Tramadol for Osteoarthritis: A Systematic Review and Metaanalysis

M. SOLEDAD CEPEDA, FRANCISCO CAMARGO, CARLOTA ZEA, and LINA VALENCIA

ABSTRACT. ***Objective.*** Tramadol is increasingly used for the treatment of osteoarthritis (OA) because it does not produce gastrointestinal bleeding or renal problems and does not affect articular cartilage. We sought to determine the analgesic effectiveness, the effect on physical function, the duration of benefit, and the safety of oral tramadol in people with OA.

Methods. We searched the Cochrane Central Register of Controlled Trials (Central), Medline, Embase, and Lilacs databases up to August 2005. We included randomized controlled trials (RCT) that evaluated the effect of tramadol or tramadol plus paracetamol on pain levels and/or physical function. No language restriction was applied.

Results. We included 11 RCT with a total of 1019 participants who received tramadol or tramadol/paracetamol and 920 participants who received placebo or active control. Participants who received tramadol reported (1) less pain [–8.5 units on a 0–100 scale; (95% CI –12.0 to –5.0)], a 12% relative decrease in pain intensity; (2) higher degree of global improvement: one of every 6 individuals taking tramadol or tramadol/paracetamol exhibited at least moderate global improvement (95% CI 4 to 9); and (3) improvement in stiffness and function, an 8.5% relative improvement in Western Ontario and McMaster University Osteoarthritis Index score, than patients who received placebo. In terms of adverse events, one of every 5 participants who received tramadol or tramadol/paracetamol experienced minor adverse events and one of every eight stopped taking the medication because of adverse events (95% CI 7 to 12) compared to participants who received placebo.

Conclusion. Tramadol or tramadol/paracetamol decreases pain intensity, produces symptom relief, and improves function in patients with OA, but these benefits are small. (J Rheumatol 2007;34:543–55)

Key Indexing Terms:
TRAMADOL OSTEOARTHRITIS EVIDENCE-BASED MEDICINE
SAFETY TREATMENT OUTCOME

Osteoarthritis (OA) is one of the most frequent disorders in the population and is the most common cause of disability in older adults[1]. Pain is the most common symptom of OA, and as pain levels rise, people experience a reduced range of motion and increasing disability[2,3]. The pain and function limitations substantially reduce the quality of life of people with OA. Indeed, individuals with OA have a lower quality of life on average than individuals with gastrointestinal, cardiovascular, or chronic respiratory illnesses[1].

The treatment goals for OA are to relieve pain, to prevent complications such as muscle atrophy or joint deformities, and to maintain and/or improve functional status and quality of life[4,5].

A wide variety of pharmacological therapies are used to treat OA including nonsteroidal antiinflammatory drugs (NSAID) and analgesics such as acetaminophen and tramadol. NSAID are the cornerstone of pharmacological therapy for the management of OA. However, their use is associated with gastrointestinal and renal problems, especially in elderly people. Also, there is a theoretical concern that NSAID may accelerate the course of OA[6], as they may be toxic to articular cartilage[7]. The deleterious effect of NSAID on bone healing seems responsible for the increased incidence of nonunion following spinal fusion surgery in patients exposed to high doses of NSAID in the postoperative period[8,9]. Acetaminophen (paracetamol), although not associated with an increased risk of gastrointestinal events or with cartilage toxicity, is less effective than NSAID in reducing pain in patients with hip and knee OA who exhibit moderate or severe levels of pain[5].

Tramadol is increasingly used for the treatment of OA because, in contrast to NSAID[10,11], tramadol does not produce gastrointestinal bleeding or renal problems, and does not affect articular cartilage. Tramadol is an atypical opioid, as it

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exhibits a dual mechanism of action: tramadol activates opioid receptors and descending inhibitory pain systems[12]. This dual action makes tramadol an attractive option.

Although the analgesic effectiveness of tramadol for acute and neuropathic pain has been established, there are no systematic reviews that evaluate the effectiveness of tramadol for OA. The effectiveness of tramadol in OA is unclear: tramadol lacks peripheral action (i.e., it has no antiinflammatory properties) and its effectiveness may decline with chronic use (i.e., development of tolerance), as part of its action is opioid-related. Nonetheless, the central action of tramadol could be of great benefit, as this action could decrease the central neuronal sensitization produced by the persistent nociceptive peripheral input[13]. In addition, tolerance may not substantially affect longterm effectiveness; a systematic review has shown that 44% of participants prescribed opioids for chronic noncancer pain continued to take opioids for up to 24 months[14].

Therefore, we sought first to determine the effectiveness of oral tramadol for relieving pain and improving physical function in people with OA, second to assess the duration of any benefit, and third to determine the safety of tramadol.

MATERIALS AND METHODS

We considered for inclusion only randomized controlled trials (RCT) that evaluated the effect of tramadol or tramadol plus acetaminophen on pain levels and/or physical function in people with OA. Published or unpublished studies were eligible, but studies had to compare tramadol with placebo or with an active pharmacological treatment. We included studies that evaluated participants who met the American College of Rheumatology (ACR) clinical criteria for OA, studies that evaluated participants with radiographic evidence of OA, and studies in which authors stated that only participants with OA were included.

To be included, studies had to evaluate and report the effect of tramadol on pain intensity or physical function, or to evaluate and report adverse events of tramadol. The studies also had to compare tramadol (with or without acetaminophen) with another pharmacological treatment, either a placebo or an active treatment.

We excluded studies that evaluated other types of arthritis (e.g., rheumatoid arthritis), non-osteoarthritic joint pain, or back pain. Back pain was excluded because this symptom is associated with a variety of diseases with dissimilar pathophysiology.

Search strategy. We searched the Cochrane Central Register of Controlled Trials (Central) in The Cochrane Library to August 29, 2005, Medline 1966 to third week of August 2005, Embase 1980 to September 15, 2005, and Lilacs 1982 to August 29, 2005. We looked for unpublished trials in conference abstracts of the International Association for the Study of Pain and the ACR Annual Scientific Meetings from 2002 to 2005. In addition, we contacted Grunenthal (the manufacturer of tramadol; Grunenthal GmbH, Aachen, Germany) and Biovail Pharmaceuticals (Mississauga, ON, Canada). No language restriction was applied.

We communicated with the authors to secure information not presented in the articles. We searched bibliographies from all retrieved articles for additional studies.

Study selection. We retrieved in full all articles in which the abstract made reference to a trial of tramadol and OA. If there was no abstract, we retrieved the article in full.

Data extraction. Two independent reviewers extracted data. We discussed disagreements to reach a consensus and assigned a third reviewer when necessary. We recorded the agreement of the reviewers.

Quality assessment. We separately rated and described whether the trial reported a description of the randomization; allocation concealment; masking process; that withdrawals were 20% or more; the similarity between baseline characteristics of the treatment groups; and analysis of the outcomes according to the intention-to-treat principle.

Measures of treatment effect. Pain intensity. If authors reported pain intensity using visual analog scales or numeric rating scales, we extracted the mean and standard deviation (SD) of pain intensity in each study arm after treatment, and then we calculated the mean difference. In cases where the studies reported the difference in pain intensity with no measure of dispersion, we estimated the standard error of the difference from the p value and the number of subjects in each arm, as described in the Cochrane manual. To pool the data, we used the generic inverse variance method.

To determine the difference in pain intensity, we pooled the results from studies that assessed pain intensity using scales from 0 to 100 and 0 to 10. Two of the placebo-controlled studies reported pain intensity using a Likert scale[15,16]. These studies were excluded from the pooling of the pain intensity estimates, but were included in the estimate of patient global assessment of response to treatment.

Pain relief. If authors reported pain relief, we obtained the proportion of participants who achieved at least moderate relief.

Physical function. We extracted the mean (± SD) of the composite Western Ontario and McMaster University Osteoarthritis Index (WOMAC) score in each study arm after treatment and calculated the mean difference. This instrument assesses pain, disability, and joint stiffness. We followed the same procedure discussed above for studies with no measure of dispersion. To pool the data, we used the generic inverse variance method.

Patient global assessment of improvement. We determined the proportion of participants who reported at least moderate improvement and calculated the risk ratio (RR) and the corresponding number needed to treat to benefit (NNTB).

Safety of tramadol. To evaluate the safety of tramadol, we extracted the proportion of subjects who developed minor or major adverse events and calculated the corresponding number needed to treat to harm (NNTH).

We defined minor adverse effects as events of a mild nature (e.g., mild nausea or constipation). We defined major adverse effects as events of sufficient severity to cause participants to stop taking the medication (e.g., severe nausea).

Duration of benefit. To determine how long the benefit persisted, we divided the studies into 2 groups, depending on the duration of followup: (1) up to 8 weeks of followup, or (2) longer than 8 weeks of followup.

Assessment of heterogeneity. To evaluate heterogeneity, we used the Q test and the I^2 statistic[17]. We considered values less than 0.1 indicative of nonhomogeneous studies.

We analyzed placebo-controlled studies and active-controlled studies separately. We analyzed together studies that evaluated tramadol alone or tramadol plus acetaminophen, as the results of these trials were similar. We used a fixed-effect model for the quantitative analysis because the results were similar across studies.

Assessment of reporting biases — sensitivity analysis. To investigate the effect of publication bias, we calculated the number of undetected negative studies needed to change the conclusion that a positive effect existed. These calculations were based on the "trim and fill" method developed by Duval and Tweedie. For this analysis, we employed the command "metatrim" in Stata statistical software.

Assessment of agreement between review authors. To estimate the agreement between review authors, we calculated the percentage of agreement for nominal variables and the concordance correlation coefficient for continuous variables.

Grading of evidence and clinical relevance tables. To grade the evidence, we used the grading system recommended by the Cochrane Musculoskeletal Review Group[18] as follows: (1) Platinum: A published systematic review that has at least 2 individual controlled trials, each satisfying the following:

sample sizes of at least 50 per group, blinding of patients and assessors for outcomes, handling of withdrawals > 80% followup, concealment of treatment allocation. (2) Gold: At least one RCT meeting all of the following criteria for the major outcome(s) as reported: sample sizes of at least 50 per group, blinding of patients and assessors for outcomes, handling of withdrawals > 80% followup, concealment of treatment allocation. (3) Silver: A systematic review or randomized trial that does not meet the above criteria. And (4) Bronze: At least one high-quality case series without controls, or with the conclusion derived from expert opinion.

RESULTS

All included studies were obtained from the electronic database searches. Identified studies from conference abstracts were included in the electronic database searches. We translated articles from Croatian, Portuguese, Russian, and Spanish.

Twenty-seven studies were excluded. Table 1 displays the reasons for exclusion.

Eleven RCT were included, with a total of 1019 participants who received tramadol or tramadol/paracetamol and 920 participants who received placebo or active control (Table 2). All RCT were parallel in design, with 2 exceptions[19,20] that were crossover in design. One study provided no data on the effectiveness of tramadol[21], as the aim of the study was to evaluate the tramadol-sparing effect of naproxen. However, this study provided data for the evaluation of safety.

Table 1. Excluded studies.

Author	Year	Reason for Exclusion
Adler	2002	All arms evaluated tramadol
Altman	2004	Narrative review
Anonymous (a)	2003	Narrative review
Anonymous (b)	2003	Narrative review
Bloodworth	2001	Narrative review
Blumstein	2005	Narrative review
Bodalia	2003	All arms evaluated tramadol
Brant	2005	Narrative review
Filho Amaral	2003	OA not evaluated
Ithoh	2001	Narrative review
Lazebnik	2004	Nonrandomized
McClellan	2003	Narrative review
Monging	2004	All arms evaluated tramadol
Muller	2001	Tramadol not evaluated
Mullicam	2001	RCT, but evaluated back pain and OA, and results not reported separately
Nachamie	2005	Narrative review
Pavelka	2000	Nonrandomized
Punwani	2004	Letter to the editor
Rauck	2006	RCT, but evaluated OA and other pain syndromes and results not reported separately
Reig	2002	Narrative review
Rosenthal	2004	Subanalysis of a study already included
Roth	1998	RCT, but evaluated back pain and OA, and results not reported separately
Ruoff	1999	RCT, but evaluated back pain and OA, and results not reported separately
Schnitzer	2002	Narrative review
Schnitzer	2003	Narrative review
Spinewine	2005	Narrative review
Vlack	1996	Nonrandomized

All studies were funded by the pharmaceutical industry, with the exception of Bianchi, *et al*[22].

Six studies used placebo controls[15,16,21,23-25]. In 5 studies, the active control was either paracetamol 1.5 mg/day[22], diclofenac 89 mg/day[20], dihydrocodeine 120 mg/day[26], dextropropoxyphene 300 mg/day[27], or pentazocine[19].

Nine studies[15,19-23,26-28] evaluated tramadol alone and 2[16,24] evaluated tramadol plus paracetamol. These 2 studies evaluated the same oral presentation (tramadol 37.5 mg and paracetamol 325 mg). The mean dose of tramadol administered was 201.4 mg ± 50.15 mg.

All studies evaluated individuals with symptomatic OA of the hip and/or knee. The average number of participants in the tramadol and control groups was 91 (minimum 10, maximum 197) and 80 (minimum 10, maximum 154), respectively. The average length of followup was 35 days (minimum 7 days, maximum 91 days).

Five studies[15,16,20,23,24] reported the effect of tramadol on function using the WOMAC Index. One study[24] also evaluated function with the Medical Outcomes Study Short Form-36 Health Survey (SF-36) and one study evaluated function with daily activities[19]. None of the studies evaluated radiological improvement with imaging.

Methodological quality of included studies. Only one study did not mask the investigators[26]; in all other studies, both investigators and subjects were blinded. Only one study[16] described concealment of allocation, and 2 of the 11 studies (18%) lost 20% or more of the subjects to followup[24,28] (Table 3).

Agreement of reviewers. The agreement between the evaluators was high. The agreement for nominal variables was between 80% and 100%. For continuous variables, the concordance correlation coefficient was between 0.94 and 1 (Table 4).

Outcomes. Pain intensity. Placebo-controlled studies: 3 placebo-controlled studies reported data on pain intensity from 362 participants who received active treatment and 387 participants who received placebo. The results were homogenous (I^2 = 0%). Participants who received tramadol had an average of 8.5 units less pain [on a scale from 0 to 100 (95% CI –12.05 to –4.9)]. This represents a relative decrease of 12% from the mean baseline intensity of 69.5 in the control group (Figure 1).

Active-controlled studies: Participants who received tramadol had larger decreases in pain intensity than those who received dihydrocodeine[26], dextropropoxyphene[27], or pentazocine[19]. However, paracetamol (1500 mg/day) provided a larger decrease in pain intensity than 150 mg/day of tramadol in a small study[22] (Figure 1). The studies by Wilder-Smith, *et al*[26] and Bird, *et al*[19] are not included in the graph because they did not use a 0–10 or 0–100 scale.

Pain relief. Two placebo-controlled studies[15,24] reported data on pain relief from 216 participants who received active treat-

Table 2. Characteristics of included studies.

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation Concealment
Babul[23]	Parallel, multicenter, double-blind RCT	Participants at least 18 yrs old with OA of knee. Participants met ACR diagnostic criteria. Tramadol extended-release (ER) group N = 124 Control N = 122	Active group received tramadol ER (100 mg twice/day, up to 400 mg/day); control received placebo for 84 days	Pain and function were evaluated with VAS and WOMAC Index. Withdrawals due to adverse events: 33 of 124 in tramadol group; 9 of 122 placebo	We contacted author to clarify how WOMAC Index was reported. Author provided all information requested. For pooling we normalized WOMAC total score	Not used
Bianchi[22]	Parallel, double-blind RCT	Adults with OA of knee Tramadol group N = 10 Control N = 10	Active group received tramadol (50 mg 3 times/day);control received paracetamol (500 mg 3 times/day) for 7 days	Aim was to compare synovial fluid concentrations of interleukin and substance P. Pain intensity evaluated with VAS. Withdrawals due to adverse events: 2 of 10 in tramadol group; 0 of 10 in paracetamol group	We contacted author to ask for percentage of participants with pain relief. No response	Not used
Bird[19]	Crossover, double-blind RCT	40 adults with radiologically confirmed diagnosis of OA of hip or knee	Active group received tramadol (50 mg 4 times/day); control group received pentazocine (50 mg 4 times/day) for 7 days, No washout period	Pain intensity evaluated with verbal scale. Participants receiving tramadol reported lower pain scores and preferred it. Duration and severity of morning stiffness and number of paracetamol tablets were considered primary outcomes. Secondary outcomes were sleep pattern, functional impairment and global assessment. Participants exposed to tramadol complained of less stiffness and required fewer tablets of paracetamol. Fewer participants exposed to tramadol reported side effects		Not used
Emkey[24]	Parallel, multicenter double-blind RCT	Participants with more than 1 year of OA of hip or knee. Tramadol/paracetamol group N = 153 Control N = 154	Active group received tramadol (37.5 mg) plus paracetamol (325 mg); control group received placebo for 91 days. Dose was increased up to 4 tablets/day on Day 10 and afterwards up to 8 tablets/day if needed. Participants in both groups received COX-2 selective analgesics	Pain and function were evaluated with VAS and WOMAC Index. Physical function was evaluated with SF36. Withdrawals due to adverse events: 20 of 153 in tramadol group; 6 of 154 in placebo group		Not used
Fleischmann[15]	Parallel, multicenter, double-blind RCT	Participants with radiologically confirmed diagnosis of OA of knee Tramadol group N = 63 Control N = 66	Active group received tramadol 50 mg increments up to 400 mg/day if needed; control group received placebo for 91 days	Pain intensity evaluated with verbal scale, pain relief and overall global assessment evaluated with Likert scales. Function evaluated with WOMAC Index. Withdrawals due to adverse events: 14 of 63 in tramadol group; 10 of 66 in placebo group		Not used

Table 2. Continued *(continues next page).*

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation Concealment
Jensen[27]	Parallel, multicenter, double-blind RCT	Participants with radiologically confirmed diagnosis of OA of hip or knee Tramadol group N = 135 Control N = 129	Active group received tramadol; control group received dextropropoxyphene for 14 days. Participants were randomized to tramadol 100 mg 3 times/day or dextropropoxyphene 100 mg 3 times/day	Pain intensity evaluated with adjectives and pain relief was evaluated with VAS. Withdrawals due to adverse events: 48 of 135 in tramadol group; 14 of 129 in dextropropoxyphene group		Not used
Malonne[28]	Parallel, multicenter, double-blind RCT	Adults 45–80 years old with OA of hip or knee. Diagnosis made with the European League Against Rheumatism criteria Tramadol group N = 51 Control N = 41	Active group received tramadol LP sustained release (200 mg/day); control group received placebo for 14 days. Concomitant treatment with paracetamol rescue medication	Pain intensity evaluated with VAS. Patient global assessment and use of rescue medication also evaluated. 40% of participants took rescue medication in the tramadol group vs 63.4% in placebo group Withdrawals due to adverse events: 24 of 111 in tramadol group; 2 of 119 in placebo group		Not used
Pavelka[29]	Crossover, double-blind RCT	Adults with radiologically confirmed diagnosis of OA of hip or knee Tramadol group N = 60 Control N = 60	Participants randomized to tramadol (50 to 100 mg up to 3 times/day on demand), then diclofenac (25 to 50 mg up to 3 times/day on dem and) for 28 days with 1 wk washout period	Pain and function evaluated with WOMAC Index. Pain intensity scores, WOMAC Composite Index and global assessment were similar in both treatment phases. Withdrawals due to adverse events: 5 patients while taking tramadol stopped taking medication; 1 patient while taking diclofenac stopped taking medication	One participant who received diclofenac experienced a severe side effect (angioneurotic edema)	Not used
Schnitzer[21]	Parallel, multicenter, double-blind RCT	Adults with symptomatic OA of knee. Study had 2 phases. We evaluated the 8 week double–blind phase. Participants whose pain did not resolve with 500 mg naproxen were randomized. Randomization was stratified based on response to 1000 mg naproxen (responders/nonresponders). Active group received tramadol plus naproxen; control received placebo plus naproxen for 54 days. During double-blind phase the naproxen dose was reduced to 250 mg every 2 weeks	Primary aim was to determine whether tramadol decreased naproxen requirements. No data on pain intensity during the double–blind phase	Primary aim was to determine whether tramadol decreased naproxen requirements. No data on pain intensity during the double–blind phase. No. of participants who discontinued therapy due to adverse events was reported	We contacted the author, who suggested that we contact Ortho-McNeil	Not used

Table 2. Continued.

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation Concealment
Silverfield[16]	Parallel, multicenter, double–blind RCT	Adults 35–75 years old with symptomatic OA of hip or knee. Participants received stable doses of NSAID or COX-2 Tramadol/paracetamol group N = 197 Control N = 111	Active group received tramadol (37.5 mg) plus paracetamol (325 mg); control received placebo 10 days. No. of tablets a day was increased to a maximum of 8. Participants continued receiving NSAID or COX-2 at the same doses taken before study entry	Pain intensity and pain relief evaluated using a 4 point adjective scale (none, mild, moderate, severe). Percentage of patients in each relief category was reported. WOMAC Index score was also reported. Participants who received tramadol had less pain than participants who received placebo (data not used in the pooling because of 4 point scale). Withdrawals due to adverse events: 25 of 197 in tramadol group; 6 of 111 control	We contacted author and obtained requested information (percentage of subjects with moderate pain relief)	Adequate
Wilder-Smith[26]	Parallel multicenter RCT. Participants were blinded. Evaluators were not blinded	Adults 20–75 yrs old awaiting hip or knee replacement Tramadol group N = 28 Control N = 29	Active group received tramadol Retard (100 mg); control group received long acting dihydrocodeine (60 mg) every 12 h for 28 days. Immediate release medication of the same type that participants were randomized to was used for breakthrough pain. Previous analgesic medication remained unchanged. Participants were hospitalized for dose titration for first 4 days	Pain intensity was evaluated at rest and with movement using a 4 point adjective scale. Authors reported lower pain intensity at rest with tramadol than with dihydrocodeine, but no difference in pain intensity with movement. Minor adverse events were more common in the tramadol group. Percentages of subjects with minor or severe adverse events were not reported	We contacted the author to determine percentage of participants with minor and major adverse events. No response	Not used

ER: extended release.

Table 3. Quality of studies.

Trial	Randomization	Concealment of Allocation	Evaluators Blinded	Patients Blinded	Groups Similar at Baseline	Intention-to-treat Analysis	< 20% Lost to Followup
Babul[23]	Yes	No	Yes	Yes	Yes	Yes	No
Bianchi[22]	Yes	No	Yes	Yes	Yes	Yes	Yes
Bird[19]	No	No	Yes	Yes	Yes	Yes	Yes
Emkey[24]	No	No	Yes	Yes	Yes	Yes	Yes
Fleischmann[15]	Yes	No	Yes	Yes	Yes	No	Yes
Jensen[27]	Yes	No	Yes	Yes	Yes	No	No
Malonne[28]	Yes	No	Yes	Yes	Yes	No	Yes
Pavelka[29]	Yes	No	Yes	Yes	Yes	Yes	Yes
Schnitzer[21]	No	No	Yes	Yes	Yes	No	Yes
Silverfield[16]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wilder-Smith[26]	Yes	No	No	Yes	Yes	Yes	Yes

Table 4. Agreement between evaluators.

Nominal Variables	Agreement (%)
Include	90
Study design	90
Method of randomization	90
Concealment of randomization	90
Blinding of investigators	100
Blinding of patients	100
Similarity of groups at baseline	100
Type of analysis	80
Losses to followup	80
Continuous variables	Concordance correlation coefficient
Mean pain intensity (tramadol group)	1
Mean pain intensity (control group)	1
No. of patients with at least 50% pain relief (tramadol group)	1
No. of patients with minor adverse events (tramadol group)	0.94
No. of patients with major adverse events (tramadol group)	0.94

ment and 218 participants who received placebo. The results were homogenous (I^2 = 0%). Tramadol increased (by 53%) the likelihood of a moderate improvement compared to placebo (95% CI 1.1 to 2.0). This is equivalent to an NNTB of 8 (95% CI 5 to 25).

Global assessment of improvement. Improvement in placebo-controlled studies: 4 placebo-controlled studies reported the percentage of participants with at least moderate improvement. The results were homogenous (I^2 = 0%). Tramadol increased (by 35%) the likelihood of a moderate improvement compared to placebo (95% CI 1.2 to 1.5). This is equivalent to an NNTB of 6 (95% CI 4 to 9; Figure 2).

Improvement in active-controlled studies: Tramadol increased the likelihood of a moderate improvement compared to dextropropoxyphene (by 38%) and pentazocine (by 150%), and was as effective as diclofenac in the crossover study (Figure 2).

Physical function. WOMAC Index score in placebo-controlled trials: 4 studies evaluated the WOMAC. A reduction in the WOMAC score represents an improvement in participants' pain, stiffness, and function. The reduction in the score was larger in the tramadol group than the placebo group (–0.34 on a 0–10 scale; 95% CI –0.49 to –0.19). This represents an 8.5% relative reduction in the mean baseline score of 4 (i.e., an 8.5% relative improvement; Figure 3).

WOMAC score in active-controlled trials: In the study by Pavelka, *et al*[20], the improvement in the WOMAC score was similar when participants received either tramadol (3.9 ± 1.6) or diclofenac (4.0 ± 1.7).

Duration of benefit. Placebo-controlled studies: In the 3 placebo-controlled studies that followed participants for more than 8 weeks (84, 91, and 91 days, respectively), tramadol was more effective than placebo. Similar results were found in a study with a shorter followup[28].

In terms of pain intensity, the mean difference between the tramadol and placebo groups was –9.1 units on a 0–100 scale in the studies with longer followup, and –7.6 units on a 0–100 scale in the study with shorter followup (Figure 4). In terms of patient global assessment of response, the relative risk of an improvement with tramadol was 1.36 in the studies with longer followup and 1.38 in the studies with shorter followup (Figure 5). A summary of all the above outcomes is presented in Tables 5 and 6.

Safety. The most common adverse events reported in participants exposed to tramadol or tramadol plus paracetamol were nausea, vomiting, dizziness, constipation, somnolence, tiredness, and headache. In these short-term studies, there was no report of any life-threatening event in participants exposed to tramadol or tramadol plus paracetamol. There was one serious event in the study by Pavelka, *et al*[20] — one participant who received diclofenac experienced angioneurotic edema.

Minor adverse events in placebo-controlled studies: 4 placebo-controlled studies reported the proportion of subjects with minor adverse events. The results were homogenous (I^2 = 32.9%). Participants who received tramadol had 2.17 times the risk of developing minor adverse events (95% CI

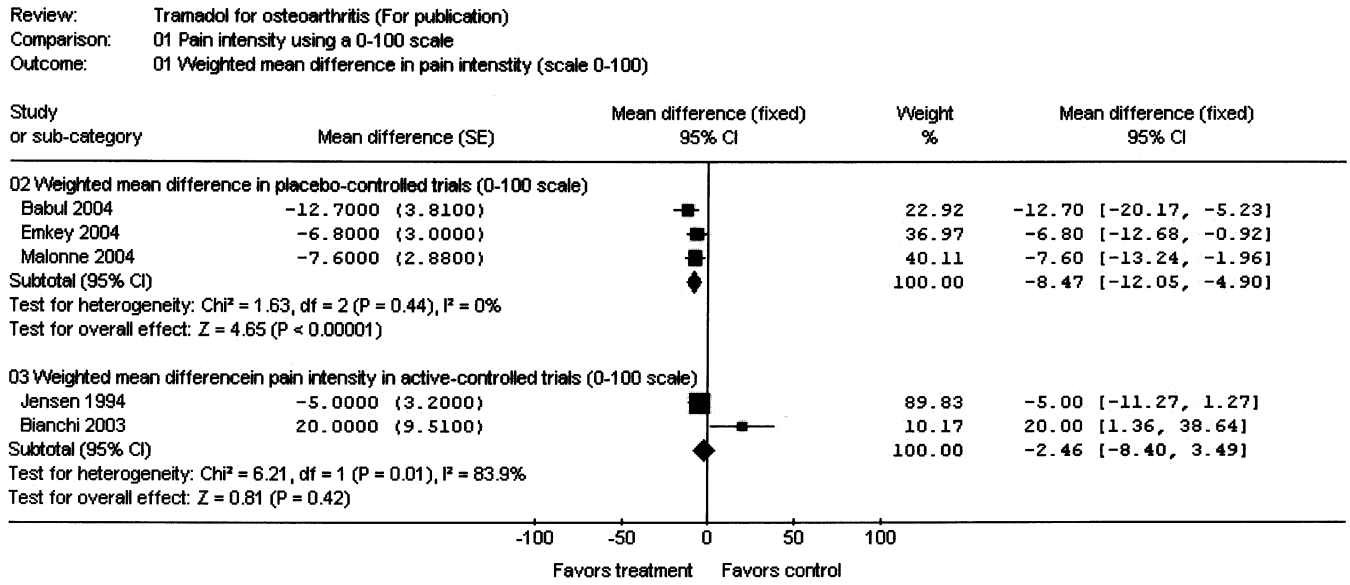

Figure 1. Pain intensity in placebo and active controlled trials.

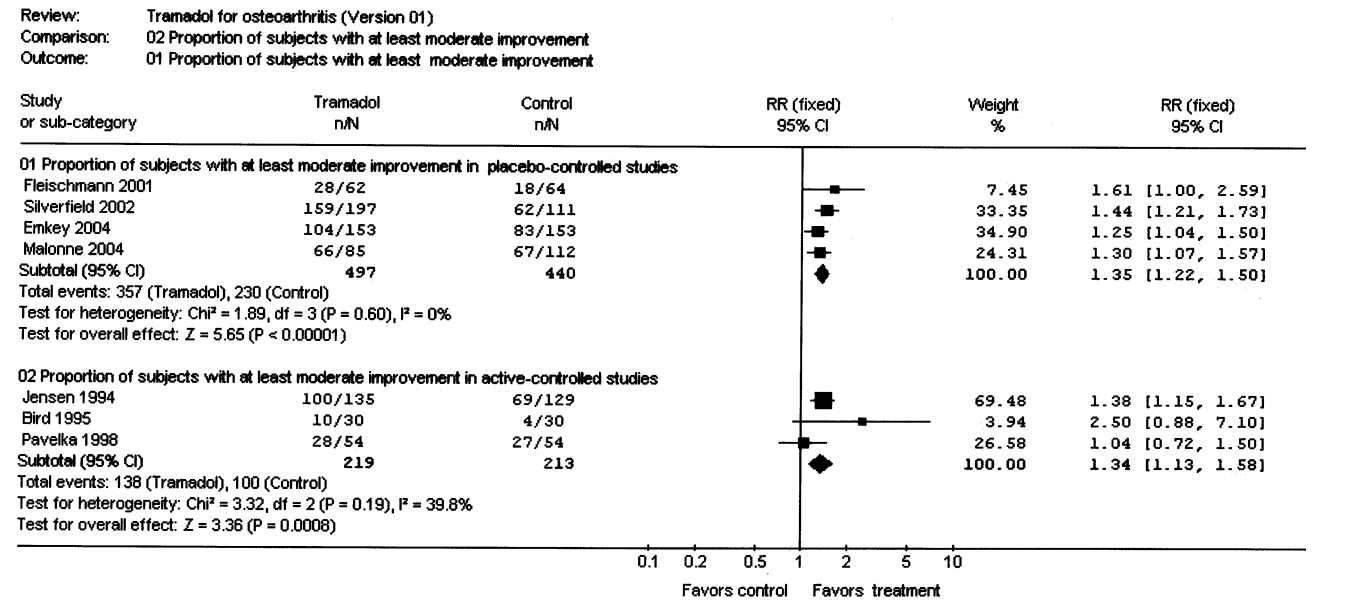

Figure 2. Risk of having at least moderate improvement in placebo and active controlled trials.

1.77 to 2.66), compared to those receiving placebo (Figure 6). This risk is equivalent to an NNTH of 5 (95% CI 4 to 7).

Minor adverse events in active-controlled studies: Participants who received tramadol had a higher risk of developing adverse events than participants who received diclofenac[20] or dextropropoxyphene[27]. This risk is equivalent to an NNTH of 5 (95% CI 4 to 8). However, participants exposed to tramadol had lower risk of developing adverse events than participants exposed to pentazocine[19] (Figure 6).

Major adverse events in placebo-controlled studies: 7 studies reported major adverse events that resulted in participants suspending the treatment. The results were homogenous (I^2 = 38.8%). Participants who received tramadol (143 subjects of 710) had 2.6 times the risk of developing major adverse events (95% CI 1.96 to 3.63) compared to those receiving placebo (49 subjects of 626; Figure 7). This risk is equivalent to an NNTH of 8 (95% CI 7 to 12). These adverse events were nausea, constipation, dizziness, somnolence, pruritus, and headaches.

Major adverse events in active-controlled studies: Participants who received tramadol developed more adverse events (53 subjects of 189) than participants who received diclofenac or dextropropoxyphene (15 subjects of 183). This risk is equivalent to an NNTH of 5 (95% CI 4 to 9). Similarly,

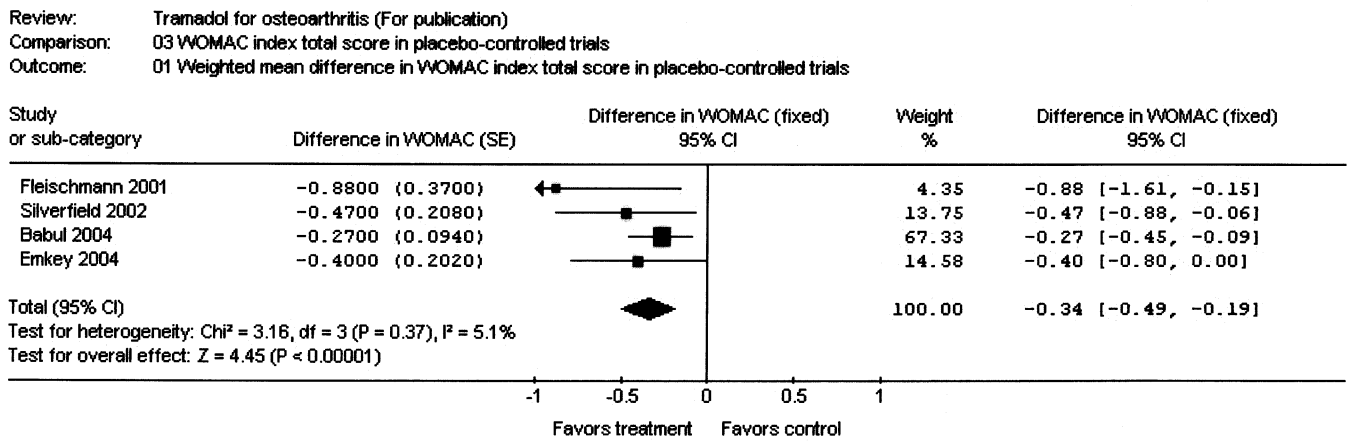

Figure 3. WOMAC index.

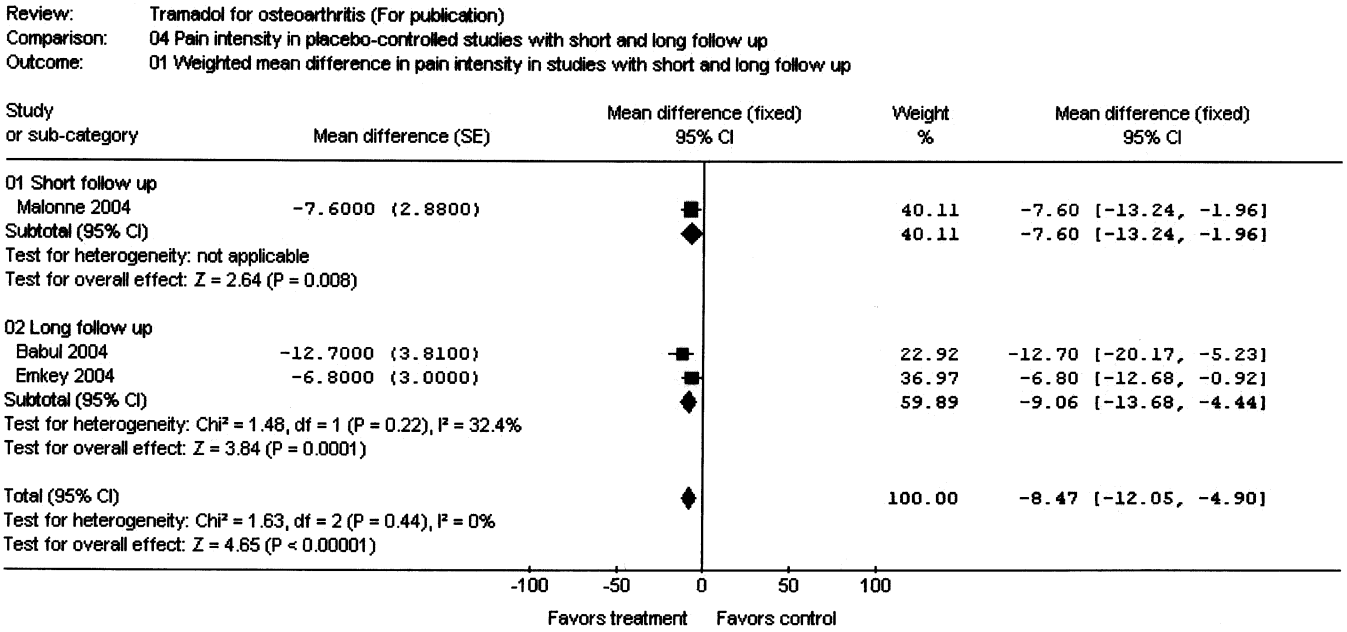

Figure 4. Pain intensity in studies with short and long followup.

subjects taking tramadol experienced more withdrawals than patients receiving paracetamol (Figure 7). However, participants who received tramadol (9 subjects of 30) developed fewer adverse events than participants who received pentazocine (11 subjects of 30).

Sensitivity analysis. Four unpublished placebo-controlled studies that showed no effect of tramadol on pain intensity would render the results of this systematic review not statistically significant.

DISCUSSION

There is gold-standard evidence that in OA tramadol is more effective than placebo at reducing pain intensity, producing relief of symptoms, and improving function. However, these benefits are small.

In terms of a decrease in pain intensity, the maximum decrease expected with tramadol or tramadol/paracetamol would not be more than 12.5 units on a scale from 0 to 100. This decrease represents the smallest change that people can discern when pain is moderate; however, the same decrease would be unnoticed when pain is severe[31]. In terms of pain relief or global assessment of improvement, the NNTB of tramadol is 6. This NNTB is similar to the NNTB of paracetamol in trial participants with OA[32]. Paracetamol is also less effective than NSAID[32]. In terms of function, the improvement in the WOMAC score is also small (8.5%)[33].

The above benefits could be outweighed by adverse events, as tramadol's NNTH for minor adverse events is the same as its NNTB for pain relief. In addition, the NNTH for major adverse events indicates that, of every 8 people who receive tramadol or tramadol/paracetamol, one will stop taking the medication because of adverse events. In clinical practice, tra-

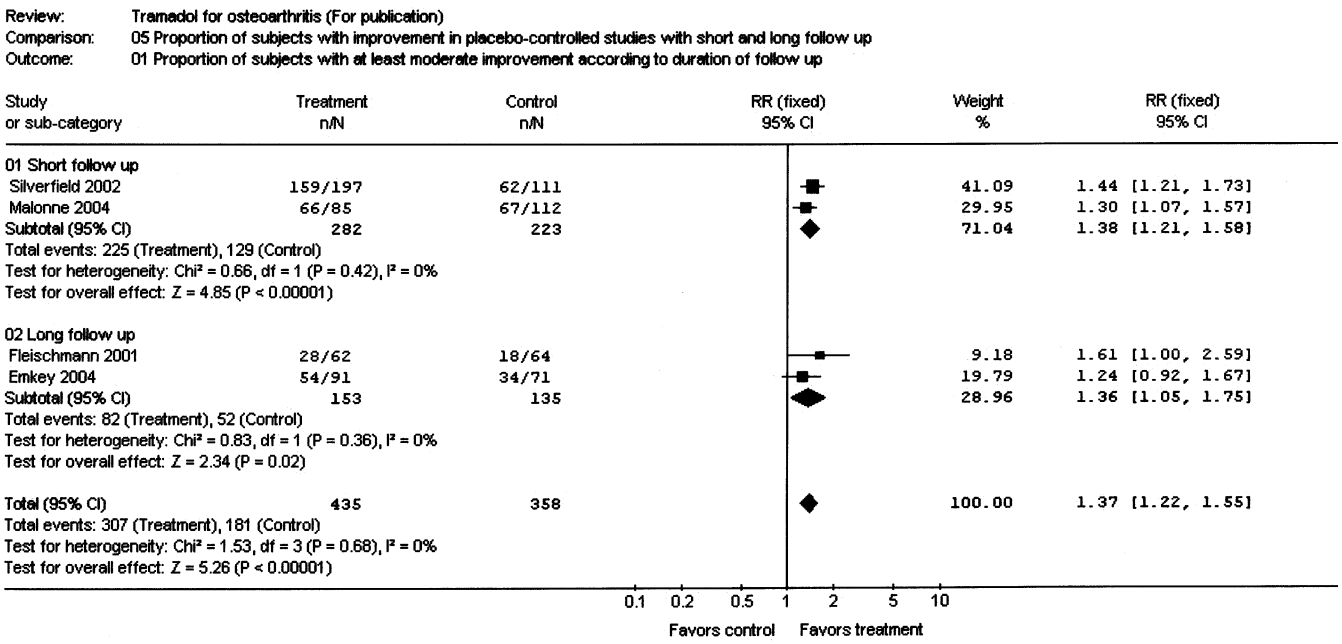

Figure 5. Risk of having at least moderate improvement in studies with short and long followup.

Table 5. Clinical relevance table for global assessment of improvement.

Outcome	Event Rate in Treatment Group, (%)	Event Rate in Placebo Group, (%)	Relative Risk (95% CI)	Absolute Risk Difference, % (95% CI)	Relative Change, % (95% CI)	NNTB (95% CI)	No. of people taking treatment who achieved at least moderate improvement out of 100	No. of people taking placebo who achieved at least moderate improvement out of 100	Quality of Evidence
Global assessment	307/435 (70)	181/358 (50)	1.37 (1.2 to 1.5)	19 (12 to 26)	37 (20 to 50)	6 (4 to 9)	69	50	Gold

NNTB: number needed to treat to benefit.

Table 6. Clinical relevance table for pain intensity and WOMAC index total score.

Outcome	No. of Patients in Treatment Group/No. of Patients in Control Group	Baseline Mean in Control Group	Weighted Mean Difference (95% CI)	Absolute Change	Relative Change, %	Quality of Evidence
Pain intensity (0–100 scale)	362/387	69.5 ± 7.5	-8.5 (-12.05 to -4.9)	8.5	12	Gold
WOMAC index total score (0–10 scale)	533/451	4 ± 1.18	–0.3 (0.49 to –0.19)	0.34	8.5	Gold

madol tolerability may increase if a slow titration regimen is implemented (e.g., 100 mg/day tramadol for 7 or 10 days, then 200 mg/day). This approach halves the proportion of people who interrupt the therapy because of adverse events[34,35] and would translate into a much better NNTH — of every 33 people who receive tramadol or tramadol/paracetamol, one will stop taking the medication because of adverse events.

Contrary to the adverse events associated with the use of tramadol, the chronic use of NSAID is associated with serious and life-threatening events especially in the elderly — gas-

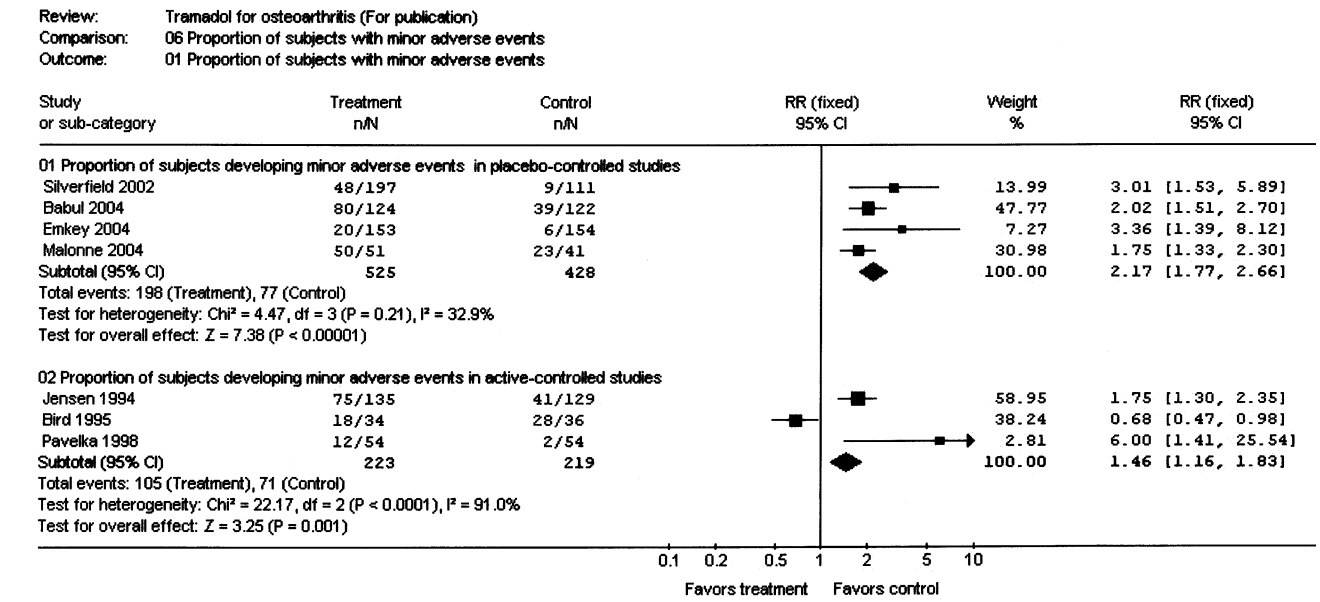

Figure 6. Risk of having minor side effects in placebo and active controlled trials.

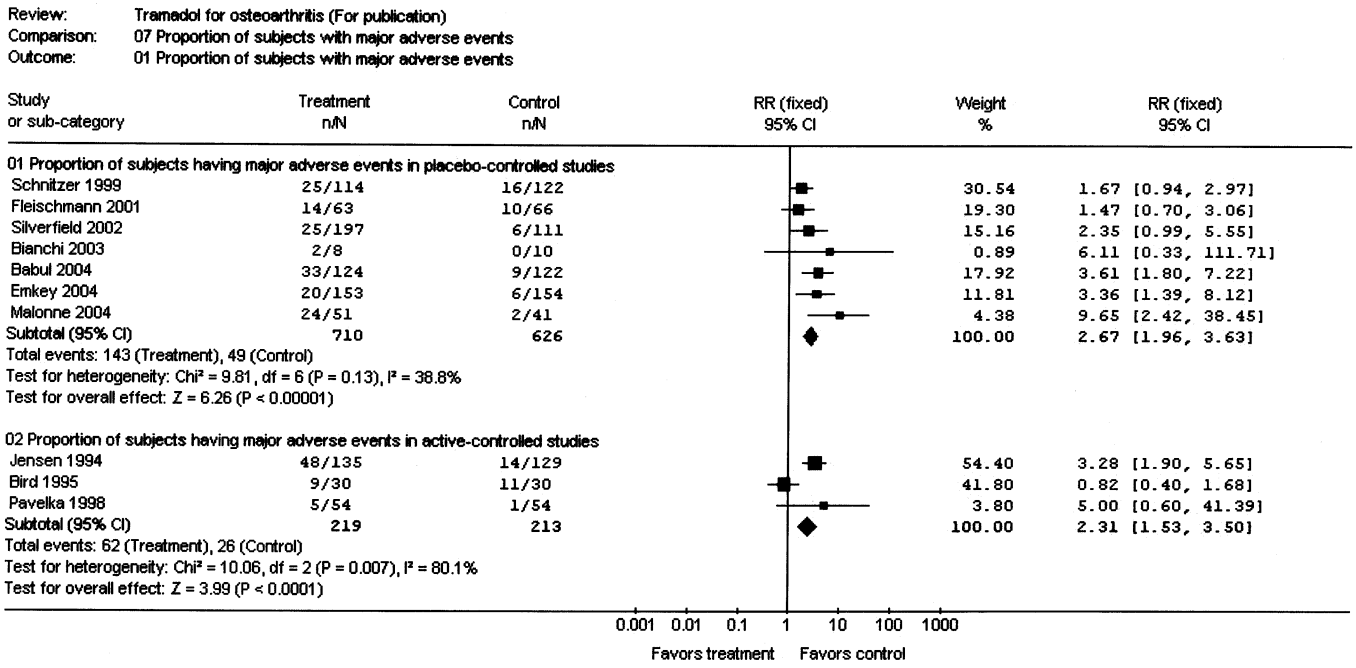

Figure 7. Risk of having major side effects in placebo and active controlled trials.

trointestinal bleeding, perforation, or renal failure[36]. Further, recent evidence challenges the longterm efficacy of NSAID for osteoarthritic knee pain as these medications were only 15% better than placebo; these are the findings of a recent metaanalysis of RCT[2].

Tramadol and the combination of tramadol/paracetamol exhibited similar degrees of effectiveness and safety. However, only 2 of the 11 studies evaluated the combination form and, therefore, small differences cannot be ruled out.

Limited available evidence suggests that traditional opioids are not more effective than tramadol for OA. The active-controlled studies included in this review showed that tramadol was superior to weak opioids, and the NNTB for the strong opioid oxycodone (40 mg/day) in OA is around 6[14,37]. In OA, opioids seem less effective than NSAID, which have NNTB of around 4[38,39].

Medications that act through opioid receptors may lose effectiveness with chronic use. In this systematic review, we

found only 2 studies that evaluated tramadol for more than 8 weeks, the longest followup being 3 months. Therefore, we could not determine whether the effectiveness of tramadol decreases with chronic use.

The active-controlled studies showed that tramadol was superior to weak opioids, similar to diclofenac, but inferior to paracetamol in regard to analgesia. In terms of safety, tramadol was associated with a higher incidence of opioid-related side effects than dihydrocodeine or dextropropoxyphene, with the exception of pentazocine, which was less tolerated. Tramadol had a higher incidence of minor effects than diclofenac, but one participant receiving diclofenac exhibited a serious adverse event. In view of the limited number of studies that evaluated tramadol with other active medications, one study for each of the above analgesics, no conclusions can be drawn on how tramadol or tramadol/paracetamol compare with other available pharmacological treatments.

RCT that compare head to head the effectiveness and safety profiles of tramadol or tramadol/paracetamol and NSAID should be performed to guide clinicians selecting the best treatment approach.

One potential limitation of our systematic review is that with one exception, all the studies were industry-funded, and there is evidence suggesting that industry-funded studies could overestimate treatment effects[40].

In summary, there is gold-standard evidence that tramadol or tramadol/paracetamol decreases pain intensity, produces symptom relief, and improves function, but these benefits are small. Adverse events, although reversible and not life-threatening, often cause participants to stop taking the medication and could limit the usefulness of tramadol or tramadol/paracetamol, unless slow titration regimens substantially reduce adverse events.

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