Observational Study

Long-Term Effectiveness and Tolerability of Pain Treatment with Tapentadol Prolonged Release

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Background: The central analgesic tapentadol prolonged release (PR) has proven effective and generally well tolerated in a broad range of chronic pain conditions. Long-term data of its use are still scarce.

Objectives: To evaluate long-term effectiveness, tolerability, and safety of tapentadol PR in patients with severe chronic osteoarthritis (OA) knee pain or low back pain (LBP) who responded to tapentadol in 1 of 4 preceding 12-week phase 3b clinical trials.

Study Design: Open-label, uncontrolled, observational extension study of up to 72 weeks.

Setting: Fourteen centers in Spain. Protocol approval by the reference ethics committee for all the participating centers.

Methods: Eligible patients started the extension trial on the tapentadol PR dosage optimized for them in the preceding trial; dose adjustments were permitted throughout the extension. Treatment effectiveness outcomes included changes in pain intensity, sleep, state of health, quality of life, patient and clinician global impression of change, and patients' satisfaction with treatment. Patients with OA knee pain also answered the Western Ontario and McMaster Universities OA index, and patients with LBP with a possible neuropathic pain component completed neuropathic pain-related questionnaires.

Results: Eighty-three patients were enrolled: 40 with OA knee pain, 43 with LBP. The full analysis set consisted of 81 patients. Mean pain intensity remained relatively stable over the 72-week extension period with mean increases from baseline of 0.44 (95% confidence interval [CI], -0.1,1.0; Numeric Rating Scale) for all patients, 0.2 (95% CI, -0.5, 0.9) for patients with OA, and 0.68 (95% CI, -0.2, 1.6) for patients with LBP. State of health and quality of life baseline ratings were maintained; overall impression of change was "improved." Most patients (88.9%) reported at least good treatment satisfaction at the end of treatment. Mean daily tapentadol PR doses slightly increased from 313.3 ± 139.5 mg at baseline to 315.7 ± 140.1 mg at end of study. Uptitration was required for 8.4% of the patients, 4.8% had a dose reduction during the trial. Adverse events considered probably/likely or certainly related to tapentadol PR treatment by the investigator were documented for 18.1% of all patients, most commonly constipation (7.2%). Seven patients (8.4%) experienced adverse events leading to premature discontinuation.

Limitations: An open-label design, stable concomitant analgesics (World Health Organization step I), and dose adjustments were allowed during the study. All patients had benefitted from tapentadol PR in preceding trials.

Conclusions: Sustained pain relief and quality of life for up to 72 treatment weeks under relatively stable dosing, as well as the good safety profile, indicate the usefulness of tapentadol PR for patients who suffer from severe chronic OA knee pain and LBP with limited risk for tolerance development.

Key words: Tapentadol prolonged release, extension study, long-term, chronic pain, osteoarthritis, low back pain, efficacy, safety

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Chronic pain is a common health problem that affects an estimated 19% of the adult European population with often considerable restrictions in daily functioning, overall well-being, and quality of life (1). In Spain, the burden of severe and frequent pain on individuals and the economy is substantial; the impact on quality of life is greater than observed with major comorbidities or health risk factors, such as obesity, alcohol, and smoking, and pain is the primary factor associated with increased health care resource utilization (2,3).

The centrally acting analgesic tapentadol prolonged release (PR) is indicated in Europe "for the management of severe chronic pain in adults, which can be adequately managed only with opioid analgesics" (4). In the tapentadol molecule, the mechanism of action of classical strong opioids, μ-opioid receptor agonism, is combined with a different, complementary analgesic mechanism, noradrenaline reuptake inhibition (5). Both mechanisms contribute in a synergistic manner to the analgesic activity of tapentadol PR resulting in analgesic effects comparable to strong opioids but with reduced μ-opioid receptor activation, which might reduce the incidence of opioid-typical side effects (5). Tapentadol has a predictable pharmacokinetic profile (6) with no active metabolites contributing to the analgesic effect (7) and a low potential for drug interactions (8,9). Clinical trials and routine clinical practice observations have shown the effectiveness of tapentadol PR in a broad range of chronic pain conditions; treatment was generally well tolerated (10). In addition, sustained pain relief and a good tolerability profile under relatively stable mean daily tapentadol PR doses was demonstrated in the long-term treatment of moderate to severe chronic knee or hip osteoarthritis (OA) pain and low back pain (LBP) in 2 open-label clinical studies (11,12). This was confirmed in routine clinical practice by long-term data from pain specialists (13).

Patients with severe chronic OA knee pain or LBP in Spain participated in 4 open-label, multinational, phase 3b clinical tapentadol PR trials (14-17). Table 1 summarizes characteristics and main outcomes of these trials. As tapentadol PR had not yet received market approval in Spain at completion of these trials, we designed an extension study for completers of the maintenance phase of the previous trials who might, in the opinion of the investigator, benefit from further tapentadol PR treatment. Analyses of the collected data could then provide further insight into the long-term effectiveness, tolerability, and safety of tapentadol PR in the treatment of severe chronic musculoskeletal pain.

Table 1. *Main characteristics and outcomes of the 4 previous trials.*

	Steigerwald et al (14) NCT 00983073	**Steigerwald et al (15) NCT 00982280**	**Steigerwald et al (16) NCT 00983385**	**Gálvez et al (17) NCT 00986258**
Trial design	Open-label, multicenter, 12-week, phase 3b with 5-week titration and 7-week maintenance period			
	Previous WHO II analgesics were discontinued prior to TAP PR treatment initiation, WHO I and/or coanalgesics were continued at the same stable dose	Direct rotation from prior WHO III opioids to equianalgesic doses of TAP PR. All previous WHO II/III analgesics were discontinued prior to TAP PR treatment initiation, WHO I and/or coanalgesics were continued at the same stable dose Premature trial termination due to slow recruitment and trial drug shortages	Previous WHO II analgesics were discontinued prior to TAP PR treatment initiation, WHO I and/or coanalgesics were continued at the same stable dose	Direct rotation from prior WHO III opioids to equianalgesic doses of TAP PR All previous WHO II/III analgesics were discontinued prior to TAP PR treatment initiation, WHO I and/or co-analgesics were continued at the same stable dose Premature trial termination due to slow recruitment and trial drug shortages
Main inclusion criteria				
Age	≥ 40 years	≥ 40 years	≥ 18 years	≥ 18 years

Table 1. *Main characteristics and outcomes of the 4 previous trials. (cont)*

	Steigerwald et al (14) NCT 00983073	**Steigerwald et al (15) NCT 00982280**	**Steigerwald et al (16) NCT 00983385**	**Gálvez et al (17) NCT 00986258**
Pain indication	Chronic OA knee pain requiring a WHO III analgesic Previous treatment with WHO I or II analgesics or no regular analgesic treatment inadequate	Chronic OA knee pain requiring a WHO III analgesic Response but poor tolerance to prior WHO III opioid treatment	Chronic LBP with or without a neuropathic component requiring a WHO III analgesic Previous treatment with WHO I or II analgesics or no regular analgesic treatment inadequate	Chronic LBP with or without a neuropathic component requiring a WHO III analgesic Response but poor tolerance to prior WHO III opioid treatment
Satisfaction with prior analgesic treatment	≤ 1 (fair) on a 0-4 verbal rating scale (0 = poor to 4 = excellent))			
Patients	Safety population n = 200 Mean age 67.4 ± 10.8 years 67.5% female Pain duration 8.3 ± 7.4 years Effectiveness n = 195	Safety population n = 63 Mean age 65.4 ± 9.8 years 58.7% female Pain duration 6.5 ± 5.9 years Effectiveness n = 53 (per protocol)	Safety population n = 176 Mean age 59.5 ± 11.8 years 63.1% female Pain duration mean 11.7 years Effectiveness n = 175	Safety population n = 125 Mean age 57.1 ± 12 years 60.8% female Pain duration 12.4 ± 11.1 years Effectiveness n = 94 (per protocol)
Previous analgesic medication	WHO I: 64.5% of patients WHO II: 29% Coanalgesics: 17%	WHO I: 52.4% of patients WHO II: 11.1% WHO III: 100% Coanalgesics: 14.3%	WHO I: 69.9% of patients WHO II: 50.6% Coanalgesics: 38.6%	WHO I: na WHO II: 21.6% WHO III: 100%[a] Coanalgesics: na
Tapentadol doses at week 6 (when doses had stabilized)	TAP PR permitted 50-250 mg bid; TAP IR permitted 50 mg ≤ bid ≥ 4 h apart (TAP IR was not to be given to patients who were taking TAP PR 250 mg bid (500 mg total daily dose).			
	Mean daily TAP PR dose 257 ± 111 mg Mean daily TAP IR dose 6.7 ± 21.2 mg	Mean daily TAP PR dose 233 ± 145 mg Mean daily TAP IR dose 7.0 ± 17.5 mg	Mean daily TAP PR dose 311 ± 125 mg Mean daily TAP IR dose 15.2 ± 32 mg	Mean daily TAP PR dose 323 ± 121 mg Mean daily TAP IR dose 24.6 ± 33 mg
Effectiveness (primary endpoint)	Change from baseline pain intensity (7.5 ± 1.1 [NRS-11]) at week 6: -3.4 ± 2.1 ($P < 0.0001$; LOCF)	Proportion of patients at week 6 with the same/less pain compared with previous WHO III treatment: 94.3% ($P < 0.0001$ vs. null responder hypothesis rate of < 60%; LOCF)	Change from baseline pain intensity (7.4 ± 1.0 [NRS-11]) at week 6: -2.8 ± 2.1 ($P < 0.0001$; LOCF)	Proportion of patients at week 6 with the same/less pain compared with previous WHO III treatment: 80.9% ($P <$ 0.0001 vs. null responder hypothesis rate of < 60%; LOCF)
Tolerability	TEAEs (mostly mild or moderate in intensity) documented for 71% of patients (gastrointestinal disorders 38.5%, nervous system disorders 27.5%) Premature withdrawal due to TEAE in 12.5% of patients	TEAEs (mostly mild or moderate in intensity) documented for 34.9% of patients Decline in TEAEs associated with previous WHO III treatment (e.g., nausea 46% to 24.1%, constipation 31.7% to 7.4%) Premature withdrawal due to TEAE in 9.5% of patients	TEAEs (mostly mild or moderate in intensity) documented for 84.7% of patients (most commonly nausea 21%) Premature withdrawal due to TEAE in 20.5% of patients	TEAEs (mostly mild or moderate in intensity) documented for 68% of patients Decline in TEAEs associated with previous WHO III treatment (e.g., constipation 36% to 18.3%, nausea 20% to 14%) Premature withdrawal due to TEAE in 14.4% of patients

[a]Two patients did not take WHO III analgesics in the week before tapentadol PR initiation. Bid, twice daily; LOCF, last observation carried forward; na, not available; TAP, tapentadol.

Methods

This open-label, uncontrolled, long-term extension trial was conducted at 14 centers in Spain from December 2009 to December 2011 in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and Spanish laws. The study protocol and amendments were reviewed and approved by the reference ethics committee for the participating study centers. All participating patients provided written informed consent before enrolment. The trial is registered as EudraCT no. 2009-015527-82.

Patients

Patients in Spain who participated in 1 of 4 open-label, multicenter, 12-week, phase 3b clinical trials (14-17) were examined for eligibility. They could participate in the extension study if they had completed the maintenance period of 1 of these 4 trials without any major protocol violations, had attained the minimum target of titration during the preceding trial and maintained it until the baseline visit of this extension, would, in the opinion of the investigator, benefit from continued treatment with tapentadol PR, and had provided written informed consent. The minimum titration target was a clinically relevant improvement in pain relief defined as a reduction in pain intensity of at least 1 point on the 11-point Numeric Rating Scale (NRS-11) from baseline. Main exclusion criteria were a history of severe renal impairment or moderately/severely impaired hepatic function; history or active hepatitis B or C, or HIV infection within the last 3 months; history of alcohol or drug abuse; history of seizure disorder or epilepsy; mild/moderate traumatic brain injury, stroke, transient ischemic attack, or brain neoplasm within the last year; severe traumatic brain injury occurring within the last 15 years or residual sequelae suggesting transient changes in consciousness; pregnancy or lactation; any contraindications to tapentadol; the administration of monoamine oxidase inhibitors or nonstable dosing of selective serotonin reuptake inhibitors; or the premature discontinuation of tapentadol in the preceding trial, for any reason.

Study Design

Eligible patients entered the extension study at the final visit (week 12) of the preceding trial and continued taking the tapentadol PR dosage optimized for them for pain relief and tolerability in the previous treatment weeks. World Health Organization (WHO) step I analgesics and coanalgesics received at completion of the preceding trial had to be kept as stable as possible during this extension; 50 mg tapentadol immediate release (IR) was permitted as rescue medication twice daily (at least 4 hours apart) except for patients already taking the maximum recommended daily tapentadol PR dosage of 500 mg. WHO step II analgesics had been discontinued at the start of the preceding trials (Table 1). The intake of WHO step III analgesics was not permitted. During extension, tapentadol PR could be uptitrated in weekly intervals up to a maximum daily tapentadol dosage of 500 mg (including tapentadol IR as rescue medication) in case pain intensity worsened by at least 1 point from the week 12 score of the preceding trial in any of the subsequent visits or 100 mg tapentadol IR was taken for 7 consecutive days. Any dose increases, irrespective of titration target related to improve effectiveness, could be limited by tolerability. Dose reductions were permitted in case of tolerability issues.

The study included an initial 4-week transition period with weekly telephone calls and one visit in week 4 followed by quarterly visits, and one visit in week 72.

Outcome Measures

Treatment effectiveness measures were:

- The NRS-3 to assess average pain intensity during the last 3 days before a visit (referring to the reference knee for OA pain or overall LBP).
- The EuroQol-5Dimensions (EQ-5D) questionnaire to assess health-related quality of life in the 5 dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (18). Rating options for patients were "no problems," "some problems," and "extreme problems." Patients also rated their state of health on the EQ Visual Analog Scale (VAS) from 0 mm (worst imaginable state) to 100 mm (best imaginable state).
- The Short Form-36 Health Survey (SF-36) to determine quality of life using 8 physical and mental dimensions, which were then summarized in a physical and mental component score (19). Higher scores indicate less impairment.
- The Patient Global Impression of Change (PGIC) and Clinician Global Impression of Change (CGIC) to rate the change in overall health status from 1 (very much improved) to 7 (very much worse) (20).
- A 4-item self-assessment sleep questionnaire assessing sleep latency, time slept, number of awakenings, and sleep quality during the previous night (21).
- A 5-point verbal rating scale from excellent (4) to

poor (0) to determine patients' satisfaction with treatment.

- For patients with OA knee pain
  - The Western Ontario and McMaster Universities (WOMAC) OA index, a patient questionnaire using a Likert scale from 0 to 4 (higher scores indicate worse pain, stiffness, and functional limitations) (22).
- For patients with LBP with an at least possible neuropathic component in the pain radiating toward or into the leg.
  - The NRS-3 to assess pain intensity.
  - The Neuropathic Pain Symptom Inventory (NPSI) to discriminate and quantify 5 distinct clinically relevant dimensions of neuropathic pain syndromes (23) including 10 descriptors of pain quality and 2 items for frequency and duration of pain.
  - The Short Form McGill Pain Questionnaire (SF-MPQ) with a pain rating index of 15 descriptors (11 sensory, 5 affective; intensity rating from 0 = none to 3 = severe), a VAS (0-100 mm) to rate pain intensity during the last week, and an assessment of present pain intensity (24).

The need to increase tapentadol PR dosages and possible reductions in concomitant WHO step I analgesics and coanalgesics during the trial were also used to evaluate treatment effectiveness.

Adverse events (AEs) were monitored throughout the trial. Tolerability and safety were assessed by analyzing all treatment-emergent AEs (TEAEs) and adverse drug reactions (ADRs), vital signs (at baseline, weeks 4, 20, 36, 52, 68, 72, and 88, and laboratory data [at baseline and week 88]).

Statistical Analyses

The effectiveness analysis included all patients who took at least one dose of tapentadol PR in this extension trial and had at least one postbaseline assessment of any effectiveness parameter (full analysis set [FAS]). All data were analyzed descriptively and are "as observed"; missing data were not imputed. End of treatment data are patients' last available values. A 95% confidence interval (CI) on the mean was calculated for efficacy variables.

All patients who received at least one dose of tapentadol PR were included in the safety analysis. All AEs were encoded with the Medical Dictionary for Regulatory Activities (MedDRA) version 12.1. ADRs were defined as AEs considered probably/likely or certainly related to tapentadol PR treatment by the investigator. AE analysis was descriptive. AE incidence rates (events per patient per year) were calculated using Kaplan-Meier estimates. Missing values because of premature withdrawal or any other reason were not imputed.

Results

Patients

In Spain, a total of 132 pain patients participated in 1 of the 4 preceding trials; 83 (62.9%) of those were enrolled in the extension trial. Forty-three patients suffered from chronic LBP, 40 from chronic OA knee pain (Fig.1). Twenty-one patients (25.3%) discontinued prematurely: 7 patients due to AEs (8.4%), 5 patients were lost to follow-up (6.0%), 4 patients due to lack of efficacy (4.8%), 3 patients withdrew informed consent (3.6%), and 2 patients (2.4%) withdrew because pain symptoms resolved.Baseline characteristics of the patients are shown in Table 2. Many patients were women (73.5%), mean age was 64 years (95% CI, 61.6, 66.5), many were overweight with a mean body mass index of 29.4 kg/m^2 (95% CI, 28.4, 30.4). The proportion of women was higher in the OA population; patients with LBP were on average younger. Main concomitant diseases were musculoskeletal and connective tissue disorders (66.3% of all patients), and metabolism and nutrition, gastrointestinal, and vascular disorders (47% each).

Analgesic Treatment

Mean daily tapentadol PR dose at start of the extension trial was 313.3 ± 139.5 mg and was higher in patients with LBP (344.2 ± 138.5 mg) than in patients with OA knee pain (280 ± 134.4 mg). Overall, mean daily doses only slightly increased over the study period to 315.7 ± 140.1 mg. Patients spent a median of 505 days in the study; on average, tapentadol PR was taken 93.6% of the days under treatment. Six patients received daily doses over 500 mg (up to 586 mg). Uptitrations were required for 3 OA and 3 LBP patients once; one patient with OA had 2 dose increases. In addition, 6 dose reductions were documented for 4 patients.

At the end of the preceding trials, nearly half of our study population (48.2%) was taking concomitant WHO step I analgesics (Table 2), most commonly paracetamol (22.9%), traditional nonsteroidal anti-inflammatory drugs (19.3%), and COX-2-inhibitors (10.8%). Only a few changes occurred during exten-

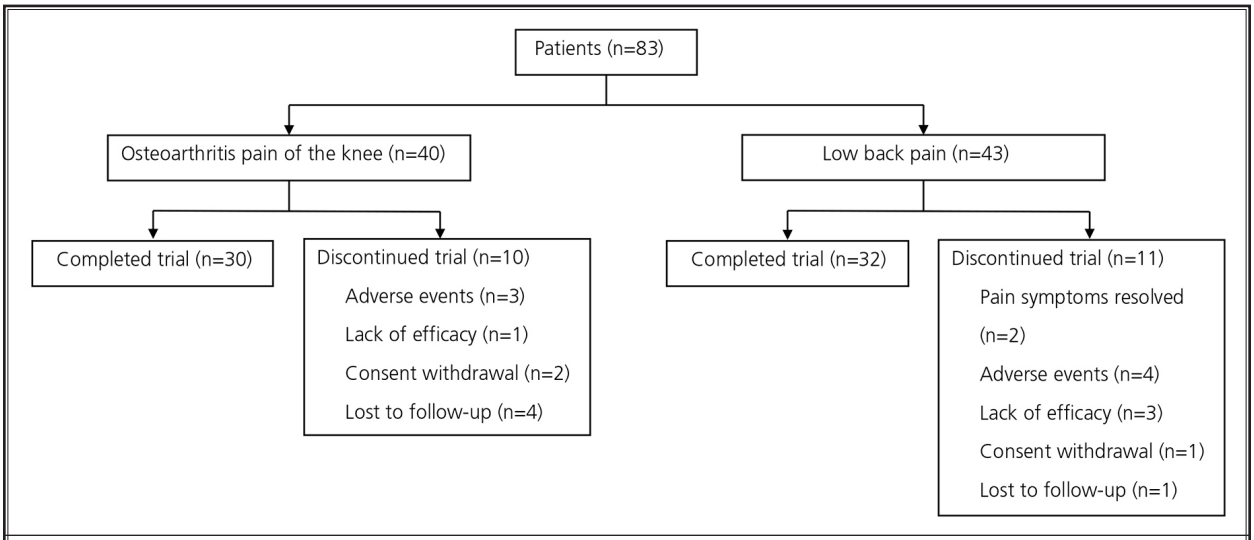

Fig. 1. *Patient flow.*

Table 2. *Baseline characteristics of the patients (safety population).*

	OA Pain (n = 40)	LBP (n = 43)	All Patients (n = 83)
Age, years	69.2 (66.5, 71.9)	59.2 (55.7, 62.7)	64.0 (61.6, 66.5)
Gender			
Female	34 (85%)	27 (62.8%)	61 (73.5%)
Male	6 (15%)	16 (37.2%)	22 (26.5%)
Body mass index, kg/m^2	29.7 (28.3, 31.1)	29.1 (27.7, 30.5)[a]	29.4 (28.4, 30.4)[b]
Concomitant WHO step I analgesics	21 (52.5%)	19 (44.2%)	40 (48.2%)
Coanalgensics	18 (45%)	14 (32.6%)	32 (38.6%)

Data are mean (95% CI) or number of patients (%). [a]n = 42; [b]n = 82.

sion: 3 OA and 4 LBP patients were administered a new concomitant analgesic, and daily ibuprofen intake was reduced for one patient with LBP from 1800 to 600 mg. Coanalgesics were documented for 38.6% of the patients at baseline with higher frequencies in OA than LBP patients (Table 2). Intake of coanalgesics was changed during the extension in 3 OA and 4 LBP patients. The use of tapentadol IR as rescue medication was reported at baseline for 7 patients (59 patients had no need, data missing for 17 patients).

Effectiveness Outcomes

Two patients did not have any postbaseline effectiveness assessment and were excluded from the effectiveness analysis. The FAS thus comprised 81 patients.

At the end of the preceding trials, mean pain intensity on an 11-point NRS-3 was 3.11 (95% CI, 2.7, 3.5), and 91.6% of all patients rated their satisfaction with tapentadol PR treatment as at least good. Mean pain intensity remained relatively stable over the 72-week extension period (Fig. 2); mean increase from baseline to end of treatment (last available value) was 0.44 (95% CI, -0.1, 1.0) for all patients, 0.2 (95% CI, -0.5, 0.9) for patients with OA, and 0.68 (95% CI, -0.2, 1.6) for patients with LBP. Most patients (88.9%) still reported at least good treatment satisfaction (80% patients with OA, 97.6% patients with LBP).

Overall, sleep duration, number of nightly awakenings, and sleep latency determined at patients' final visit did not differ greatly from baseline, and more than 60% of all patients rated their sleep quality as "good" or "excellent" at the final assessment (Table 3). Patients with LBP experienced a mean increase of 0.63 in the number of awakenings.

Patients' mean state of health at baseline (69 mm [95% CI, 65, 73]) was maintained over the extension period with a change of -2.9 mm (95% CI, -6.9, 1.1). The proportion of patients reporting "no problems" on the EQ-5D remained similar to baseline values at the end of treatment for the dimension "self-care" and improved for all other dimensions (Table 4). End of treatment SF-36 quality of life data were only available for 55 patients; the physical component score slightly worsened by -1.4 (95% CI, -5.6, 2.9) and the mental component scores

slightly increased by 3.5 (95% CI, -0.9, 7.9). At the end of the preceding trials, most patients and clinicians had rated the change in overall health status as much improved (mean 2.27 [95% CI, 2.1, 2.4] on the PGIC, mean 2.25 [95% CI, 2.1, 2.4] on the CGIC); changes at the end of treatment were 0.19 (95% CI, -0.0, 0.4; PGIC) and 0.09 (95% CI, -0.1, 0.3; CGIC). Changes in the 2 subgroups were: PGIC 0.25 (95% CI, -0.1, 0.6), CGIC 0.0 (95% CI, -0.2, 0.2) for patients with OA, and PGIC 0.12 (95% CI, -0.1, 0.3), CGIC 0.18 (95% CI, -0.1, 0.4) for patients with LBP.

Patients with OA also assessed pain, disability, and joint stiffness on the WOMAC over the study period (Table 5). Small improvements from baseline were noted for the physical function subscale and the global score. Two-thirds of patients (29/43; 67.4%) in our LBP subgroup had an at least possible neuropathic component in the pain radiating toward or into the leg (assessed with the PainDETECT questionnaire in the preceding trials [16,17]). NPSI and SF-MPQ ratings slightly improved during the extension in patients with LBP and neuropathic pain component who had been treated with WHO step III analgesics in the preceding studies (Table 6).

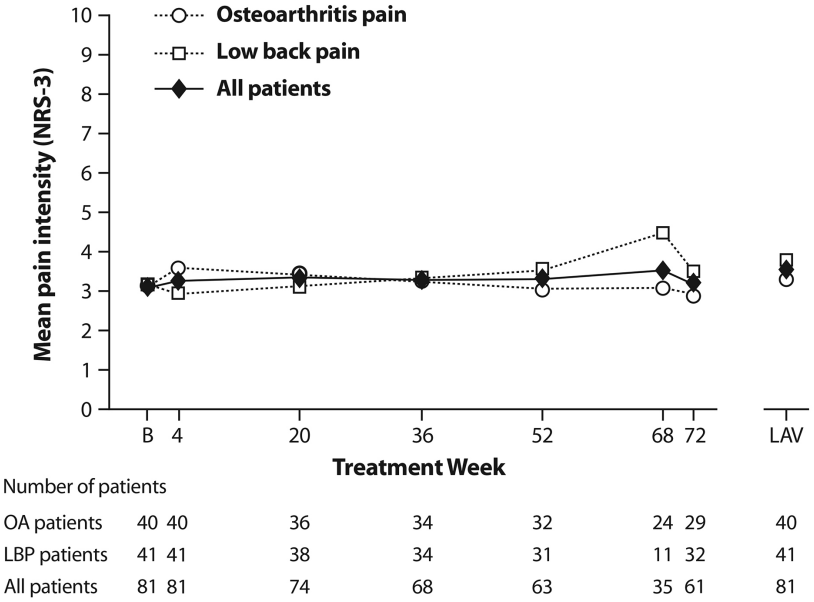

Fig. 2. *Mean pain intensity over the extension period (FAS). Data are "as observed."* B, baseline; LAV, last available value.

Safety and Tolerability Outcomes

Safety data are provided in Table 7. Forty-six patients (55.4%) reported 138 mostly mild or moderate TEAEs; in 15 patients (18.1%), the event was considered probably/likely or certainly related to tapentadol PR treatment by the investigator. Most frequent ADRs were constipation (7.2% of all patients) and pruritus not otherwise specified (NOS; 2.4%), both known and common ADRs for tapentadol PR. A relationship to concomitant analgesics or coanalgesics was considered in 6% of the patients. Serious AEs were documented for 6 patients, none were considered related to tapentadol PR treatment (2x infection, gonarthritis, colpocele, knee prosthesis insertion, thyroidectomy total). Only 1 of the 6 patients receiving a daily dose over 500 mg tapentadol PR experienced AEs (rotator cuff tendinitis, odontalgia, worsening right knee pain), which were

Table 3. *Assessment of sleep over the study period.*

	OA Pain (n = 40)	LBP (n = 41)	All Patients (n = 81)
Mean sleep latency (h)			
Baseline	0.51 (0.3, 0.7)[a]	0.49 (0.4, 0.6)	0.5 (0.4, 0.6)[b]
End of treatment (LAV)	0.75 (0.5, 1.0)[a]	0.73 (0.4, 1.0)	0.74 (0.6, 0.9)[b]
Mean nightly awakenings			
Baseline	2.28 (1.2, 3.3)[a]	1.51 (1.0, 2.0)	1.89 (1.3, 2.5)[b]
End of treatment (LAV)	2.03 (1.6, 2.4)	2.15 (1.6, 2.7)	2.09 (1.8, 2.4)
Mean sleep duration (h)			
Baseline	6.81 (6.3, 7.3)[a]	6.33 (5.7, 6.9)	6.56 (6.2, 7.0)[b]
End of treatment (LAV)	6.67 (6.2, 7.1)	6.24 (5.7, 6.7)	6.45 (6.1, 6.8)
Number of patients reporting good or excellent sleep quality			
Baseline	25 (64.1%)[a]	32 (74.4%)[c]	57 (69.5%)[d]
End of treatment (LAV)	24 (60%)	27 (65.9%)	51 (63%)

Data are mean (95% CI) or number (%). LAV, last available value.
[a]n = 39, [b]n = 80, [c]n = 43 (safety set), [d]n = 82.

Table 4. *Proportion of patients for each dimension of the EuroQoL-5D at baseline and end of treatment (last available value).*

	Knee OA		LBP		All Patients	
	Baseline (%) (n = 40)	End of treatment (%) (n)	Baseline (n = 43)	End of treatment (%) (n)	Baseline (n = 83)	End of treatment (%) (n)
Mobility						
I have no problems in walking about	27.50%	32.50% (13)	51.16%	53.66% (22)	39.76%	43.2% (35)
I have some problems in walking about	72.50%	67.50% (22)	44.19%	41.46% (17)	57.83%	54.32% (44)
I am confined to bed	-	-	4.65%	4.88% (2)	2.41%	2.47% (2)
Self-care						
I have no problems with self-care	72.50%	72.50% (29)	76.64%	75.61% (31)	74.70%	74.07% (60)
I have some problems washing or dressing myself	27.50%	27.50% (11)	20.93%	21.95% (9)	24.10%	24.69% (20)
I am unable to wash or dress myself	-	-	2.33%	2.44% (1)	1.20%	1.23% (1)
Usual activities						
I have no problems with performing my usual activities	42.50%	42.50% (17)	51.16%	53.66% (22)	46.99%	48.15% (39)
I have some problems with performing my usual activities	57.50%	57.50% (23)	39.53%	41.46% (17)	48.19%	49.38% (40)
I am unable to perform my usual activities	-	-	9.30%	4.88% (2)	4.82%	2.47% (2)
Pain/discomfort						
I have no pain or discomfort	20.00%	27.50% (11)	23.26%	29.27% (12)	21.69%	28.4% (23)
I have moderate pain or discomfort	75.00%	65.00% (26)	69.77%	65.85% (27)	72.29%	65.43% (53)
I have extreme pain or discomfort	5.00%	7.50% (3)	6.98%	4.88% (2)	6.02%	6.17% (5)
Anxiety/depression						
I am not anxious or depressed	60.00%	67.50% (27)	62.79%	58.54% (24)	61.45%	62.96% (51)
I am moderate anxious or depressed	35.00%	27.50% (11)	32.56%	31.71% (13)	33.73%	29.63% (24)
I am extremely anxious or depressed	5.00%	5.00% (2)	4.65%	9.76% (4)	4.82%	7.41% (6)

Table 5. *Changes in pain, physical function, and joint stiffness at end of treatment (last available value) in patients with OA (Western Ontario and McMaster Universities Osteoarthritis index).*

Pain subscale	n = 38	-0.11 (-0.8, 0.6)
Physical function subscale	n = 35	-1.35 (-4.3, 1.6)
Stiffness subscale	n = 34	0.18 (-0.3, 0.7)
Global score	n = 32	-0.99 (-5.1, 3.2)

Data are mean (95% CI). Score reductions denote improvement.

deemed unrelated to tapentadol PR treatment (mean 506 mg daily). Seven patients (8.4%) experienced AEs leading to premature discontinuation: constipation, mouth dry aggravated, nausea, vomiting NOS, mucositis NOS, prosthesis-related infection, anorexia, dizzy spells, headache NOS, disorientation, dysphoria, and knee prosthesis insertion. The overall AE incidence rate was 0.9 events per patient per treatment year (OA 1.1, LBP 0.8). There were no clinically relevant changes in

Table 6. *Changes from baseline in the NPSI and SF-MPQ in LBP patients with a neuropathic pain component (n = 28).*

Pain intensity (NRS-3)	
Baseline	2.96 (95% CI, 1.9, 4.0)
Change at end of treatment	-0.61 (95% CI, -1.3, 0.1)
Total NPSI score	
Baseline	20.18 (95% CI, 12.5, 27.9)
Change at end of treatment	-3.07 (95% CI, -9.2, 3.1)
SF-MPQ sensory pain rating	
Baseline	7.07 (95% CI, 4.6, 9.6)
Change at end of treatment	-0.43 (95% CI, -3.3, 2.4)
SF-MPQ affective pain rating	
Baseline	2.64 (95% CI, 1.6, 3.7)
Change at end of treatment	-1.04 (95% CI, -2.1, 0.0)
SF-MPQ total pain rating	
Baseline	9.71 (95% CI, 6.3, 13.1)
Change at end of treatment	-1.43 (95% CI, -4.9, 2.1)
SF-MPQ pain intensity during the last week (VAS 0-100 mm)	
Baseline	29.4 mm (95% CI, 22.8, 36.1)
Change at end of treatment	-4.6 mm (95% CI, -14.5, 5.3)
SF-MPQ present pain intensity	
No pain	10 (35.7%)
Mild pain	11 (39.3%)
Moderate pain	6 (21.4%)
Severe pain	1 (3.6%)

Data are mean (95% CI) or number of patients (%). Reductions denote improvements. End of treatment data are last available values.

Table 7. *AE profile (safety population).*

	OA Pain (n = 40)	LBP (n = 43)	All Patients (n = 83)
Any AE	23 (57.5%)	23 (53.5%)	46 (55.4%)
Most frequent AEs			
Constipation	4 (10%)	3 (7%)	7 (8.4%)
Arthropathy aggravated	5 (12.5%)	0	5 (6%)
LBP	3 (7.5%)	1 (2.3%)	4 (4.8%)
Any serious AE	3 (7.5%)	3 (7%)	6 (7.2%)
Any ADR	8 (20%)	7 (16.3%)	15 (18.1%)
Most frequent ADRs			
Constipation	4 (10%)	2 (4.7%)	6 (7.2%)
Pruritus NOS	1 (2.5%)	1 (2.3%)	2 (2.4%)
Any AE leading to study discontinuation	3 (7.5%)	4 (9.3%)	7 (8.4%)
Any AE related to concomitant analgesics or coanalgesics	4 (10%)	1 (2.3%)	5 (6%)

Data are number of patients (%).

laboratory parameters and vital signs. The increase of lactate dehydrogenase by approximately 170 U/l is the sole finding of interest. Values were below the upper limit of normal range that was set at 500 U/l.

Discussion

Treatment of severe chronic OA knee pain and LBP with tapentadol PR was continued in patients who had benefitted from tapentadol PR in previous 12-week clinical trials. At the end of the preceding trials (i.e., the baseline for the extension trial), these patients had experienced sufficient pain relief as reflected in their NRS-11 score and improved quality of life, and most were satisfied with treatment. Further tapentadol PR treatment was maintained for up to 72 weeks and provided sustained pain relief; it was generally well tolerated, and both physical and mental quality of life baseline ratings could be maintained. Overall health status ratings remained relatively constant, and most patients were satisfied with treatment. Our results support the findings of 2 previous trials investigating long-term treatment of chronic musculoskeletal pain with tapentadol PR (11,12) and observations by German pain specialists in chronic pain patients suffering mainly from LBP (82.5%) and/or hip or knee OA pain (30.7%) (13).

Very few patients required dose adjustments to maintain effective analgesia, and changes in the intake of concomitant analgesics and coanalgesics were also only reported for a few patients. The loss of analgesic efficacy over time is a common complication of opioid treatment (25) with ever-increasing doses to maintain effectiveness potentially causing tolerability issues and treatment discontinuation. There was no indication of acquired tolerance in our trial, as both tapentadol PR dosing and mean pain intensity scores remained relatively stable over the study period, although further data beyond 72 weeks are needed to corroborate this finding. This result is in line with previous long-term tapentadol PR studies (11-13).

In two-thirds of our patients with LBP, a neuropathic pain component could not be excluded. Patients with a neuropathic pain component to their chronic LBP often suffer longer and more severely than patients with predominantly nociceptive LBP; comorbidities such as depression, panic/anxiety, and sleep disorders occur more frequently, and functionality is affected (26). As more than one pain mechanism are involved, treatment is challenging. Tapentadol PR with its dual

mechanism of action has been proven useful in the treatment of LBP with or without a neuropathic component (16,17); pain relief was at least comparable to oxycodone CR (11,27) and oxycodone/naloxone PR (28). Tapentadol PR was also effective in our long-term trial and nearly all patients with LBP were satisfied with the treatment. Slight improvements from baseline were noted for neuropathic pain-related ratings and 36% of the patients reported "no pain at present" at the end of treatment. It should, however, be noted that the sample size for this group was only 28 patients.

Long-term treatment was generally well tolerated. The number of patients with TEAEs was lower than in the 1-year tapentadol PR safety study by Wild et al (11) (55.4% vs. 85.7%), which is probably owing to the fact that our study population had already experienced and tolerated tapentadol PR treatment in the preceding trials, whereas patients in the safety study had not previously taken this medication. The proportion of safety study patients, for example reporting a first TEAE of nausea, vomiting, or constipation, increased rapidly in the first 4 treatment weeks and remained relatively stable for the remainder of the study (11). This probably also accounts for the fact that a smaller proportion of our patients discontinued treatment prematurely due to side effects (8.4% vs. 22.1%) (11). The number of discontinuations among those safety study patients who continued for a second year was much lower (6.4%) (12). In this study, patients were also enrolled after participating in previous short- and long-term studies.

Gastrointestinal tolerability after 1 year of treatment was good considering that gastrointestinal comorbidities were present in 47% of the trial patients (most commonly constipation [27%]) thus increasing their baseline vulnerability for such effects. The favorable gastrointestinal tolerability profile observed for tapentadol PR over 1 year of treatment in this study is comparable to previous tapentadol long-term safety studies (11,12). The incidence of some common opioid-related TEAEs, such as constipation, was lower in the present open-label study than in previous long-term safety studies (7.2% vs. 22.6% and 11.1%) (11,12).

Among the laboratory evaluations, a significant increase of lactate dehydrogenase is the sole finding of interest; there is a shift to the left in the distribution values of the last visit, which may have been caused owing to the fact that 2 different laboratories were involved in the trial (one for the baseline results from preceding trials and a local laboratory for the last visit) and the methods to determine the lactate dehydrogenase may have been different.

Evaluation of our findings needs to consider the open-label study design and lack of placebo or control group; it should also be noted that our study population consisted of patients who had benefitted from previous tapentadol PR treatment. Although flexible dose adjustment and concomitant analgesic and co-analgesic treatment could have been a confounding factor, intake of these medications only changed in a small number of patients.

Conclusions

Patients with severe chronic OA knee pain or LBP who had benefitted from previous 12-week tapentadol PR treatment experienced sustained pain relief and quality of life under further relatively stable tapentadol PR dosing for up to 72 treatment weeks. The observed effectiveness, as well as the good safety profile, indicate the usefulness of tapentadol PR for this patient population with limited risk of tolerance development.

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Author contributions

RGM was the principal investigator of the study and was involved in conception and design of the study and data analyses and interpretation. He had full access to the study data. All authors critically revised the manuscript for intellectual content and approved the final version to be published.

References

1. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: Prevalence, impact on daily life, and treatment. *Eur J Pain* 2006; 10:287-333.
2. Langley PC, Ruiz-Iban MA, Tornero Molina J, De Andres J, González-Escalada Castellón JR. The prevalence, correlates and treatment of pain in Spain. *J Med Econ* 2011; 14:367-380.
3. Langley P, Pérez Hernández C, Ferri CM, Ruiz Hidalgo D, Lubián López M. Pain, health related quality of life and healthcare resource utilization in Spain. *J Med Econ* 2011; 14:628-638.
4. Electronic Medicines Compendium. Palexia SR prolonged release tablets. Available at: https://www.medicines.org.uk/emc/medicine/28373. Accessed 12/01/2020.
5. Tzschentke TM, Christoph T, Kögel BY. The mu-opioid receptor agonist/noradrenaline reuptake inhibition (MOR-NRI) concept in analgesia: The case of tapentadol. *CNS Drugs* 2014; 28:319-329.
6. Göhler K, Brett M, Smit JW, Rengelshausen J, Terlinden R. Comparative pharmacokinetics and bioavailability of tapentadol following oral administration of immediate- and prolonged-release formulations. *Int J Clin Pharmacol Ther* 2013; 51:338-348.
7. Terlinden R, Kogel BY, Englberger W, Tzschentke TM. In vitro and in vivo characterization of tapentadol metabolites. *Methods Find Exp Clin Pharmacol* 2010; 32:31-38.
8. Kneip C, Terlinden R, Beier H, Chen G. Investigations into the drug-drug interaction potential of tapentadol in human liver microsomes and fresh human hepatocytes. *Drug Metab Lett* 2008; 2:67-75.
9. Smit JW, Oh C, Rengelshausen J, et al. Effects of acetaminophen, naproxen, and acetylsalicylic acid on tapentadol pharmacokinetics: Results of two randomized, open-label, crossover, drug-drug interaction studies. *Pharmacotherapy* 2010; 30:25-34.
10. Baron R, Eberhart L, Kern KU, et al. Tapentadol prolonged release for chronic pain: A review of clinical trials and 5 years of routine clinical practice data. *Pain Pract* 2017; 17:678-700.
11. Wild JE, Grond S, Kuperwasser B, et al. Long-term safety and tolerability of tapentadol extended release for the management of chronic low back pain or osteoarthritis pain. *Pain Pract* 2010; 10:416-427.
12. Buynak R, Rappaport SA, Rod K, et al. Long-term safety and efficacy of tapentadol extended release following up to 2 years of treatment in patients with moderate to severe, chronic pain: Results of an open-label extension trial. *Clin Ther* 2015; 37:2420-2438.
13. Strick V. Management of severe chronic pain with tapentadol prolonged release-Long-term data from pain specialists. *Curr Med Res Opin* 2014; 30:2085-2092.
14. Steigerwald I, Müller M, Kujawa J, Balblanc JC, Calvo-Alén J. Effectiveness and safety of tapentadol prolonged release with tapentadol immediate release on-demand for the management of severe, chronic osteoarthritis-related knee pain: Results of an open-label, phase 3b study. *J Pain Res* 2012; 5:121-138.
15. Steigerwald I, Schenk M, Lahne U, Gebuhr P, Falke D, Hoggart B. Effectiveness and tolerability of tapentadol prolonged release compared with prior opioid therapy for the management of severe, chronic osteoarthritis pain. *Clin Drug Investig* 2013; 33:607-619.
16. Steigerwald I, Müller M, Davies A, et al. Effectiveness and safety of tapentadol prolonged release for severe, chronic low back pain with or without a neuropathic pain component: Results of an open-label, phase 3b study. *Curr Med Res Opin* 2012; 28:911-936.
17. Gálvez R, Schäfer M, Hans G, Falke D, Steigerwald I. Tapentadol prolonged release versus strong opioids for severe, chronic low back pain: Results of an open-label, phase 3b study. *Adv Ther* 2013; 30:229-259.
18. The EuroQol Group. EuroQol--A new facility for the measurement of health-related quality of life. *Health Policy* 1990; 16:199-208.
19. Ware JE Jr, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; 30:473-483.
20. Guy W. ECDEU assessment manual for psychopharmacology (DHEW publication no. ADM 76-338). Washington, DC, US Government Printing Office, 1976.
21. Haythornthwaite JA, Hegel MT, Kerns RD. Development of a sleep diary for chronic pain patients. *J Pain Symptom Manage* 1991; 6:65-72.
22. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: A health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol* 1988; 15:1833-1840.
23. Bouhassira D, Attal N, Fermanian J, et al. Development and validation of the Neuropathic Pain Symptom Inventory. *Pain* 2004; 108:248-257.
24. Melzack R. The short-form McGill Pain Questionnaire. *Pain* 1987; 30:191-197.
25. Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. *Pain Physician* 2008; 11:105-120.
26. Freynhagen R, Baron R, Gockel U, Tölle TR. PainDetect: A new screening questionnaire to identify neuropathic components in patients with back pain. *Curr Med Res Opin* 2006; 22:1911-1920.
27. Buynak R, Shapiro DY, Okamoto A, et al. Efficacy and safety of tapentadol extended release for the management of chronic low back pain: Results of a prospective, randomized, double-blind, placebo- and active-controlled phase III study. *Expert Opin Pharmacother* 2010; 11:1787-1804.
28. Baron R, Likar R, Martin-Mola E, et al. Effectiveness of tapentadol prolonged release (PR) compared with oxycodone/naloxone PR for the management of severe chronic low back pain with a neuropathic component: A randomized, controlled, open-label, phase 3b/4 study. *Pain Pract* 2016; 16:580-599.