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Tramadol Extended-Release Tablets[1]

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Contents

Abstract

▲ Tramadol is a synthetic, centrally acting opioid analgesic. An extended-release tablet formulation of tramadol (tramadol ER) allows gradual release of the active drug, permitting once-daily administration.

▲ Tramadol ER administered once daily is equivalent in bioavailability to immediate-release tramadol administered four times daily, with prolonged absorption and lower peak plasma concentrations.

▲ Tramadol ER was significantly more effective than placebo in the treatment of moderate to moderately severe chronic pain in patients with osteoarthritis of the knee and/or hip in randomised, double-blind, placebo-controlled trials. In a flexible-dose trial in patients with osteoarthritis of the knee, the mean reduction from baseline in pain intensity scores over 12 weeks was significantly greater in recipients of tramadol ER than in placebo recipients.

▲ In a fixed-dose trial in patients with osteoarthritis of the knee and/or hip, the mean improvements from baseline in the pain and physical function subscale scores of the Western Ontario and McMaster Universities Osteoarthritis Index over 12 weeks were significantly greater in tramadol ER than placebo recipients.

▲ Common adverse events reported in patients with moderate to moderately severe chronic pain treated with tramadol ER 100–300mg once daily were dizziness (excluding vertigo), nausea, constipation, somnolence and flushing.

Features and properties of tramadol extended-release tablets (ULTRAM® ER)	
Indication	
Management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time	
Mechanism of action	
Centrally acting analgesic	μ-Opioid agonist; weakly inhibits the neuronal reuptake of noradrenaline (norepinephrine) and serotonin
Dosage and administration	
Recommended initial dosage	100 mg/day
Recommended maximum dosage	300 mg/day
Route of administration	Oral
Frequency of administration	Once daily
Mean steady-state pharmacokinetic parameters in healthy volunteers (once-daily tramadol ER 200mg)	
Maximum plasma concentration (C_{max})	335 μg/L
Time to C_{max}	12h
Area under the plasma concentration-time curve from time 0 to 24 hours	5975 μg • h/L
Adverse events (most frequent)	
Dizziness (excluding vertigo), nausea, constipation, somnolence, flushing	

1 Various sections of the manuscript reviewed by: ***M.P. Davis,*** Harry R. Horvitz Center for Palliative Medicine, Cleveland Clinic Foundation, Cleveland, Ohio, USA; ***B.H. McCarberg,*** Kaiser Permanente, Escondido, California, USA; ***C.J. Sachs,*** UCLA Emergency Medicine Center, Los Angeles, California, USA.

In the management of chronic pain, the oral (least invasive) route is preferred for administration of analgesics.[1] Nonscheduled opioids, such as tramadol, are among the pharmacological agents recommended for the management of chronic pain, along with NSAIDs and paracetamol.[2] An initial low dose of analgesic is followed by titration to a dose that alleviates pain without causing dose-limiting adverse effects;[1,2] several weeks of pharmacotherapy may be required before such therapeutic benefit appears.[2]

Tramadol is an analgesic agent with well established efficacy in the treatment of moderate to moderately severe pain.[3] For the treatment of chronic pain, frequent administration (at least four times daily) of oral, immediate-release (IR) tramadol is required because of the rapid (within 2 hours) attainment of peak plasma concentrations (C_{max}) and short (≈5–6 hours) elimination half-life of the drug.[4] Consequently, oral formulations of tramadol have been developed that provide a more gradual release of the drug, with the aim of reducing the frequency of administration.[5,6]

The extended-release tablet formulation of tramadol (tramadol ER) [ULTRAM® ER][2] is the first once-daily, oral formulation of tramadol to be approved in the US; it utilises Smartcoat™ (Biovail Corporation) technology.[7] This polymer diffusion-based film technology[8] is a semi-permeable coating composed of at least one water-insoluble but water-permeable film-forming polymer, at least one plasticiser and at least one water-soluble polymer.[9] The semi-permeable membrane allows water into the tablet core with resulting dissolution of drug on the core surface.[8,9] Controlled release of drug occurs as an osmotic process that is independent of the effects of pH or alcohol.[7,10]

Tramadol ER is administered once daily[11] and is therefore likely to enhance patient convenience and compliance relative to tramadol IR. The pharmacological attributes of tramadol ER and the efficacy of this formulation in the treatment of patients with moderate to moderately severe chronic pain in the US provide the focus of this review.

1. Pharmacodynamic Profile

This section briefly summarises the pharmacodynamic properties of tramadol, which have been extensively reviewed elsewhere.[4,12]

- Tramadol is a synthetic, centrally acting analgesic with multiple mechanisms of action.[4,11,12] The drug is a μ-opioid receptor agonist, with the active metabolite (+)-*O*-desmethyltramadol [(+)-M1] being the major contributor to its action at μ-opioid receptors (inhibition constant of 0.0034 μmol/L vs 2.1 μmol/L [(±)-tramadol] and 0.00034 μmol/L [morphine]).[4] The enantiomers of tramadol also act synergistically by different mechanisms to inhibit pain transmission: the (+)-enantiomer inhibits neuronal reuptake of serotonin (5-hydroxytryptamine) and the (−)-enantiomer inhibits neuronal reuptake of noradrenaline (norepinephrine).[4,12]
- The analgesic effect of tramadol was greater than that of placebo in healthy volunteers with experimental pain.[4,12] The metabolism of tramadol via the cytochrome P450 (CYP) isoenzyme CYP2D6 to produce the active metabolite (+)-M1 is critical for maximum analgesic effect; tramadol-induced analgesia was reduced in poor, relative to extensive, metabolisers of CYP2D6 substrates.[4,12]
- Tramadol is without clinically significant haemodynamic effects, has only a modest delaying effect on colonic transit in healthy volunteers and is unlikely to induce clinically pertinent respiratory depression at therapeutic dosages.[4,12]

2. Pharmacokinetic Profile

This section provides an overview of the pharmacokinetics of tramadol ER, based on randomised, non-blind, crossover studies in healthy adult volunteers (available as abstracts and poster presentations; n = 15,[13] 24,[14] 32[15] and 25[16]), non-blind studies in special patient populations (available as abstracts and posters)[17,18] and data from the manufacturer's prescribing information[11] and a review.[4]

2 The use of trade names is for product identification purposes only and does not imply endorsement.

Equivalence of tramadol ER with tramadol IR was demonstrated if the 90% geometric confidence interval (CI) for the ratio of the area under the plasma concentration-time curve (AUC) for tramadol ER versus tramadol IR was within the range 0.80–1.25.[15] Geometric means of the AUC data were transformed logarithmically prior to equivalence assessment.[15]

Absorption and Distribution

- Release of tramadol was substantially prolonged in recipients of the ER formulation, relative to those receiving IR tablets.[15] The mean time to C_{max} (t_{max}) of tramadol was increased significantly (13.6 vs 2.2 hours) and the mean C_{max} was reduced significantly (234 vs 258 μg/L) in recipients of a single tramadol ER 200mg tablet versus tramadol IR 50mg administered four times over 24 hours (at 6-hour intervals) [all $p < 0.05$].[15]
- Steady-state plasma concentrations were achieved within 4 days of initiation of multiple-dose administration of tramadol ER 200mg once daily or tramadol IR 50mg once every 6 hours.[15] At steady-state, mean tramadol t_{max} (11.9 vs 1.5 hours) was significantly longer and mean tramadol C_{max} (335 vs 383 μg/L) was significantly lower in recipients of tramadol ER versus tramadol IR tablets (both $p < 0.05$) [see figure 1 for plasma tramadol concentration versus time curves for the two formulations].[15] At steady-state, respective (+)-M1 t_{max} values were 15 versus 1.9 hours and respective (+)-M1 C_{max} values were 95 versus 104 μg/L (both $p < 0.05$).[11,15]
- Although slightly less bioavailable tramadol was released with a single tramadol ER 200mg tablet than with tramadol IR 50mg administered four times daily at 6-hour intervals, the difference was within the preset equivalence limits.[15] The respective mean AUC values for the first 24-hour dose administration interval (AUC_{24}) were 4792 and 5095 μg • h/L. Mean steady-state AUC_{24} values were 5975 and 6613 μg • h/L. The ER : IR ratio of the tramadol AUC values was 0.90 (90% CI 0.83, 0.99) after the first day and 0.89 (90% CI 0.84, 0.94) at steady state.[15]

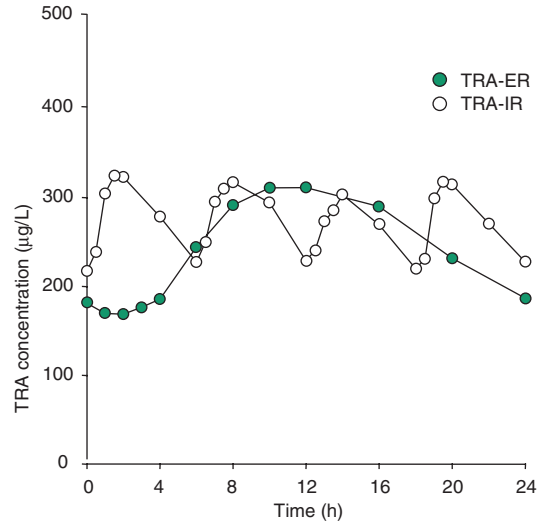

Fig. 1. Pharmacokinetics of tramadol (TRA). Bioavailability of extended-release (ER) and immediate-release (IR) oral formulations of TRA at steady state, with administration of TRA-IR at fixed 6-hour intervals. Data were derived from day 8 of administration in a randomised, non-blind, crossover study in 32 healthy adult volunteers who received TRA-ER 200mg once daily or TRA-IR 50mg once every 6 hours.[15] Adapted from the manufacturer's prescribing information,[11] copyright 2006 by Biovail Corporation, reprinted by permission of Biovail Corporation.

- The equivalence of once-daily tramadol ER (administered as two 100mg tablets) to tramadol IR 50mg tablets administered four times daily was maintained when tramadol IR was administered according to an unequal, but clinically realistic, administration schedule (7am, 12 noon, 6pm and 10pm).[13] The ER : IR ratio and associated 90% geometric CI for the tramadol AUC values at steady state (achieved by day 2) were within the 0.80–1.25 range required for equivalence (see figure 2 for plasma tramadol concentration versus time curves).[13]
- Approximate dose-proportionality was observed at steady state, following multiple-dose administration of tramadol ER 100–400mg.[16] Mean C_{max} values were 179, 409 and 910 μg/L and mean AUC_{24} values were 2778, 6365 and 15213 μg • h/L in recipients of tramadol ER 100, 200 and 400mg, respectively;[16] mean AUC_{24} in subjects receiving the 400mg dose was too large for strict dose-proportionality.[11]

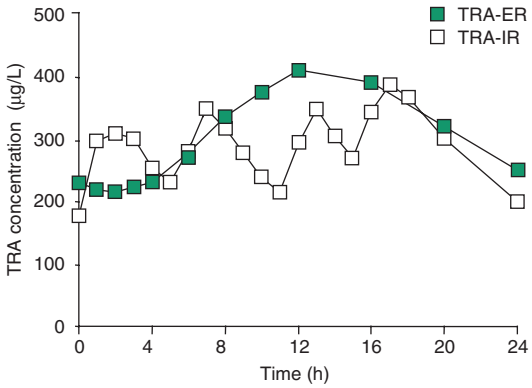

Fig. 2. Pharmacokinetics of tramadol (TRA). Bioavailability of extended-release (ER) and immediate-release (IR) oral formulations of TRA at steady state, with administration of TRA-IR according to an unequal, but clinically realistic, administration schedule. Data were derived from day 5 of administration in a randomised, non-blind, crossover study in 15 healthy adult volunteers who received TRA-ER as two 100mg tablets once daily or TRA-IR 50mg four times daily (at 7am, 12 noon, 6pm and 10pm).[13] Adapted from Eradiri et al.,[13] copyright 2006 by Sage Publications, Inc., reprinted by permission of Sage Publications, Inc.

- In fed, versus fasting, subjects receiving a single dose of tramadol ER 200mg, changes in C_{max} (28% reduction) and AUC from time 0 to infinity (16% reduction) and t_{max} (increase from 14 to 17 hours) were not clinically significant, indicating that the drug may be taken without regard to food (see section 5).[11]
- Limited distribution data are available for tramadol ER. The volume of distribution of intravenously administered tramadol 100mg was 2.6 (men) and 2.9 (women) L/kg.[11] Plasma protein binding was ≈20% for concentrations of tramadol ≤10 µg/mL.[11]

Metabolism and Elimination

- Tramadol undergoes extensive hepatic metabolism: *N*- (via CYP3A4 and CYP2B6) and *O*- (via CYP2D6) demethylation, as well as glucuronidation or sulphation.[11]
- Tramadol and its metabolites are excreted mainly (≈90%) in the urine.[4] Mean elimination half-life ($t_{1/2}$) values for tramadol and its active metabolite (+)-M1 were significantly (both $p < 0.05$) longer in recipients of a single tramadol ER 200mg tablet than in those receiving tramadol IR 50mg every 6 hours over 24 hours (7.7 vs 5.8 hours [tramadol]; 9.0 vs 6.9 hours [(+)-M1]).[15]

Special Patient Populations

- The effect of mild to moderate renal impairment on systemic exposure of tramadol and its active metabolite after administration of tramadol ER has been examined in a small study.[17] Patients with renal function ranging from normal (n = 6; creatinine clearance [CL_{CR}] ≥80 mL/min [≥4.8 L/h]) to mildly (n = 6; CL_{CR} 50–79 mL/min [3.0–4.7 L/h]) or moderately (n = 6; CL_{CR} 30–49 mL/min [1.8–2.9 L/h]) impaired received once-daily tramadol ER 100mg for 6 days. There was no consistent effect of renal function on the AUC of tramadol, but the AUC of (+)-M1 increased by 28–33% with increasing degree of renal impairment (from 778 µg • h/L [normal] to 997 µg • h/L [mild] or 1036 µg • h/L [moderate]).[17]
- The effect of severe renal impairment (CL_{CR} <30 mL/min [<1.8 L/h]) on the pharmacokinetics of tramadol ER has not yet been investigated (see section 5).[11]
- Mild to moderate hepatic impairment did not alter the absorption of tramadol ER.[18] In subjects with hepatic function ranging from normal (n = 6) to mildly (n = 6; Child-Pugh score 5.0–6.0) or moderately (n = 6; Child-Pugh score 7.0–9.0) impaired who received once-daily tramadol ER 100mg for 6 days, plasma concentrations of (±)-tramadol were unaffected, but plasma concentrations of (+)-M1 decreased by >50% with either mild or moderate hepatic impairment, compared with normal hepatic function.[18]
- Although the effect of severe hepatic impairment on the pharmacokinetics of tramadol ER has not yet been studied, the AUC of tramadol and $t_{1/2}$ of tramadol and (+)-M1 were increased in patients with advanced liver cirrhosis who received tramadol IR tablets, relative to subjects with normal hepatic function (see section 5).[11]
- The pharmacokinetics of tramadol ER tablets have not yet been studied in elderly patients (aged >65 years).[11]

Pharmacokinetic Drug Interactions

• Inhibitors or inducers of CYP3A4 or CYP2D6 may interfere with tramadol metabolism.[11,14] For example, administration of the CYP2D6 inhibitor quinidine 200mg 2 hours prior to administration of a single dose of tramadol ER 100mg resulted in an increase of ≈60% in the AUC of tramadol (from 2576 to 4227 μg • h/L), a decrease of ≈40% in plasma clearance of tramadol (from 730 to 430 mL/min) and a reduction of 50–60% in AUC of (+)-M1, relative to administration of tramadol ER 100mg alone.[11,14]

3. Therapeutic Efficacy

The efficacy of once-daily tramadol ER has been investigated in patients with moderate to moderately severe chronic pain associated with osteoarthritis in two 12-week, randomised, double-blind, placebo-controlled trials.[19,20] Tramadol ER was administered according to a flexible-dose regimen[19] in one trial and according to a fixed-dose regimen[20] in the other. A subanalysis of both trials (available as an abstract plus poster presentation)[21] has investigated the effect of tramadol ER on pain-related sleeping difficulties, as assessed by use of the Sleep Problems Index (defined as the average of three items in the Chronic Pain Sleep Inventory [CPSI]: trouble falling asleep because of pain, being awakened by night pain and being awakened by pain in the morning).

Patients included in both clinical trials had chronic pain (≥40mm on a 0–100mm visual analogue scale [VAS]) associated with osteoarthritis and had withdrawn from previous medications after undergoing treatment of at least one painful knee or hip with NSAIDs or other analgesics for ≥75 of the previous 90 days.[19,20] Patients were aged ≥18 years and had a diagnosis of Functional Class I–III primary osteoarthritis of the knee or hip meeting American College of Rheumatology diagnostic criteria, defined by knee or hip pain and recent radiographic evidence of osteophytes.[19,20] There were no clinically significant differences in patient characteristics between treatment groups in either trial.[19,20]

In both clinical trials,[19,20] NSAIDs or other analgesics were discontinued, with the exceptions of paracetamol for conditions other than chronic pain or, in the flexible-dose trial,[19] aspirin for cardiovascular indications. However, use of paracetamol was excluded ≤24 hours (flexible-dose trial)[19] or ≤48 hours (fixed-dose trial)[20] prior to clinic visits for pain intensity assessments.

Efficacy variables (each rated on a 0–100mm VAS, unless otherwise stated) in both clinical trials included the pain (0–500mm VAS), stiffness (0–200mm VAS) and physical function (0–1700mm VAS) subscales of the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index, arthritis pain intensity in the index joint (assessed over 48 hours in the fixed-dose trial[20]), the patient's global assessment of arthritis, the daily diary pain intensity score and sleeping problems (assessed by use of the CPSI[21]).[19-21] All the above endpoints were patient-rated. Efficacy analyses were based on the intent-to-treat population.[19-21]

Flexible-Dose Trial

The efficacy of once-daily tramadol ER, administered according to a flexible-dose regimen, was investigated in patients with moderate to moderately severe chronic pain associated with osteoarthritis of the knee (n = 246).[19] Patients received placebo or a mean daily tramadol ER dose of 276mg. The daily dose of tramadol ER was selected according to a flexible titration design based on tolerability and the adequacy of pain relief: treatment was initiated with a once-daily dose of 100mg and was then titrated to 200mg (beginning no earlier than day 4 and no later than day 8) or then to 200, 300 or 400mg after day 8.[19]

Exclusion criteria included the use of intra-articular corticosteroids in the index knee joint (most painful joint) within the previous 2 months, use of corticosteroids (not intra-articular) ≤1 month previously and intra-articular viscosupplementation in the index knee joint (≤6 months previously) or non-index knee (≤3 months previously).[19] Continued use of glucosamine and/or chondroitin was permitted.[19]

The primary efficacy endpoint was the arthritis pain intensity score in the index joint.[19] All efficacy variables (with the exception of the daily diary pain intensity score) were assessed at weeks 1, 2, 4, 8 and 12, or at treatment discontinuation. Efficacy results were calculated as the least-squares mean change from baseline, averaged over 12 weeks.[19]

- The analgesic efficacy of tramadol ER was significantly greater than that of placebo, in terms of the primary endpoint.[19] The mean reduction in the arthritis pain intensity score in the index joint averaged over 12 weeks was significantly ($p < 0.001$) greater in tramadol ER than placebo recipients (see figure 3a).[19] At week 1, the mean reduction from baseline in the arthritis pain intensity score was 19.6mm in recipients of tramadol ER versus 11.1mm in placebo recipients ($p < 0.003$; baseline VAS scores of 78.2 and 75.5mm); this significant difference was maintained throughout the study period.[19]

- In terms of secondary endpoints (WOMAC subscales), tramadol ER was significantly better than placebo for improvement of functional capacity and for pain relief.[19] The mean improvements from baseline, averaged over 12 weeks, in the WOMAC physical function (407.0 vs 208.5mm [baseline 1158.7 vs 1143.1mm]), pain (120.1 vs 69.0mm [baseline 334.5 vs 336.3mm]) and stiffness (48.9 vs 27.3mm [baseline 142.9 vs 143.7mm]) subscales were significantly (all $p < 0.001$) greater in tramadol ER versus placebo recipients.[19]

- There were significant improvements in other secondary efficacy endpoints in patients who received tramadol ER compared with those who received placebo.[19] The mean improvements from baseline in the patient's global assessment of arthritis (28.2 vs 16.1mm [baseline 71.5 vs 71.5mm]) and in daily diary pain intensity scores (29.0 vs 18.7mm [baseline 76.2 vs 73.9mm]) were significantly (both $p < 0.001$) greater in tramadol ER than placebo recipients.[19] A numerical separation in improvements in daily diary pain scores between tramadol ER and placebo recipients was evident from day 1 of treatment (no statistical analysis reported).[19]

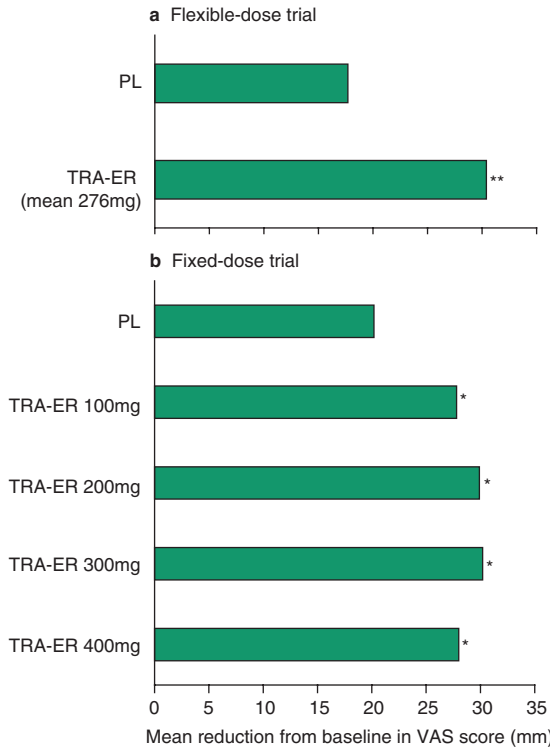

Fig. 3. Efficacy of tramadol extended-release tablets (TRA-ER) in adult patients with moderate to moderately severe chronic pain (≥40mm on a 0–100mm visual analogue scale [VAS]) associated with osteoarthritis (OA). Reduction in the arthritis pain intensity (API) score in the index joint (assessed using a 0–100mm VAS) in two 12-week, randomised, double-blind, multicentre trials: **(a)** patients with OA of the knee received once-daily treatment with placebo (PL; n = 122) or TRA-ER (n = 124; 100mg for the first 3–7 days, followed by 200–400mg [mean daily dose 276mg] for the remainder of the study duration) [reduction in the API score calculated as mean reductions from baseline averaged over 12 weeks][19] and **(b)** patients with OA of the knee and/or hip received once-daily treatment with PL (n = 205) or TRA-ER at a fixed dose of either 100mg (n = 202), 200mg (n = 201), 300mg (n = 201) or 400mg (n = 202) [reduction in the API score calculated as the mean reduction from baseline at week 12].[20] The API score was the primary efficacy endpoint in the first trial.[19] Baseline VAS scores were 75.5mm (PL) and 78.2mm (TRA-ER) in the first trial[19] and were not reported in the second trial.[20] * $p \leq 0.01$, ** $p < 0.001$ vs PL.

- Tramadol ER was significantly better than placebo for the treatment of sleeping difficulties related to chronic pain.[19] There were significantly (all $p < 0.05$) greater mean improvements from baseline in overall sleep quality (14.8 vs 8.4mm [baseline 45.5 vs 46.0mm]), trouble falling asleep because of pain (21.9 vs 14.1mm [baseline 54.8 vs 51.1mm]),

being awakened because of night pain (23.0 vs 13.7mm [baseline 51.7 vs 53.5mm]) and being awakened by pain in the morning (24.0 vs 14.9mm [baseline 52.5 vs 55.1mm]) in patients receiving tramadol ER than in those receiving placebo.[19]

- A subanalysis of these data showed a similar outcome: the mean change from baseline in the Sleep Problems Index score was significantly ($p < 0.05$) improved in recipients of tramadol ER ($n = 101$) compared with placebo recipients ($n = 118$).[21]

Fixed-Dose Trial

The efficacy of once-daily tramadol ER, administered according to a fixed-dose regimen, was investigated in patients with moderate to moderately severe chronic pain associated with osteoarthritis of the knee and/or hip ($n = 1011$).[20] Treatment was with once-daily tramadol ER 100mg, 200mg, 300mg or 400mg or placebo; tramadol ER was initiated at a dosage of 100mg once daily for 4 days and was then increased by increments of 100mg every 5 days until the randomised fixed dosage was achieved.[20]

There were three co-primary efficacy variables in the fixed-dose trial: the WOMAC pain and physical function subscale scores and the patient's global assessment of arthritis.[20] All efficacy variables (with the exception of the daily diary pain intensity score) were assessed at weeks 1, 2, 3, 6, 9, 12 and 13 (follow-up) or at treatment discontinuation.[20] Efficacy results were calculated as the least-squares mean change from baseline at week 12.[20] A subanalysis of the fixed-dose trial (available as an abstract plus poster presentation)[22] has investigated the analgesic efficacy of tramadol ER in elderly patients (aged >65 years).

- Tramadol ER was significantly better than placebo for improvement of functional capacity and for pain relief.[20] The mean improvement from baseline at week 12 was significantly (both $p < 0.05$) greater in tramadol ER (all dosages combined) than placebo recipients for two of the three co-primary efficacy endpoints: the physical function and pain subscales of the WOMAC Index (see figure 4).[20] The improvements in these two endpoints were also significantly (all $p \leq 0.05$) greater in each individual dose group of tramadol ER recipients, compared with placebo recipients (see figure 4).[20]

- The mean change from baseline (at week 12) in the third co-primary efficacy endpoint, the patient's global assessment of arthritis, was not significantly different in tramadol ER (all dosages combined) than placebo recipients, although there were significant (both $p \leq 0.05$) improvements in recipients of once-daily tramadol ER 200mg or 300mg compared with placebo recipients (see figure 4).[20]

- The mean reduction from baseline, at week 12, in the arthritis pain intensity score in the index joint (secondary endpoint) was significantly ($p = 0.002$) greater in tramadol ER (all doses combined) than placebo recipients (see figure 3b).[20]

- Mean reductions from baseline, at week 12, in daily diary pain intensity scores were significantly (all $p < 0.001$) greater in patients receiving once-daily tramadol ER 100mg, 200mg, 300mg or 400mg than in those receiving placebo; the respective reductions were 23.5, 24.2, 27.1 and 24.2 vs 15.0mm (baseline 65.8–71.5 vs 69.2mm).[20] From day 1 of treatment onwards, there was a significantly ($p < 0.05$) greater improvement from baseline in daily pain intensity score in tramadol ER (all dosages combined) than placebo recipients. Baseline daily pain scores differed significantly ($p = 0.039$) across the treatment groups; baseline scores were included as a covariate when the assessment of change from baseline was made.[20]

- Joint stiffness was significantly reduced in patients who received tramadol ER, compared with those who received placebo.[20] The mean reductions from baseline, at week 12, in the WOMAC stiffness subscale (43.0–48.0 vs 32.2mm) were significantly ($p = 0.016$) increased in tramadol ER versus placebo recipients (baseline values not reported).[20]

- A subanalysis of elderly patients showed that, at 12 weeks, the mean improvement from baseline in the pain intensity score in the index joint was significantly ($p = 0.047$) greater in elderly tramadol ER recipients ($n = 189$) than in elderly placebo recipi-

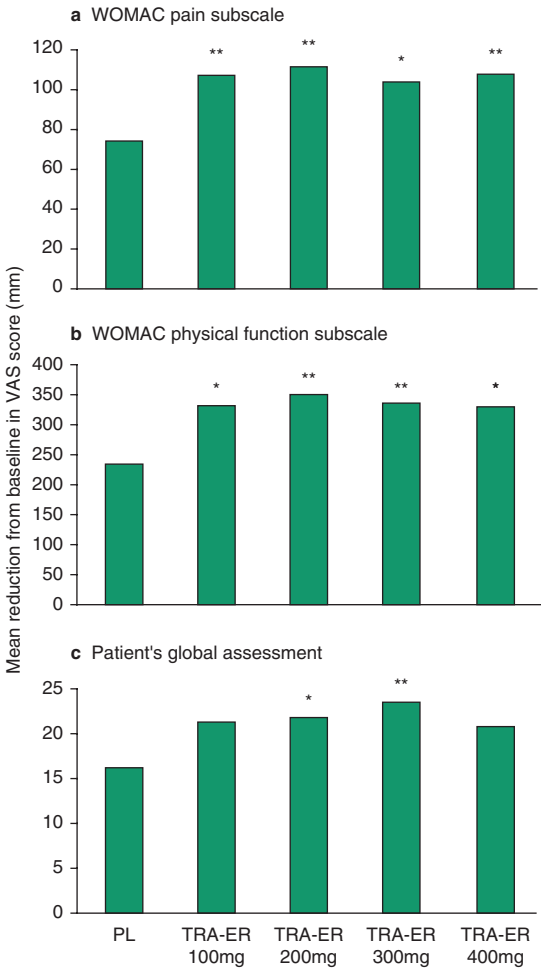

Fig. 4. Efficacy of fixed-dose tramadol extended-release (TRA-ER) tablets in adult patients with moderate to moderately severe chronic pain (≥40mm on a 0–100mm visual analogue scale [VAS]) associated with osteoarthritis of the knee and/or hip. Mean reductions from baseline, at week 12, in the three co-primary efficacy variables: **(a)** the pain subscale of the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index (assessed using a 0–500mm VAS); **(b)** the physical function subscale of the WOMAC Index (assessed using a 0–1700mm VAS); and **(c)** the patient's global assessment of arthritis (assessed using a 0–100mm VAS). In this randomised, double-blind, multicentre trial, patients received TRA-ER at a fixed dose of either 100mg (n = 202), 200mg (n = 201), 300mg (n = 201) or 400mg (n = 202) or placebo (PL; n = 205) once daily.[20] Baseline VAS scores were 297–315mm (WOMAC pain subscale), 1011–1096mm (WOMAC physical function subscale) and 61–67 (patient's global assessment of arthritis). * $p \leq 0.05$, ** $p \leq 0.01$ vs PL.

ents (n = 43) [29.7 vs 19.2mm; values estimated from a graph; baseline values not reported].[22]

- Tramadol ER was significantly better than placebo for the treatment of sleeping difficulties related to chronic pain.[20] There were significantly (all $p \leq 0.05$) greater mean improvements from baseline in sleep quality (14.4–16.1 vs 9.1mm [baseline 40.8–46.9mm]), trouble falling asleep (17.1–21.6 vs 11.8mm [baseline 49.0–52.3mm]) and being awakened because of night pain (18.3–22.7 vs 12.8mm [baseline 49.3–54.4mm]) in recipients of tramadol ER 100–400mg, and in being awakened because of morning pain (17.4–20.9 vs 12.0mm [baseline 48.0–52.8mm]) in recipients of tramadol ER 100–300mg, than in placebo recipients (all values except baseline values [reported in the text] were estimated from a graph).[20]

- A subanalysis of these data showed similar results: the mean change from baseline in the Sleep Problems Index score was significantly (all $p < 0.05$) improved in recipients of tramadol ER 100mg, 200mg and 300mg (baseline scores not reported).[21]

4. Tolerability

Tolerability data relating to tramadol ER were obtained from a pooled analysis of two randomised, double-blind, placebo-controlled studies reported in the manufacturer's prescribing information[11] in which patients with moderate to moderately severe chronic pain received tramadol ER or placebo for 12 weeks.

- The adverse events occurring with a frequency of ≥5% in at least one treatment group after administration of placebo or approved doses of tramadol ER (100–300mg once daily) are shown in figure 5.[11] Dizziness (excluding vertigo), nausea, constipation, somnolence and flushing were the most commonly reported adverse events. The incidence of each adverse event was numerically greater in tramadol ER than placebo recipients, and generally increased with increasing dose of tramadol (no statistical analysis reported).[11]

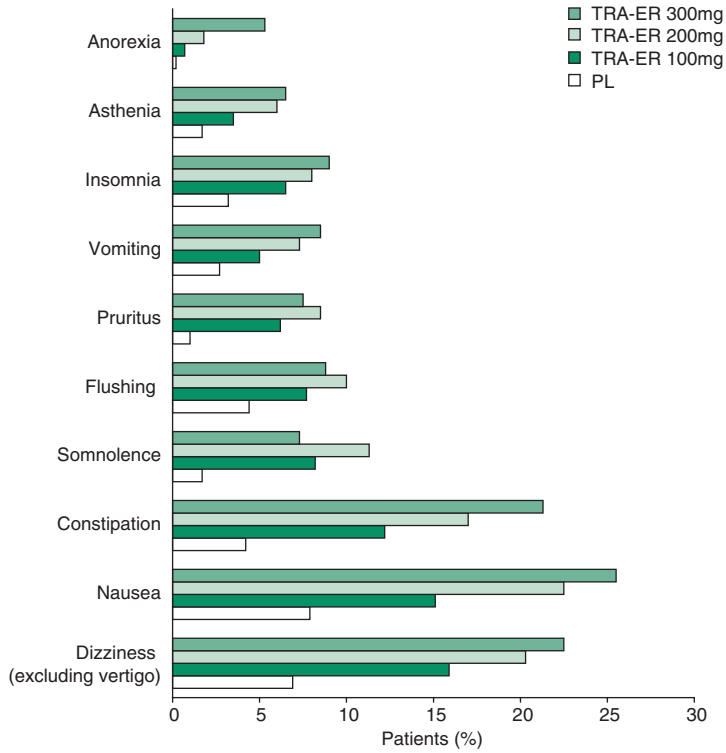

Fig. 5. Tolerability of tramadol extended-release tablets (TRA-ER) in adult patients with moderate to moderately severe chronic pain. Pooled adverse event data from two randomised, double-blind, placebo-controlled studies in patients who received placebo (PL; n = 406) or TRA-ER 100mg (n = 403), 200mg (n = 400) or 300mg (n = 400) once daily for 12 weeks.[11] Adverse events occurring in ≥5% of patients in at least one treatment group are shown. Only data pertaining to approved doses of TRA-ER (100–300mg once daily) are depicted. The severity of the adverse events was not reported, and there was no between-group statistical analysis.

5. Dosage and Administration

According to the manufacturer's prescribing information, the initial recommended dosage of tramadol ER is 100mg once daily, with titration in 100mg increments every 5 days (if required) up to a maximum dosage of 300mg once daily.[11] The drug is to be used in adults only, and may be administered without regard to food. Tramadol ER should not be used in patients with severe renal (CL_{cr} <30 mL/min [<1.8 L/h]) or hepatic (Child-Pugh Class C) impairment.[11]

Results of a pharmacokinetic modelling study (available as an abstract plus poster presentation)[23] with tramadol ER (Smartcoat™ technology) suggest that patients receiving a daily dose of tramadol IR of ≥200mg, but <300mg, may switch directly to once-daily tramadol ER 200mg, and those receiving tramadol IR ≥300mg, but <400mg, daily may switch directly to once-daily tramadol ER 300mg.

Local prescribing information should be consulted for detailed information, including contraindications, precautions, drug interactions and use in special patient populations.

6. Tramadol Extended-Release Tablets: Place in Therapy and Current Status

Tramadol ER is approved in the US for the management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time.[11] Data from fully published, well designed trials (section 3) have indicated that once-daily administration of tramadol ER was significantly more effective than placebo for the treatment of chronic

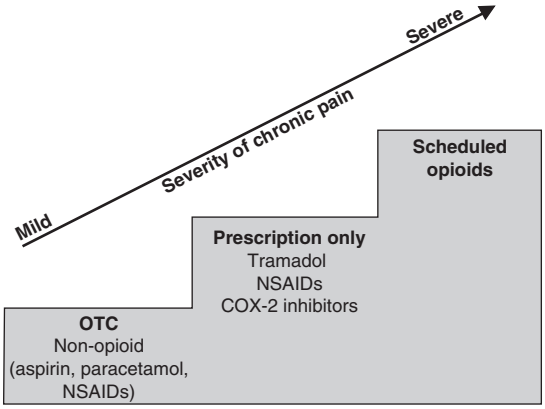

Fig. 6. Pharmacological management of chronic pain. Position of tramadol in the analgesic ladder in relation to other pharmacological strategies for the treatment of chronic pain. The successive steps on the ladder (an adaptation of the WHO ladder[24] for cancer pain relief and current guidelines of the American College of Rheumatology[25] for the management of osteoarthritis) show the appropriate therapeutic options available as the severity of chronic pain increases. **COX-2** = cyclo-oxygenase 2; **OTC** = over-the-counter medications.

pain (≥40mm on a 0–100mm VAS) associated with osteoarthritis of the knee and/or hip.

The therapeutic position of tramadol (both ER and IR formulations) within the array of analgesics available for the management of chronic pain is shown in figure 6 (an analgesic ladder adapted from the WHO ladder[24] for cancer pain relief and current guidelines of the American College of Rheumatology[25] for the management of osteoarthritis). Non-opioid analgesia is regarded as the starting point in pharmacological pain management.[26] The use of tramadol is appropriate in patients with chronic pain not controlled by non-opioids, such as paracetamol or NSAIDs/cyclo-oxygenase 2 (COX-2) inhibitors, or in patients with chronic pain who are not able to tolerate NSAIDs or scheduled opioids.[26] Combined use of a non-opioid with tramadol is well tolerated.[26] The improvement in pain-related sleeping problems with use of tramadol ER is a further advantage (section 3). It is possible that management of chronic pain with tramadol ER (as monotherapy or in combination with other analgesics) may prevent or at least delay the need to progress to use of scheduled opioids, such as morphine, which should be reserved for severe pain because of the increased risk of addiction and abuse.[7]

Tramadol has a low potential for induction of respiratory depression (section 1) and dependence.[27] Unlike NSAIDs and COX-2 inhibitors,[28-31] tramadol[3,11] does not have black box warnings regarding cardiovascular or gastrointestinal risk or lower level warnings for renal toxicity with long-term use in the prescribing information.

Tramadol ER once daily was shown to be equivalent to tramadol IR administered in divided doses in terms of the quantity of bioavailable tramadol absorbed after administration of a daily therapeutic dose (section 2). In patients with moderate to moderately severe chronic pain who are receiving maintenance treatment with divided doses of tramadol IR, a switch to once-daily tramadol ER would provide a more convenient dose administration schedule, with the potential to improve compliance.[6]

Tramadol ER is an effective and well tolerated, once-daily formulation that is more convenient for patients than the established divided-dose tramadol IR formulation, and is a useful addition to the analgesics available for the management of chronic pain.

Disclosure

During the peer review process, the manufacturer of the agent under review was also offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

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