and forty tapentadol PR-treated patients did not transition from titration to maintenance period and were not included in the analyses. In addition, three patients each in the <100 mg and the 100–<200 mg modal-dose groups, respectively, are not shown in the results summaries because of the small sample sizes. For the analyses of tapentadol maintenance-dose groups, 738 patients in the ITT set who entered the maintenance period in the tapentadol arm were included in the mITT population.

Mean total daily doses of tapentadol in the maintenance-dose groups during the titration and maintenance periods are shown in Figure 1. All patients were titrated from a 100 mg total daily dose at study initiation and the majority had reached a total daily dose of approximately 350 mg by week 3 of the titration period. Following the titration period, patients in each maintenance-dose group continued at approximately the same dose through the majority of the maintenance period.

Based on descriptive statistics, patient demographics across the different WHO step classes were similar except for age, where WHO Step I patients tended to be older than those in WHO Step II, who in turn were older than patients in WHO Step III (mean ages 58.1, 55.3 and 50.6 years, respectively; tapentadol PR group). There were also slight differences in the time since diagnosis, which was less in WHO Step I patients than in those in WHO Steps II or III (median 5.13, 6.89 and 5.37 years, respectively; tapentadol PR group). Similar patterns were

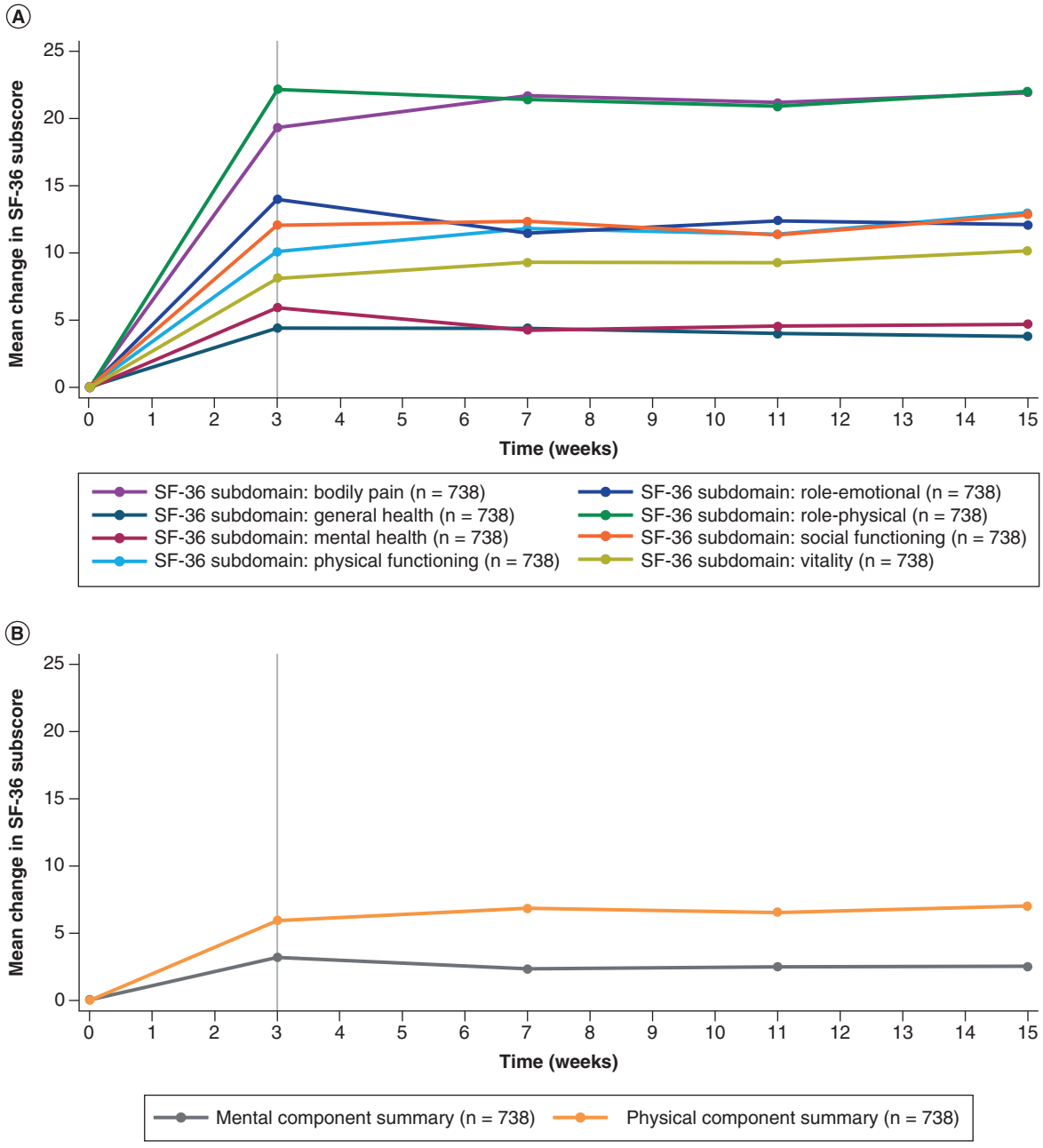

Figure 2. Changes in SF-36 scores over time during tapentadol prolonged release treatment (doses combined, ITT set who entered maintenance period). (A) Subdomain scores; (B) summary scores.
ITT: Intent to treat set; mITT: ITT set who entered maintenance period; ~~PR: Prolonged release;~~ SF-36: 36-item Short-Form Health Survey.

observed in the oxycodone CR group. The demographic details of patients categorized by WHO step class in the tapentadol PR and oxycodone CR groups are summarized in Table 1.

Time course of SF-36 score changes during tapentadol PR treatment

All SF-36 subdomain and summary scale scores increased (i.e., improved) progressively from week 0 to week 3 of the titration period for tapentadol PR (Figure 2, doses combined). These SF-36 score improvements were then maintained during the 12-week maintenance period (Figure 2).

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Table 1. Subject demographics categorized by treatment group and WHO steps (intent to treat).

Parameter, baseline	Tapentadol				Oxycodone			
	No WHO pretreatment n = 391	WHO Step I pretreatment n = 271	WHO Step II pretreatment n = 255	WHO Step III pretreatment n = 61	No WHO pretreatment n = 453	WHO Step I pretreatment n = 250	WHO Step II pretreatment n = 238	WHO Step III pretreatment n = 58
Age, years, mean (SD)	57.9 (11.82)	58.1 (12.31)	55.3 (11.72)	50.6 (13.92)	57.4 (11.43)	57.6 (13.22)	55.0 (13.14)	54.3 (12.09)
Sex, female, n (%)	247 (63.2)	192 (70.8)	167 (65.5)	33 (54.1)	259 (57.2)	162 (64.8)	140 (58.8)	40 (69.0)
Weight, kg, mean (SD)	91.3 (21.61)	87.6 (22.29)	90.9 (23.31)	95.6 (24.03)	90.9 (21.06)	89.1 (23.03)	92.5 (22.69)	86.8 (17.03)
Height, cm, mean (SD)	168.0 (10.73)	166.3 (9.86)	166.9 (9.88)	171.7 (10.23)	168.4 (10.01)	166.2 (9.46)	167.8 (11.22)	167.3 (10.96)
BMI, kg/m^2, mean (SD)	32.5 (7.91)	31.6 (7.09)	32.6 (7.93)	32.3 (7.40)	32.0 (6.64)	32.2 (7.82)	33.0 (8.03)	31.1 (6.06)
Medical history, n (%) – musculoskeletal	 385 (98.5)	 268 (98.9)	 245 (96.1)	 60 (98.4)	 445 (98.2)	 248 (99.2)	 232 (97.5)	 57 (98.3)
Pain intensity score, mean (SD)	7.2 (1.27)	7.3 (1.23)	7.6 (1.23)	7.9 (1.24)	7.2 (1.18)	7.3 (1.19)	7.6 (1.27)	7.5 (1.25)
Time since diagnosis, years, median (Q1, Q3)	5.20 (2.22, 10.24)	5.13 (2.60, 10.37)	6.89 (2.77, 13.41)	5.37 (2.69, 15.15)	5.28 (2.35, 10.16)	5.38 (2.30, 10.32)	6.16 (2.68, 10.70)	6.90 (2.05, 15.04)
Prior opioid use, n (%)[†]	32 (8.2)	13 (4.8)	232 (91.0)	60 (98.4)	29 (6.4)	13 (5.2)	220 (92.4)	56 (96.6)
Prior nonopioid analgesic use, n (%)	381 (97.4)	268 (98.9)	186 (72.9)	34 (55.7)	436 (96.2)	248 (99.2)	168 (70.6)	36 (62.1)
Reason for dissatisfaction with treatment, n (%) – inadequate analgesia – poor tolerability	 389 (99.5) 2 (0.5)	 269 (99.3) 2 (0.7)	 249 (97.6) 6 (2.4)	 57 (93.4) 4 (6.6)	 452 (99.8) 1 (0.2)	 250 (100) 0	 233 (97.9) 5 (2.1)	 56 (96.6) 1 (1.7)
SF-36 Mental component summary score, mean (SD)	50.8 (11.6)	50.3 (11.4)	46.8 (12.2)	45.8 (13.6)	50.0 (11.6)	49.1 (11.3)	48.2 (12.7)	45.0 (12.8)
SF-36 Physical component summary score, mean (SD)	28.7 (7.7)	29.6 (8.1)	27.0 (7.6)	26.7 (7.5)	29.3 (7.3)	28.8 (7.6)	28.1 (7.3)	26.2 (6.6)

[†]During 3 months prior to screening visit.
ITT: intent to treat set; Q: Quarter; SD: Standard deviation; SF-36: 36-item Short-Form Health Survey.

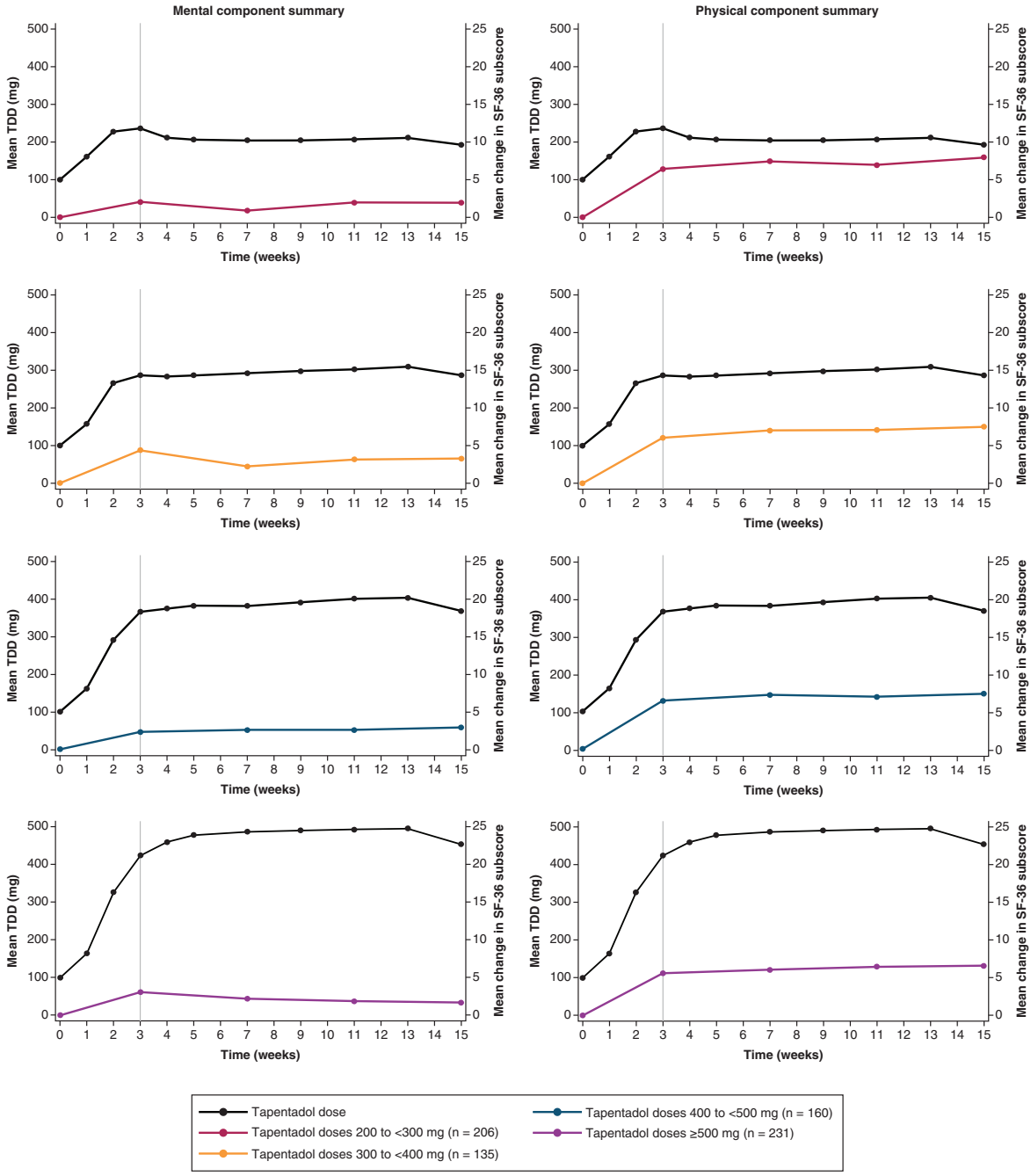

Figure 3. Changes in SF-36 summary scale score compared with mean total daily doses over time in tapentadol prolonged release maintenance dose groups (ITT set who entered maintenance period).
ITT: Intent to treat set; mITT: ITT set who entered maintenance period; ~~PR: Prolonged release;~~ SF-36: 36-item Short-Form Health Survey; TDD: Total daily dose.

Extent of SF-36 score changes with respect to tapentadol PR maintenance-dose group

The improvements in QOL and functionality measured by SF-36 scores in the tapentadol PR group were similar across maintenance groups; in other words, patients on a 200–<300 mg total daily dose experienced similar score benefits to those on higher (e.g., ≥500 mg) doses of tapentadol PR. This is illustrated by the mental and physical component summary score changes shown in Figure 3.

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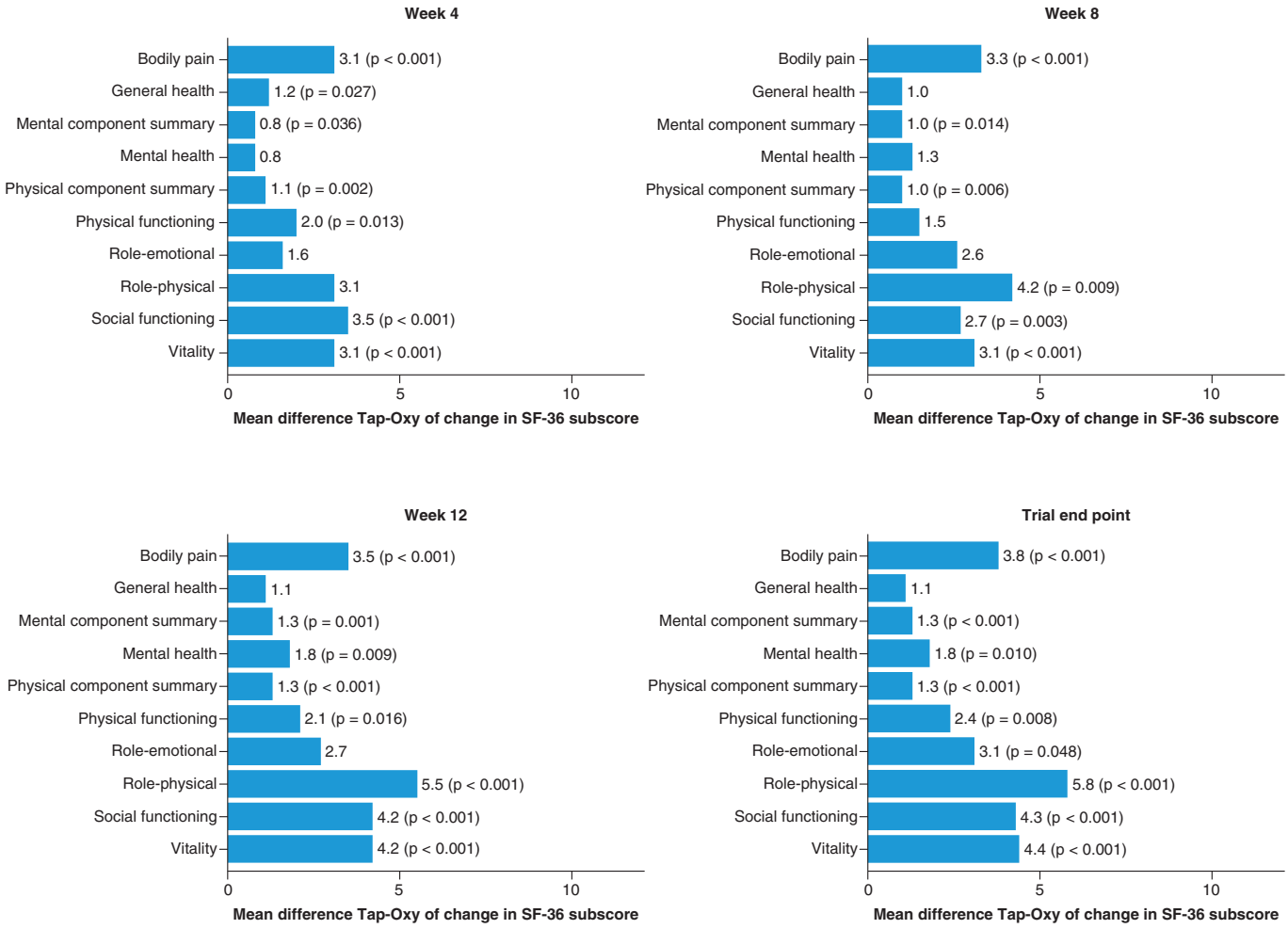

Figure 4. SF-36 score changes at weeks 4, 8 and 12 of the maintenance period and trial end point during tapentadol prolonged release and oxycodone controlled release treatment (doses combined, ~~intent to treat~~). Least squares mean from ANCOVA of change from baseline in SF-36 score at the specified week with factors treatment group and pooled site, and covariate baseline score. Missing SF-36 subdomain scores imputed using last observation carried forward over the 15-week treatment period. p-values only shown where point estimate was significantly different from zero.
ANCOVA: Analysis of covariance; ~~CR: Controlled release;~~ ITT: Intent to treat; Oxy: Oxycodone; ~~PR: Prolonged release;~~ SF-36: 36-item Short-Form Health Survey; Tap: Tapentadol.

Comparison of SF-36 score changes in tapentadol PR versus oxycodone CR groups

Tapentadol PR provided significantly greater improvements from baseline to trial end point than oxycodone CR in QOL and functionality as measured by all subdomain scores ($p \leq 0.048$, all comparisons), with the exception of general health ($p = 0.061$) (Figure 4). Tapentadol PR also produced significantly greater improvements than oxycodone CR in both physical component (LS mean difference: -1.3, 95% CI: -2.06—0.63; $p < 0.001$) and mental component summary scores (LS mean difference: -1.3, 95% CI: -2.12—0.56; $p < 0.001$) at trial end point, as previously reported [54,60].

Assessments at weeks 4, 8 and 12 also showed that tapentadol PR provided greater improvements than oxycodone CR in the majority of SF-36 scores, including statistically significant greater improvements in the subdomains of social functioning, vitality and bodily pain at all time points ($p < 0.05$) (Figure 4).

In WHO step class analyses of prior pain medication, tapentadol PR was superior to oxycodone CR in QOL and functionality measured by SF-36 score changes in patients with no prior medication, similar to findings in the overall study population (Figure 5). Tapentadol PR also provided greater benefits than oxycodone CR in patients with prior WHO Step I medication. For patients with prior Step II medication, comparisons of tapentadol PR

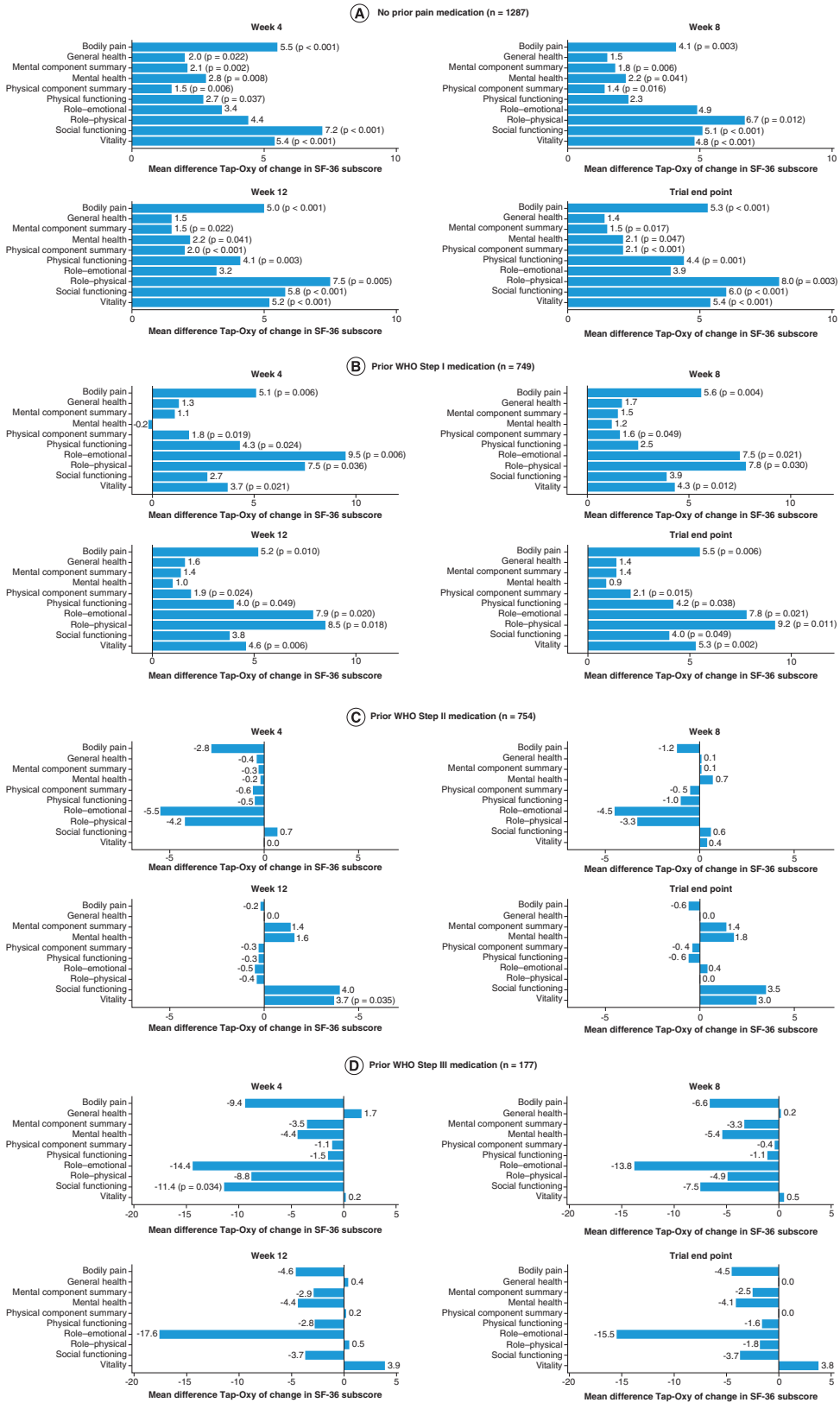

Figure 5. SF-36 score changes at weeks 4, 8 and 12 of the maintenance period and trial end point during tapentadol ~~PR~~ and oxycodone controlled release treatment according to WHO step class (doses combined, ~~intent to treat~~). Least squares mean from ANCOVA for change from baseline in SF-36 score at the specified week with factors treatment group and pooled site and covariate baseline score. Missing SF-36 subdomain scores imputed using last observation carried forward over the 15-week treatment period. p-values only shown where point estimate was significantly different from zero.

ANCOVA: Analysis of covariance; ~~CR: Controlled release;~~ ITT: ~~Intent~~ to treat; Oxy: Oxycodone; ~~PR: Prolonged release;~~ SF-36: 36-item Short-Form Health Survey; Tap: Tapentadol.

and oxycodone CR provided inconsistent outcomes, while oxycodone CR appeared to provide greater SF-36 score changes in the Step III analysis, although the lower patient numbers preclude statistical significance.

Discussion

This was a *post hoc* analysis of pooled data from three placebo-controlled Phase III trials comparing tapentadol PR with oxycodone CR. A total of 2968 patients (ITT population) with chronic osteoarthritis or cLBP were included. The study was performed to aid recognition of the importance of improved QOL and functionality as major goals in chronic pain treatment and it had the specific objective to compare the impact of tapentadol PR versus oxycodone CR on individual subdomains of the SF-36 health survey.

Tapentadol is an atypical opioid with a unique dual mechanism of action via MOR agonism and NRI, which is considered to explain its effectiveness in multiple forms of chronic pain, including pain with a neuropathic component. The reported presence of a neuropathic component in patients with severe cLBP varies, with one study suggesting that a neuropathic component is likely or else not excluded in 77% [61], while another study reports the figure as high as 90% [62]. This is relevant because a neuropathic component is associated with higher pain intensity, greater number and greater severity of comorbidities, predisposition to chronification, higher disability scores and reductions in QOL and functionality [63–67]. Failure to identify patients with occult neuropathic components may lead to suboptimal treatment regimens [67].

The combination of MOR agonism and NRI activity of tapentadol PR could theoretically have different effects on QOL and functionality than classical opioids such as oxycodone, which act primarily via the MOR. In our study, tapentadol PR produced improvements over time in all QOL and functional outcomes measured by the SF-36 subdomain and summary scale scores, starting at the initiation of treatment in the titration period. A total of 738 patients in the tapentadol arm entered the maintenance phase after the titration period (mITT population). After achieving maximal SF-36 score changes by week 3, the QOL and functionality improvements were sustained at the same levels over the 12-week maintenance period. This is similar to the reduction in pain observed over time (see Figure 2 in Sanchez *et al.* [60]). Using a definition of minimally important difference as a 10-point change for subdomain scores and a 5-point change for component scores [68], almost all SF-36 subdomains showed an improvement on tapentadol PR treatment that patients and physicians would recognize as clinically relevant.

Provided that patients received an average maintenance dose of 200–300 mg per day, there were no observable differences in the improvements in QOL and functional outcomes, measured by SF-36, compared with tapentadol PR doses ≥500 mg/day (Figure 3).

Tapentadol PR provided greater improvements than oxycodone CR in the majority of SF-36 subdomains during the maintenance period for the overall study population (Figure 4). Notably, tapentadol PR provided greater benefits compared with oxycodone CR in the subdomains of bodily pain, social functionality and vitality, which are of clinical relevance to patients with chronic pain of musculoskeletal origin impacting their QOL. QOL and functionality improvements were also greater with tapentadol PR than oxycodone CR in patient subgroups who received no prior pain medication and those on prior WHO Step I medication (except for mental health score, week 4 only) (Figure 5). For patients on prior WHO Step II medication, tapentadol PR and oxycodone CR showed inconsistent numerical differences in SF-36 scores; while, for the low numbers of patients on prior WHO Step III medication, oxycodone CR appeared to provide greater changes than tapentadol PR in most SF-36 scores.

The improvements in QOL and functionality shown for tapentadol PR in our study are supported by an open-label Phase IIIb/IV trial of patients with LBP [69], where tapentadol PR provided significant improvements in QOL (Short Form-12 physical component summary and EuroQol-5 Dimension Health Status Index and Health State Assessment) compared with oxycodone/naloxone PR. Tapentadol PR was also associated with lower incidences of constipation and vomiting than oxycodone CR in that study, consistent with the three randomized Phase III studies reported here and other studies that used oxycodone as the comparator [37,38,57,70–74]. Any contribution of these effects to the QOL and functionality benefits of tapentadol PR described will need to be further investigated in dedicated trials.

Strengths of our study include the large study population, the randomized controlled design of the studies and the use of SF-36 as a validated measure of QOL and functional outcomes. Limitations of the study include its retrospective analysis of outcomes pooled from multiple studies (albeit with similar designs), limited generalizability related to the inclusion/exclusion criteria that excluded comorbidities and concurrent medication use typical in chronic pain populations, and a study duration of 15 weeks (3 weeks' titration followed by 12 weeks' maintenance treatment) that is insufficient to confirm that improvements in QOL and functionality were sustained over the

longer term. An additional limitation was that the number of analyzable patients included in the tapentadol PR and oxycodone CR groups decreased over time, as observed in the three individual Phase III studies. Confirmation of the observations in our study would require a prospective trial design, with inclusion of dose-effect analyses in patients with comorbidities and concurrent medications representative of the wider chronic pain population, and with a longer follow-up to demonstrate that the improvements in QOL and functionality are sustained in the long-term.

Our findings have a number of implications for clinical practice. First, patients may expect to achieve benefits in QOL and functionality on tapentadol PR already by the end of the 3-week titration period. Second, these improvements in QOL and functionality are sustained for at least 12 weeks during continued tapentadol PR treatment, demonstrating the importance of maintained treatment for patients who are regaining functionality. Third, the SF-36 subdomain score changes show that clinically relevant improvements occur across the range of QOL and functionality parameters during tapentadol PR treatment. Fourth, tapentadol PR at a dose of approximately 300 mg provides QOL and functionality improvements equivalent to higher doses; this supports the approach of titrating tapentadol PR to an appropriate or adequate dose within the recommended dose range based on patient needs of efficacy and tolerability, which was approximately 300 mg in the majority of patients in these studies. Fifth, QOL and functionality improvements are consistently greater with tapentadol PR than oxycodone CR, both in the overall patient population and in those patients who previously received either no pain medication or WHO Step I medication.

Conclusion

In our pooled *post hoc* analysis, tapentadol PR treatment provided consistent, robust improvements in QOL and functional outcomes in patients with chronic osteoarthritis or LBP during the 3-week titration period. The benefits were seen from the start of treatment and increased until the third week, when they were most noticeable. The improvements were then sustained over 12 weeks of maintenance treatment with tapentadol PR. Tapentadol PR provided superior improvements in QOL and functionality measured by SF-36 subdomain scores compared with oxycodone CR in the overall study population; these observations add to previous studies reporting superior tolerability for tapentadol PR than oxycodone CR. There were no relevant differences in QOL and functionality improvements between patients who received an average dose of approximately 300 mg tapentadol PR versus those on ≥500 mg daily (500 mg is the maximum-approved daily dose), demonstrating the importance of titrating to an appropriate dose based on patient needs for an optimal balance of efficacy and tolerability.

Summary points

- Quality of life (QOL) and functional outcomes are increasingly recognized to be major parameters in the evaluation of pain management.
- Tapentadol prolonged release (PR) was compared with oxycodone controlled release in three pivotal, randomized, double-blind, placebo-controlled, Phase III studies with similar designs in patients with chronic osteoarthritis or low back pain.
- Changes in QOL and functionality during treatment were assessed by SF-36 scores.
- Pooled *post hoc* analysis showed all SF-36 subdomains and summary scale scores for QOL and functionality improved progressively to week 3 of the titration period of tapentadol PR and were sustained during the maintenance period.
- Improvements in SF-36 scores were similar between tapentadol PR dose groups (e.g., 200–<300 vs ≥500 mg maintenance doses), with no greater effect from higher doses.
- QOL and functionality improvements were consistently greater with tapentadol PR than oxycodone controlled release in the overall population.
- Tapentadol PR therefore provides consistent, clinically relevant improvements in SF-36 score-based changes in QOL and functionality in chronic osteoarthritis or low back pain.

Author contributions

All authors contributed to the analysis and interpretation of data for the work, revised it critically for important intellectual content; and provided final approval of the version to be published.

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