Tramadol for osteoarthritis (Review)

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Tramadol for osteoarthritis

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A B S T R A C T

Background
Tramadol is increasingly used for the treatment of osteoarthritis because, in contrast to nonsteroidal anti-inflammatory drugs (NSAIDs), tramadol does not produce gastrointestinal bleeding or renal problems, and does not affect articular cartilage.

Objectives
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 osteoarthritis.

Search methods
We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and LILACS databases up to August 2005.

Selection criteria
We included randomized controlled trials (RCTs) that evaluated the effect of tramadol or tramadol plus paracetamol on pain levels and/or physical function in people with osteoarthritis. No language restriction was applied.

Data collection and analysis
We analyzed separately placebo-controlled and active-controlled studies. We used fixed-effect models for the meta-analyses as the results across studies were similar.

Main results
We included eleven RCTs with a total of 1019 participants who received tramadol or tramadol/paracetamol and 920 participants who received placebo or active-control.

The placebo-controlled studies indicated that participants who received tramadol had less pain (-8.5 units on a 0 to 100 scale; 95% confidence interval (CI) -12.0 to -5.0) than patients who received placebo. This represents a 12% relative decrease in pain intensity from baseline. Participants who received tramadol had a 37% increase (95% CI 1.2 to 1.5) in the likelihood of reporting moderate improvement (number needed to treat to benefit = 6; 95% CI 4 to 9). Participants who received tramadol had 2.27 times the risk of...
developing minor adverse events and 2.6 times the risk of developing major adverse events, compared to participants who received placebo. Of every eight people who receive tramadol or tramadol/paracetamol, one will stop taking the medication because of adverse events, number needed to treat to harm (NNTH)= 8 (95% CI 7 to 12) for major adverse events.

No conclusion could be drawn on how tramadol or tramadol/paracetamol compared with available pharmacological treatments because of the limited number of studies that evaluated such therapies.

**Authors’ conclusions**

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 tramadol or tramadol plus paracetamol usefulness.

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**PLAIN LANGUAGE SUMMARY**

**Tramadol for osteoarthritis**

This summary of a Cochrane review presents what we know from research about the effect of tramadol for osteoarthritis. The review shows that:

* There is gold level evidence that to treat osteoarthritis, tramadol taken for up to three months may decrease pain, may improve stiffness and function and overall well-being. Tramadol may cause side effects such as nausea, vomiting, dizziness, constipation, tiredness, and headache.

The benefits of tramadol are small and the side effects may cause people to stop taking it which may limit how useful tramadol is to treat osteoarthritis.

**What is osteoarthritis and what drugs are used to treat it?**

Osteoarthritis (OA) is the most common form of arthritis that can affect the hands, hips, shoulders and knees. In OA, the cartilage that protects the ends of the bones breaks down and causes pain and swelling. There are two main types of drug treatments in OA. Pain relievers (such as acetaminophen/paracetamol and opioids) are used to relieve pain but do not affect swelling. Non-steroidal anti-inflammatory drugs (NSAIDs, such as ibuprofen and cox II) are used to decrease pain and swelling. Tramadol is a type of opioid being used more for OA. It does not cause bleeding in the stomach and intestines or kidney problems that may occur with other pain relievers. It also does not affect the cartilage at the end of the bones. But tramadol does not decrease swelling and may not work well after long use. It is therefore important to know the benefits and harms of tramadol.

**What are the results of this review?**

People in the studies took about 200 mg of tramadol per day or a placebo (fake tablets or powder) or an NSAID or a different pain reliever. People took the drugs for up to one week to three months.

**Benefits of tramadol**

In people with osteoarthritis:

- tramadol may decrease pain more than a placebo
- pain may decrease by 8.5 more points on a scale of 0 to 100 with tramadol
- tramadol may improve overall well-being more than placebo
- 50 out of 100 people may improve when taking a placebo
- 69 out of 100 people may improve when taking tramadol
- tramadol may slightly decrease stiffness and slightly improve function more than placebo
- function may improve by 0.32 more points on a scale of 0 to 10 with tramadol

It is not known whether tramadol improves symptoms of osteoarthritis more than other drugs. It is also not known whether tramadol still works well after long use. This is because the follow-up of the studies was short.
Harms of tramadol

In people with osteoarthritis:

- tramadol may cause minor side effects in more people than placebo, such as nausea, vomiting, dizziness, constipation, tiredness, and headache
  - 18 out of 100 people may have minor side effects when taking a placebo
  - 39 out of 100 people may have minor side effects when taking tramadol

- tramadol may cause major side effects that would make people stop taking it
  - 8 out of 100 people had major side effects when taking a placebo
  - 21 out of 100 people had major side effects when taking tramadol

It is not known whether tramadol causes more side effects than other drugs for osteoarthritis.

BACKGROUND

Osteoarthritis (OA) is a disease characterized by joint pain, distortion of joint architecture, and impaired joint function due to degeneration of articular cartilage and local inflammation (Altman 1997).

Osteoarthritis, also known as degenerative arthritis, is one of the most frequent disorders in the population and is the most common cause of disability in older adults (Reginster 2002). Osteoarthritis frequently affects the hands, feet, and large weight-bearing joints such as the hips and the knees (Buckwalter 2004). The prevalence of OA increases with age. For example, the prevalence of self-reported OA increases from 11% in people over 35 years to 36% in people over 85 years (Buckwalter 2004; De Filippis 2004). The prevalence of OA can be expected to increase as the proportion of elderly people in the population rises.

Osteoarthritis is classified as primary or secondary. Primary OA includes any osteoarthritis for which a definite cause can not be found. Secondary OA includes any osteoarthritis for which a definite cause (e.g. trauma or obesity) can be found.

The enzymatic and mechanical breakdown of the matrix of the joint cartilage, and the cartilage's decreased capacity for regeneration are key features of the pathophysiology of OA. In OA, an excessive amount of chondrocytic nitric oxide and other inflammatory mediators, such as eicosanoids and cytokines, are produced. These mediators cause cellular injury, inhibit cartilage synthesis and render the chondrocytes susceptible to apoptosis. These inflammatory phenomena, in addition to promoting cartilage damage, stimulate A delta and C fibers in the synovium and surrounding tissues. This neural stimulation leads to peripheral and central sensitization, and chronic pain (Kean 2004).

Pain is the most common symptom of OA, and as pain levels rise, people experience a reduced range of motion and increasing disability (Bjordal 2004; Dieppe 2005). 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 than individuals with gastrointestinal, cardiovascular or chronic respiratory illnesses (Reginster 2002).

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 (Odding 1998; Towheed 2003). Treatment for OA may include invasive procedures and non-pharmacological and pharmacological therapies.

Invasive procedures include the application of intra-articular corticosteroids and surgery. Intra-articular corticosteroids produce only short term (one week) relief (Godwin 2004). Total hip and knee arthroplasties are quite effective in improving health-related quality of life dimensions (Ethgen 2004; Towheed 1996). However, surgical-related improvements in quality of life must take into account that such improvements are usually greatest in patients who have the lowest quality of life before surgery (Ethgen 2004). In clinical practice, surgery is not the first line treatment to improve quality of life in patients with OA.

Non-pharmacological therapies include weight reduction in obese people, physiotherapy (for muscle strengthening), exercise and occupational therapy (e.g. training in the use of devices to assist ambulation).

A wide variety of pharmacological therapies are used to treat OA including NSAIDs and analgesics, such as acetaminophen and tra-
NSAIDs 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 NSAIDs may accelerate the course of OA (Rashad 1989) as NSAIDs may be toxic to articular cartilage (Herman 1986). The deleterious effect of NSAIDs on bone healing seems responsible for the increased incidence of nonunion following spinal fusion surgery in patients exposed to high doses of NSAIDs in the postoperative period (Park 2005; Reuben 1998). Acetaminophen (paracetamol), although not associated with an increased risk of gastrointestinal events or with cartilage toxicity, is less effective than NSAIDs in reducing pain (Towheed 2003).

Tramadol is increasingly used for the treatment of OA because, in contrast to NSAIDs (Reig 2002; Zhang 2004), tramadol does not produce gastrointestinal bleeding or renal problems, and does not affect articular cartilage. Tramadol is an atypical opioid, as it exhibits a dual mechanism of action: tramadol activates opioid receptors and descending inhibitory pain systems (Gibson 1996). 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 anti-inflammatory 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 (Jett 1997). In addition, tolerance may not substantially affect long term effectiveness. Systematic reviews have shown that 44% of participants prescribed opioids for chronic non-cancer pain continued to take opioids for up to 24 months (Kalso 2004).

**Objectives**

1. To determine the analgesic effectiveness of oral tramadol or tramadol/paracetamol for osteoarthritic pain.
2. To determine the effectiveness of tramadol for improving physical function in people with OA.
3. To assess the duration of any benefit.
4. To determine the safety of tramadol.

**Methods**

**Criteria for considering studies for this review**

**Types of studies**

We considered for inclusion only randomized controlled trials (RCTs) 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 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.

**Types of participants**

We included studies that evaluated the effect of oral tramadol or tramadol plus acetaminophen in adults with primary or secondary osteoarthritis. 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.

**Types of interventions**

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.

**Types of outcome measures**

The primary outcomes were:

1. Pain
   a. Patient reported pain intensity, or
   b. Patient reported pain relief
2. Patient global assessment of improvement
3. Physical function
   a. Self-reported, or
   b. Performance-based measures of function, or
   c. Any physical function scale
4. Safety of tramadol
   a. Presence and degree of severity of adverse events, or
   b. Total withdrawals due to adverse events
5. Joint imaging

The above outcomes represent the core set of outcome measures recommended at the OMERACT (outcome measures in rheumatology) III conference (Bellamy 1997; Pham 2004). A secondary outcome was the duration of benefits.
Search methods for identification of studies

Electronic databases
We searched the following databases:
1. The Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library to 29 August 2005
2. MEDLINE 1966 to third week of August 2005
3. EMBASE 1980 to 15 September 2005
4. LILACS 1982 to 29 August 2005

Search terms
For the identification of the studies in MEDLINE we used the MeSH / EMTREE terms: Appendix 1.
No language restriction was applied. We translated non-English language articles (from Croatian, Portuguese, Russian, and Spanish) and assessed them. We communicated with the authors to secure information not presented in the manuscripts.
For each of the other databases, search strategies were based on the search strategy developed for MEDLINE, but revised appropriately. We searched bibliographies from all retrieved articles for additional studies.

In order to minimize the impact of publication bias, 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) and Biovial Pharmaceuticals.

Data collection and analysis

Study selection
We retrieved in full all articles in which the abstract made reference to a trial of tramadol and osteoarthritis. If there was no abstract, we retrieved the article in full. For a trial to be included, it had to provide information on any of the outcomes described above.

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.

Methodological quality
The articles that fulfilled the inclusion criteria underwent quality appraisal. 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
Primary outcomes:
1. Pain and pain relief
a. If authors reported pain intensity using visual analogue 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 (Fleischmann 2001; Silverfield 2002). These studies were excluded from the pooling of the pain intensity estimates, but were included in the estimate of patient global assessment of improvement.

b. If authors reported pain relief, we calculated the proportion of participants who achieved at least 50% pain relief or a similar outcome (i.e. at least moderate pain relief). We also used this proportion as a surrogate marker for the outcome measure “global assessment of improvement” for studies that did not report this global outcome measure.

2. Physical function
We extracted the mean (± SD) of the composite Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index score in each study arm after treatment and calculated the mean difference.

If studies reported the mean difference in pain intensity or mean difference in WOMAC Index score between treatments without a measure of dispersion, we estimated the standard error of the difference from the P value and the number of participants in each arm (as described in the Cochrane Manual). To pool the data, we used the generic inverse variance method.

3. 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).

4. 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).

Secondary outcome:
Duration of benefit
To determine how long the benefit persisted, we divided the studies into two groups, depending on the duration of follow up: 1) up to eight weeks of follow up or 2) longer than eight weeks of follow up.

Assessment of heterogeneity
To evaluate heterogeneity, we used the Q test and the I² statistic (Higgins 2003). We considered P values less than 0.1 indicative of non-homogeneous studies.
We analyzed separately placebo-controlled studies and active-controlled studies. 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 impact 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 filled” method developed by Duval and Tweedie (Buckwalter 2004). For this analysis, we employed the command ‘metatrim’ in STATA (a 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 (Tugwell 2004) as follows:
1. Platinum: A published systematic review that has at least two 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% follow up
   - Concealment of treatment allocation
2. Gold: At least one randomized clinical trial 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% follow up
   - Concealment of treatment allocation
3. Silver: A systematic review or randomized trial that does not meet the above criteria.
4. Bronze: At least one high quality case series without controls, or if the conclusion is derived from expert opinion.

RESULTS

Description of studies
See: Characteristics of included studies; Characteristics of excluded studies.

All included studies were obtained from the electronic database searches. Identified studies from conference abstracts were included in the electronic database searches. Three of the excluded studies were obtained from Grunenthal.

Twenty seven studies were excluded: fourteen were narrative reviews; three were nonrandomized studies; three studies evaluated tramadol in all arms; four studies evaluated back pain and OA, but the results were not reported separately; one study did not evaluate OA; one study did not evaluate tramadol; and one study was a secondary report of a clinical trial already included in the present systematic review (see Characteristics of Excluded Studies Table).

Eleven RCTs, with a total of 1019 participants who received tramadol or tramadol/paracetamol and 920 participants who received placebo or active control, were included (see the Characteristics of Included Studies Table for further details). All RCTs were parallel in design, with two exceptions (Bird 1995; Pavelka 1998), which were cross-over design. One study provided no data on the effectiveness of tramadol (Schnitzer 1999), 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.

All studies were funded by the pharmaceutical industry with the exception of the study by Bianchi 2003.

Six studies used placebo controls (Babul 2004; Emkey 2004; Fleischmann 2001; Malonne 2004; Schnitzer 1999; Silverfield 2002). In five studies, the active control was either paracetamol 1.5 mg/day (Bianchi 2003), diclofenac 89 mg/day (Pavelka 1998), dihydrocodeine 120 mg/day (Wilder-Smith 2001), dextropropoxyphene 300 mg/day (Jensen 1994), or pentazocine (Bird 1995).

Nine studies (Babul 2004; Bianchi 2003; Bird 1995; Fleischmann 2001; Jensen 1994; Malonne 2004; Pavelka 1998; Schnitzer 1999; Wilder-Smith 2001) evaluated tramadol alone and two (Emkey 2004; Silverfield 2002) evaluated tramadol plus paracetamol (Table 4). These two 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 follow up was 35 days (minimum = 7 days, maximum = 91 days).

Five studies (Babul 2004; Emkey 2004; Fleischmann 2001; Pavelka 1998; Silverfield 2002) reported the effect of tramadol on function using the WOMAC Index. One study (Emkey 2004) also evaluated function with the SF-36 survey and one study evaluated function with daily activities (Bird 1995). None of the studies evaluated radiological improvement with imaging.

Risk of bias in included studies
Only one study did not mask the investigators (Wilder-Smith 2001); in all other studies, both investigators and subjects were blinded. Only one study (Silverfield 2002) described concealment of allocation and two of the eleven studies (18%) lost to follow up 20% or more of the subjects (Babul 2004; Jensen 1994) (Table 1).
Effects of interventions

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 (see Figure 1).

Table 2 Agreement between evaluators

<table>
<thead>
<tr>
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<th>Agreement (%)</th>
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<tr>
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<td>Blinding of patients</td>
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<tr>
<td>Continuous variables</td>
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<tr>
<td>Mean pain intensity (control group)</td>
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<tr>
<td>Number of patients with at least 50% pain relief (tramadol group)</td>
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</tr>
<tr>
<td>Number of patients with minor adverse events (tramadol group)</td>
<td>0.94</td>
</tr>
<tr>
<td>Number of patients with major adverse events (tramadol group)</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Pain intensity

Placebo-controlled studies

Three 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% confidence interval (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 (Comparison 1).

Active-controlled studies

Participants who received tramadol had larger decreases in pain intensity than those who received dihydrocodeine (Wilder-Smith 2001), dextropropoxyphene (Jensen 1994), or pentazocine (Bird 1995). However, paracetamol (1500 mg/day) provided a larger decrease in pain intensity than 150 mg/day of tramadol (Bianchi 2003) (Comparison 1). The studies by Wilder-Smith 2001 and Bird 1995 are not included in the graph because they did not use a 0 to 10 or to 0-100 scale.

Global assessment of improvement

Improvement in placebo-controlled studies
Four placebo-controlled studies reported the percentage of participants with at least moderate improvement or a similar outcome. The results were homogenous ($I^2=0\%$). Tramadol increased (by 37%) the likelihood of a moderate improvement compared to placebo (95% CI 1.2 to 1.5). This is equivalent to an NNNT of 6 (95% CI 4 to 9) (Comparison 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 similarly effective than diclofenac in the cross over study Pavelka 1998 (Comparison 2).

**Physical Function**

**WOMAC Index score in placebo-controlled trials**

Four studies evaluated the WOMAC index. A reduction in the WOMAC score represents an improvement in participant’s pain, stiffness and function. The reduction in the score was larger in the tramadol group than the placebo group (-0.34; 95% CI -0.49 to -0.19). This represents a 8.5% relative reduction in the mean baseline score of 4 (i.e. a 8.5% relative improvement) (Comparison 3).

**WOMAC index score in active-controlled trials**

In the study by Pavelka 2000, the improvement in the WOMAC score was similar when participants received either tramadol (3.9±1.6) or diclofenac (4.0 ± 1.7); the improvement in the WOMAC score was similar when participants received either tramadol (3.9 1.6) or diclofenac (4.0 1.7).

A summary of all the above outcomes is also presented in Additional figures 02.

**Duration of benefit**

**Placebo-controlled studies**

In the three placebo-controlled studies (Babul 2004; Emkey 2004; Fleischmann 2001) that followed participants for more than eight weeks (84 days, 91, and 91 days, respectively), tramadol was more effective than placebo. Similar results were found in a study with a shorter follow up (Malonne 2004).

In terms of pain intensity, the mean difference between the tramadol and placebo groups was -9.1 units in the studies with longer follow up and -7.6 units in the study with shorter follow up (Comparison 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 follow up and 1.38 in the studies with shorter follow up (Comparison 5).

**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. 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 1998 – one participant who received diclofenac experienced angioneurotic edema.

**Minor adverse events**

**Minor adverse events in placebo-controlled studies**

Four placebo-controlled studies reported the proportion of subjects with minor adverse events. The results were homogeneous ($I^2=32.9\%$). Participants who received tramadol had 2.27 times the risk of developing minor adverse events (95% CI 1.77 to 2.66), compared to those receiving placebo (Comparison 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 (Pavelka 1998) or dextropropoxyphene (Jensen 1994). 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 (Bird 1995) (Comparison 6).

**Major adverse events**

**Major adverse events in placebo-controlled studies**

Seven studies reported major adverse events that resulted in participants suspending the treatment. The results were homogeneous ($I^2=38.8\%$). 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) (Comparison 7). This risk is equivalent to an NNTH of 8 (95% CI 7 to 12).

**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) (Comparison 7). This risk is equivalent to an NNTH of 5 (95% CI 4 to 9). However, participants who received tramadol (9 subjects of 30) developed fewer adverse events than participants who received pentazocine (11 subjects of 30).

**Assessment of reporting biases - 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 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 (Cepeda 2003). 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 (Towheed 2006). Paracetamol is also less effective than NSAIDs (Towheed 2006). In terms of function, the improvement in the WOMAC Index score is also small (8.5%) (Angst 2001).

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 eight people who receive tramadol or tramadol/paracetamol, one will stop taking the medication because of adverse events. In clinical practice, tramadol 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 (Tagarro 2005; Ruoff 1999) 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 NSAIDs is associated with serious and life threatening events especially in the elderly --gastrointestinal bleeding, perforation, or renal failure (Garcia 2001). Furthermore, recent evidence challenges the long-term efficacy of NSAIDs for osteoarthritic knee pain as these medications were only 15% better than placebo, these are the findings of a recent meta-analysis of RCTs (Bjordal 2004).

Tramadol and the combination of tramadol/paracetamol exhibited similar degree of effectiveness and safety. However, only two of the eleven 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 (Kalso 2004; Kean 2004). In OA, opioids seem less effective than NSAIDs, which have NNTBs of around 4 (Garner 2002a; Garner 2002b).

Medications that act through opioid receptors may lose effectiveness with chronic use. In this systematic review, we found only two studies that evaluated tramadol for more than eight weeks, the longest follow up being three 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 dicycodeine 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.

One potential limitation of this systematic review is that with the exception of one study, all the rest were industry funded and there is evidence suggesting that industry funded studies could overestimate treatment effects (Bhandari 2004).

In summary, there is gold 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 tramadol or tramadol/paracetamol usefulness.

**AUTHORS’ CONCLUSIONS**

**Implications for practice**

The benefits of tramadol are comparable with those obtained with paracetamol and these benefits are coupled with a less favorable safety profile. Although these adverse events are not life threatening, they greatly disadvantage tramadol compared to other treatments for OA, unless slow titration regimens substantially reduce adverse events.

**Implications for research**

Available treatments for OA have small analgesic effects and there is an urgent need for more effective treatments in OA.

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

The evaluation of the effectiveness of other opioids for the treatment of OA is also important: these agents are increasingly used to treat OA despite a lack of strong supporting evidence for their long-term effectiveness, and despite concerns about their tolerability and long-term safety.
References to studies included in this review

Babul 2004 {published data only}

Bianchi 2003 {published data only}

Bird 1995 {published data only}

Emkey 2004 {published data only}

Fleischmann 2001 {published data only}

Jensen 1994 {published data only}

Malonne 2004 {published data only}

Pavelka 1998 {published data only}

Schnitzer 1999 {published data only}

Silverfield 2002 {published data only}

Wilder-Smith 2001 {published data only}

References to studies excluded from this review

Alman 2004 {published data only}

Anonymous 2003 {published data only}

Anonymous 2004 {published data only}

Bloodworth 2005 {published data only}

Blumstein 2005 {published data only}

Bodalia 2003 {published data only}


Rosenthal 2004 (published data only)


Ruoff 1999 (published data only)


Schnitzer 2002 (published data only)


Schnitzer 2003 (published data only)


Mongin 2004 (published data only)


Muller 2001 (published data only)


Mullican 2004 (published data only)


Nachamie 2005 (published data only)


Pavelka 2000 (published data only)


Punwani 2004 (published data only)


Itoh 2001 (published data only)


Lazebnik 2001 (published data only)


McClellan 2003 (published data only)


Mongin 2004 (published data only)


Muller 2001 (published data only)


Mullican 2004 (published data only)


Nachamie 2005 (published data only)


Pavelka 2000 (published data only)


Punwani 2004 (published data only)


Rauck 2006 (published data only)


Rosenthal 2004 (published data only)


Roth 1998 (published data only)


Ruoff 1999 (published data only)


Schnitzer 2002 (published data only)


Schnitzer 2003 (published data only)


Spinewine 2005 (published data only)


Vlak 1996 (published data only)


Additional references

Altman 1997


Angst 2001

Bellamy 1997

Bhandari 2004

Bjordal 2004

Buckwalter 2004

Cepeda 2003

Cepeda 2004

De Filippis 2004

Dieppe 2005

Ethgen 2004

Garcia 2001

Garner 2002a

Garner 2002b

Gibson 1996
Gibson TP. Pharmacokinetics, efficacy, and safety of analgesia with a focus on tramadol HCl. *American Journal of Medicine* 1996;101(1A):475–53S.

Godwin 2004

Herman 1986

Higgins 2003

Jett 1997

Kalso 2004

Kean 2004

Odding 1998

Park 2005

Pham 2004

Rashad 1989

**Reginster 2002**

**Reig 2002**

**Reuben 1998**

**Tagarro 2005**

**Towheed 1996**

**Towheed 2003**

**Towheed 2006**

**Tugwell 2004**

**Zhang 2004**

* Indicates the major publication for the study
## Characteristics of included studies [ordered by study ID]

### Babul 2004

<table>
<thead>
<tr>
<th>Methods</th>
<th>Parallel Multicenter Double blind RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Participants at least 18 years old with OA of knee. Participants met the American College of Rheumatology (ACR) diagnostic criteria. Tramadol extended-release (ER) group N = 124. Control group N = 122</td>
</tr>
<tr>
<td>Interventions</td>
<td>Active group received tramadol ER (100 mg twice/day, up to 400 mg/day); control group received placebo for 84 days</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Pain and function were evaluated with VAS and WOMAC Index. Withdrawals due to adverse events: 33 of 124 in tramadol group; 9 of 122 in placebo group</td>
</tr>
<tr>
<td>Notes</td>
<td>We contacted the author to clarify how the WOMAC Index was reported. The author provided all the information requested. For the pooling we normalized the WOMAC total score</td>
</tr>
</tbody>
</table>

#### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
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<td>D - Not used</td>
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### Bianchi 2003

<table>
<thead>
<tr>
<th>Methods</th>
<th>Parallel Double blind RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Adult participants with OA of knee. Tramadol group N = 10. Control group N = 10</td>
</tr>
<tr>
<td>Interventions</td>
<td>Active group received tramadol (50 mg three times/day); control group received paracetamol (500 mg three times/day) for 7 days</td>
</tr>
<tr>
<td>Outcomes</td>
<td>The aim of the study was to compare the synovial fluid concentrations of interleukin and substance P. Pain intensity was evaluated with VAS. Withdrawals due to adverse events: 2 of 10 in tramadol group; 0 of 10 in paracetamol group</td>
</tr>
<tr>
<td>Notes</td>
<td>We contacted the author to ask for the percentage of participants with pain relief. We obtained no response</td>
</tr>
</tbody>
</table>

#### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
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<tbody>
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<td>Allocation concealment?</td>
<td>Unclear</td>
<td>D - Not used</td>
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</tbody>
</table>
### Bird 1995

<table>
<thead>
<tr>
<th><strong>Methods</strong></th>
<th>Crossover Double blind RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants</strong></td>
<td>Participants with radiologically confirmed diagnosis of OA of hip or knee 40 adult participants</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Active group received tramadol (50 mg for times/day); control group received pentazocine (50 mg for times/day) for 7 days No washout period</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Pain intensity was evaluated with verbal scale Participants while 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 complaint of less stiffness and required fewer tablets of paracetamol Fewer participants while exposed to tramadol reported side effects</td>
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<td><strong>Notes</strong></td>
<td>Pain intensity was evaluated with verbal scale Participants while 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 complaint of less stiffness and required fewer tablets of paracetamol Fewer participants while exposed to tramadol reported side effects</td>
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<tbody>
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<td>Unclear</td>
<td>D - Not used</td>
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</table>

### Emkey 2004

<table>
<thead>
<tr>
<th><strong>Methods</strong></th>
<th>Parallel Multicenter Double blind RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants</strong></td>
<td>Participants with more than one year of OA of hip or knee Tramadol/paracetamol group N = 153 Control group N = 154</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>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</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Pain and function were evaluated with VAS and WOMAC Index Physical function was also evaluated with the SF 36 Withdrawals due to adverse events: 20 of 153 in tramadol group; 6 of 154 in placebo group</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td></td>
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</table>

### Risk of bias

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<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>D - Not used</td>
</tr>
</tbody>
</table>
### Fleischmann 2001

**Methods**
Parallel Multicenter Double blind RCT

**Participants**
Participants with radiologically confirmed diagnosis of OA of knee Tramadol group N = 63 Control group N = 66

**Interventions**
Active group received tramadol 50-mg increments up to 400mg/day if needed; control group received placebo for 91 days

**Outcomes**
Pain intensity was evaluated with verbal scale, pain relief and overall global assessment were evaluated with Likert scales Function was evaluated with WOMAC Index Withdrawals due to adverse events: 14 of 63 in tramadol group; 10 of 66 in placebo group

**Notes**

#### Risk of bias

<table>
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<th>Item</th>
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<tbody>
<tr>
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</tbody>
</table>

### Jensen 1994

**Methods**
Parallel Multicenter Double blind RCT

**Participants**
Participants with radiologically confirmed diagnosis of OA of hip or knee Tramadol group N = 135 Control group N = 129

**Interventions**
Active group received tramadol; control group received dextropropoxyphene for 14 days Participants were randomized to tramadol 100 mg three times/day or dextropropoxyphene 100 mg three times/day

**Outcomes**
Pain intensity was 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

**Notes**

#### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
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<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>D - Not used</td>
</tr>
</tbody>
</table>

### Malonne 2004

**Methods**
Parallel Multicenter Double blind RCT

**Participants**
Adult participants between 45 and 80 years old with OA of hip or knee Diagnosis made with the European League Against Rheumatism criteria Tramadol group N = 51 Control group N = 41
### Malonne 2004

(Continued)

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Active group received tramadol LP sustained release (200 mg/day); control group received placebo for 14 days Concomitant treatment with paracetamol as a rescue medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcomes</td>
<td>Pain intensity was evaluated with VAS Patient global assessment and use of rescue medication were also evaluated Forty per cent of participants took rescue medication in the tramadol group versus 63.4% in the placebo group Withdrawals due to adverse events: 24 of 111 in tramadol group; 2 of 119 in placebo group</td>
</tr>
<tr>
<td>Notes</td>
<td></td>
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</tbody>
</table>

### Risk of bias

<table>
<thead>
<tr>
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<tbody>
<tr>
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<td>Unclear</td>
<td>D - Not used</td>
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</tbody>
</table>

### Pavelka 1998

<table>
<thead>
<tr>
<th>Methods</th>
<th>Crossover Double blind RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Adult participants with radiologically confirmed diagnosis of OA of hip or knee Tramadol group N = 60 Control group N = 60</td>
</tr>
<tr>
<td>Interventions</td>
<td>Participants randomized to tramadol (50 to 100 mg up to three times/day on demand), then diclofenac (25 to 50 mg up to three times/day on demand) for 28 days with one week washout period</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Pain and function were 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 the medication; 1 patient while taking diclofenac stopped taking the medication</td>
</tr>
<tr>
<td>Notes</td>
<td>One participant who received diclofenac experienced a severe side effect (angioneurotic edema)</td>
</tr>
</tbody>
</table>

### Risk of bias

<table>
<thead>
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<th>Description</th>
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<tbody>
<tr>
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<td>D - Not used</td>
</tr>
</tbody>
</table>

### Schnitzer 1999

<table>
<thead>
<tr>
<th>Methods</th>
<th>Parallel Multicenter Double blind RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Adult participants with symptomatic OA of knee The study had two phases. We evaluated the eight-week double blind phase Participants whose pain did not resolve with 500 mg of naproxen were randomized Randomization was stratified based on response to 1000 mg of naproxen (responders and nonresponders) Active group received tramadol plus naproxen; control group received placebo plus naproxen for 54 days</td>
</tr>
<tr>
<td>Notes</td>
<td></td>
</tr>
</tbody>
</table>

Tramadol for osteoarthritis (Review)

Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
During the double blind phase the naproxen dose was reduced to 250 mg every two weeks

<table>
<thead>
<tr>
<th>Interventions</th>
<th>The primary aim of the study was to determine whether tramadol decreased naproxen requirements. No data on pain intensity during the double blind phase. Number of participants who discontinued therapy due to adverse events was reported.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcomes</td>
<td>We contacted the author, who suggested that we contact Ortho-McNeil.</td>
</tr>
<tr>
<td>Notes</td>
<td></td>
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</table>

### Risk of bias

<table>
<thead>
<tr>
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<tbody>
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</tr>
</tbody>
</table>

#### Silverfield 2002

<table>
<thead>
<tr>
<th>Methods</th>
<th>Parallel Multicenter Double blind RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Adult participants between 35 and 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 group N = 111</td>
</tr>
<tr>
<td>Interventions</td>
<td>Active group received tramadol (37.5 mg) plus paracetamol (325 mg); control group received placebo for 10 days. Number of tablets a day was increased up to a maximum of eight. Participants continued receiving NSAID or COX-2 at the same doses taken before study entry.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Pain intensity and pain relief were evaluated using a four point adjective scale (none, mild, moderate, severe). Percentage of patents 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 four point scale). Withdrawals due to adverse events: 25 of 197 in the tramadol group; 6 of 111 in control group.</td>
</tr>
<tr>
<td>Notes</td>
<td>We contacted one of the coauthors and obtained the requested information (the percentage of subjects with moderate pain relief).</td>
</tr>
</tbody>
</table>

### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
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<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>
### Methods

Parallel Multicenter RCT Participants were blinded Evaluators were not blinded

### Participants

Participants between 20 and 75 years old awaiting hip or knee replacement Tramadol group N = 28 Control group N = 29

### Interventions

Active group received tramadol Retard (100 mg); control group received long acting dihydrocodeine (60 mg) every 12 hours 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 the first 4 days

### Outcomes

Pain intensity was evaluated at rest and with movement using a four 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

### Notes

We contacted the author to determine the percentage of participants with minor and major adverse events. We obtained no response

### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
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### Characteristics of excluded studies [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adler 2002</td>
<td>All arms evaluated tramadol</td>
</tr>
<tr>
<td>Altman 2004</td>
<td>Narrative review</td>
</tr>
<tr>
<td>Anonymous 2003</td>
<td>Narrative review</td>
</tr>
<tr>
<td>Anonymous 2004</td>
<td>Narrative review</td>
</tr>
<tr>
<td>Bloodworth 2005</td>
<td>Narrative review</td>
</tr>
<tr>
<td>Blumstein 2005</td>
<td>Narrative review</td>
</tr>
<tr>
<td>Bodalia 2003</td>
<td>All arms evaluated tramadol</td>
</tr>
<tr>
<td>Brandt 2004</td>
<td>Narrative review</td>
</tr>
<tr>
<td>Filho 2003</td>
<td>Osteoarthritis not evaluated</td>
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<tr>
<td>Reference</td>
<td>Type</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Itoh 2001</td>
<td>Narrative review</td>
</tr>
<tr>
<td>Lazebnik 2004</td>
<td>Nonrandomized</td>
</tr>
<tr>
<td>McClellan 2003</td>
<td>Narrative review</td>
</tr>
<tr>
<td>Mongin 2004</td>
<td>All arms evaluated tramadol</td>
</tr>
<tr>
<td>Muller 2001</td>
<td>Tramadol not evaluated</td>
</tr>
<tr>
<td>Mullican 2001</td>
<td>RCT but evaluated back pain and OA and results are not reported separately</td>
</tr>
<tr>
<td>Nachamie 2005</td>
<td>Narrative review</td>
</tr>
<tr>
<td>Pavelka 2000</td>
<td>Nonrandomized</td>
</tr>
<tr>
<td>Punwani 2004</td>
<td>Narrative review</td>
</tr>
<tr>
<td>Rauck 2006</td>
<td>RCT but evaluated OA and other pain syndromes and results are not reported separately</td>
</tr>
<tr>
<td>Reig E2</td>
<td>Narrative review</td>
</tr>
<tr>
<td>Rosenthal 2004</td>
<td>Subanalysis of a study already included</td>
</tr>
<tr>
<td>Roth 1998</td>
<td>RCT but evaluated back pain and OA and results are not reported separately</td>
</tr>
<tr>
<td>Ruoff 1999</td>
<td>RCT but evaluated back pain and OA and results are not reported separately</td>
</tr>
<tr>
<td>Schnitzer 2002</td>
<td>Narrative review</td>
</tr>
<tr>
<td>Schnitzer 2003</td>
<td>Narrative review</td>
</tr>
<tr>
<td>Spinewine 2005</td>
<td>Narrative review</td>
</tr>
<tr>
<td>Vlak 1996</td>
<td>Nonrandomized</td>
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</table>
**DATA AND ANALYSES**

**Comparison 1. Pain intensity using a 0-100 scale**

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Weighted mean difference in pain intensity (scale 0-100)</td>
<td>5</td>
<td></td>
<td>Mean difference (Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>1.1 Weighted mean difference in placebo-controlled trials (0-100 scale)</td>
<td>3</td>
<td></td>
<td>Mean difference (Fixed, 95% CI)</td>
<td>-8.47 [-12.05, -4.90]</td>
</tr>
<tr>
<td>1.2 Weighted mean difference in pain intensity in active-controlled trials (0-100 scale)</td>
<td>2</td>
<td></td>
<td>Mean difference (Fixed, 95% CI)</td>
<td>-2.46 [-8.40, 3.49]</td>
</tr>
</tbody>
</table>

**Comparison 2. Proportion of subjects with at least moderate improvement**

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Proportion of subjects with at least moderate improvement</td>
<td>7</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>1.1 Proportion of subjects with at least moderate improvement in placebo-controlled studies</td>
<td>4</td>
<td>793</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.37 [1.22, 1.55]</td>
</tr>
<tr>
<td>1.2 Proportion of subjects with at least moderate improvement in active-controlled studies</td>
<td>3</td>
<td>432</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.34 [1.13, 1.58]</td>
</tr>
</tbody>
</table>

**Comparison 3. WOMAC index total score in placebo-controlled trials**

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Weighted mean difference in WOMAC index total score in placebo-controlled trials</td>
<td>4</td>
<td></td>
<td>Difference in WOMAC (Fixed, 95% CI)</td>
<td>-0.34 [-0.49, -0.19]</td>
</tr>
</tbody>
</table>
Comparison 4. Pain intensity in placebo-controlled studies with short and long follow up

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weighted mean difference in pain intensity in studies with short and long follow up</td>
<td>3</td>
<td></td>
<td>Mean difference (Fixed, 95% CI)</td>
<td>-8.47 [-12.05, -4.90]</td>
</tr>
<tr>
<td>1.1 Short follow up</td>
<td>1</td>
<td></td>
<td>Mean difference (Fixed, 95% CI)</td>
<td>-7.6 [-13.24, -1.96]</td>
</tr>
<tr>
<td>1.2 Long follow up</td>
<td>2</td>
<td></td>
<td>Mean difference (Fixed, 95% CI)</td>
<td>-9.06 [-13.68, -4.44]</td>
</tr>
</tbody>
</table>

Comparison 5. Proportion of subjects with improvement in placebo-controlled studies with short and long follow up

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of subjects with at least moderate improvement according to duration of follow up</td>
<td>4</td>
<td>793</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.37 [1.22, 1.55]</td>
</tr>
<tr>
<td>1.1 Short follow up</td>
<td>2</td>
<td>505</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.38 [1.21, 1.58]</td>
</tr>
<tr>
<td>1.2 Long follow up</td>
<td>2</td>
<td>288</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.36 [1.05, 1.75]</td>
</tr>
</tbody>
</table>

Comparison 6. Proportion of subjects with minor adverse events

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of subjects with minor adverse events</td>
<td>7</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>1.1 Proportion of subjects developing minor adverse events in placebo-controlled studies</td>
<td>4</td>
<td>953</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>2.17 [1.77, 2.66]</td>
</tr>
<tr>
<td>1.2 Proportion of subjects developing minor adverse events in active-controlled studies</td>
<td>3</td>
<td>442</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.46 [1.16, 1.83]</td>
</tr>
</tbody>
</table>
### Comparison 7. Proportion of subjects with major adverse events

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of subjects with major adverse events</td>
<td>10</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>1.1 Proportion of subjects having major adverse events in placebo-controlled studies</td>
<td>7</td>
<td>1336</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>2.67 [1.96, 3.63]</td>
</tr>
<tr>
<td>1.2 Proportion of subjects having major adverse events in active-controlled studies</td>
<td>3</td>
<td>432</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>2.31 [1.53, 3.50]</td>
</tr>
</tbody>
</table>

### Analysis 1.1. Comparison 1 Pain intensity using a 0-100 scale, Outcome 1 Weighted mean difference in pain intensity (scale 0-100).

**Review:** Tramadol for osteoarthritis

**Comparison:** Pain intensity using a 0-100 scale

**Outcome:** Weighted mean difference in pain intensity (scale 0-100)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Mean difference (SE)</th>
<th>Weight</th>
<th>Mean difference (IV, Fixed, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Babul 2004</td>
<td>-12.7 (3.81)</td>
<td>22.9 %</td>
<td>-12.70 [-20.17, -5.23]</td>
</tr>
<tr>
<td>Emkey 2004</td>
<td>-6.8 (3)</td>
<td>37.0 %</td>
<td>-6.80 [-12.68, -0.92]</td>
</tr>
<tr>
<td>Malonne 2004</td>
<td>-7.6 (2.88)</td>
<td>40.1 %</td>
<td>-7.60 [-13.24, -1.96]</td>
</tr>
</tbody>
</table>

**Subtotal (95% CI)**

Heterogeneity: $\chi^2 = 1.63, df = 2 (P = 0.44); I^2 = 0.0$

Test for overall effect: $Z = 4.65 (P < 0.00001)$

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Mean difference (SE)</th>
<th>Weight</th>
<th>Mean difference (IV, Fixed, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bianchi 2003</td>
<td>20 (9.51)</td>
<td>10.2 %</td>
<td>20.00 [1.36, 38.64]</td>
</tr>
<tr>
<td>Jensen 1994</td>
<td>-5 (3.2)</td>
<td>89.8 %</td>
<td>-5.00 [-1.27, 1.27]</td>
</tr>
</tbody>
</table>

**Subtotal (95% CI)**

Heterogeneity: $\chi^2 = 6.21, df = 1 (P = 0.04); I^2 = 84$

Test for overall effect: $Z = 0.81 (P = 0.42)$

Test for subgroup differences: $\chi^2 = 2.89, df = 1 (P = 0.09), I^2 = 65$

\[ -100 -50 0 50 100 \]

Favors treatment Favors control
## Analysis 2.1. Comparison 2 Proportion of subjects with at least moderate improvement, Outcome 1 Proportion of subjects with at least moderate improvement.

**Review:** Tramadol for osteoarthritis

**Comparison:** 2 Proportion of subjects with at least moderate improvement

**Outcome:** 1 Proportion of subjects with at least moderate improvement

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Tramadol</th>
<th>Control</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Tramadol</th>
<th>Control</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emkey 2004</td>
<td>54/91</td>
<td>34/71</td>
<td>19.8 % 1.24 [0.92, 1.67]</td>
<td>455</td>
<td>435</td>
<td>358</td>
<td>100.0 % 1.37 [1.22, 1.55]</td>
</tr>
<tr>
<td>Fleischmann 2001</td>
<td>28/62</td>
<td>18/64</td>
<td>9.2 % 1.61 [1.00, 2.59]</td>
<td></td>
<td></td>
<td></td>
<td>100.0 % 1.34 [1.13, 1.58]</td>
</tr>
<tr>
<td>Malonne 2004</td>
<td>66/85</td>
<td>67/112</td>
<td>30.0 % 1.30 [1.07, 1.57]</td>
<td></td>
<td></td>
<td></td>
<td>100.0 % 1.37 [1.22, 1.55]</td>
</tr>
<tr>
<td>Silverfield 2002</td>
<td>159/197</td>
<td>62/111</td>
<td>41.1 % 1.44 [1.21, 1.73]</td>
<td></td>
<td></td>
<td></td>
<td>100.0 % 1.37 [1.22, 1.55]</td>
</tr>
</tbody>
</table>

Subtotal (95% CI): 435 358 100.0 % 1.37 [1.22, 1.55]

Total events: 307 (Tramadol), 181 (Control)

Heterogeneity: Chi² = 1.53, df = 3 (P = 0.68); I² =0.0%

Test for overall effect: Z = 5.26 (P < 0.00001)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Tramadol</th>
<th>Control</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Tramadol</th>
<th>Control</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bird 1995</td>
<td>10/30</td>
<td>4/30</td>
<td>3.9 % 2.50 [0.88, 7.10]</td>
<td></td>
<td></td>
<td></td>
<td>100.0 % 1.34 [1.13, 1.58]</td>
</tr>
<tr>
<td>Jensen 1994</td>
<td>100/135</td>
<td>69/129</td>
<td>69.5 % 1.38 [1.15, 1.67]</td>
<td></td>
<td></td>
<td></td>
<td>100.0 % 1.34 [1.13, 1.58]</td>
</tr>
<tr>
<td>Pavelka 1998</td>
<td>28/54</td>
<td>27/54</td>
<td>26.6 % 1.04 [0.72, 1.50]</td>
<td></td>
<td></td>
<td></td>
<td>100.0 % 1.34 [1.13, 1.58]</td>
</tr>
</tbody>
</table>

Subtotal (95% CI): 219 213 100.0 % 1.34 [1.13, 1.58]

Total events: 138 (Tramadol), 100 (Control)

Heterogeneity: Chi² = 3.32, df = 2 (P = 0.19); I² =40%

Test for overall effect: Z = 3.36 (P = 0.000078)
### Analysis 3.1. Comparison 3 WOMAC index total score in placebo-controlled trials, Outcome 1 Weighted mean difference in WOMAC index total score in placebo-controlled trials.

**Review:** Tramadol for osteoarthritis  
**Comparison:** 3 WOMAC index total score in placebo-controlled trials  
**Outcome:** 1 Weighted mean difference in WOMAC index total score in placebo-controlled trials

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Difference in WOMAC (SE)</th>
<th>Difference in WOMAC Weight</th>
<th>Difference in WOMAC 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Babul 2004</td>
<td>-0.27 (0.094)</td>
<td>67.3 %</td>
<td>-0.27 [-0.45, -0.09 ]</td>
</tr>
<tr>
<td>Emkey 2004</td>
<td>-0.4 (0.202)</td>
<td>14.6 %</td>
<td>-0.40 [-0.80, 0.00 ]</td>
</tr>
<tr>
<td>Fleischmann 2001</td>
<td>-0.88 (0.37)</td>
<td>4.3 %</td>
<td>-0.88 [-1.61, -0.15 ]</td>
</tr>
<tr>
<td>Silverfield 2002</td>
<td>-0.47 (0.208)</td>
<td>13.8 %</td>
<td>-0.47 [-0.88, -0.06 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td>100.0 %</td>
<td>-0.34 [-0.49, -0.19 ]</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 3.16, df = 3 (P = 0.37), I² = 5%

Test for overall effect: Z = 4.45 (P < 0.00001)

Test for subgroup differences: Not applicable
**Analysis 4.1. Comparison 4 Pain intensity in placebo-controlled studies with short and long follow up, Outcome 1 Weighted mean difference in pain intensity in studies with short and long follow up**

Review: Tramadol for osteoarthritis

Comparison: 4 Pain intensity in placebo-controlled studies with short and long follow up

Outcome: 1 Weighted mean difference in pain intensity in studies with short and long follow up

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Mean difference (SE)</th>
<th>Weight</th>
<th>Mean difference (SE)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short follow up</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malonne 2004</td>
<td>-7.6 (2.88)</td>
<td>40.1%</td>
<td>-7.60 (-13.24, -1.96)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td>40.1%</td>
<td>-7.60 (-13.24, -1.96)</td>
<td></td>
</tr>
<tr>
<td><strong>Long follow up</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Babul 2004</td>
<td>-12.7 (3.81)</td>
<td>22.9%</td>
<td>-12.70 (-20.17, -5.23)</td>
<td></td>
</tr>
<tr>
<td>Emkey 2004</td>
<td>-6.8 (3)</td>
<td>37.0%</td>
<td>-6.80 (-12.68, -0.92)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td>59.9%</td>
<td>-9.06 (-13.68, -4.44)</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td>100.0%</td>
<td>-8.47 (-12.05, -4.90)</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable
Test for overall effect: Z = 2.64 (P = 0.0083)

Heterogeneity: Chi² = 1.48, df = 1 (P = 0.22); I² =32%
Test for overall effect: Z = 3.84 (P = 0.00012)

Heterogeneity: Chi² = 1.63, df = 2 (P = 0.44); I² =0.0%
Test for overall effect: Z = 4.65 (P < 0.00001)

Test for subgroup differences: Chi² = 0.15, df = 1 (P = 0.70), I² =0.0%
Analysis 5.1. Comparison 5 Proportion of subjects with improvement in placebo-controlled studies with short and long follow up, Outcome 1 Proportion of subjects with at least moderate improvement according to duration of follow up.

Review: Tramadol for osteoarthritis

Comparison: 5 Proportion of subjects with improvement in placebo-controlled studies with short and long follow up

Outcome: 1 Proportion of subjects with at least moderate improvement according to duration of follow up

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed</td>
<td></td>
<td>M-H,Fixed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>95% CI</td>
<td></td>
<td>95% CI</td>
</tr>
<tr>
<td>Short follow up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malonne 2004</td>
<td>66/85</td>
<td>67/112</td>
<td>30.0 %</td>
<td>1.30</td>
<td>[ 1.07, 1.57 ]</td>
</tr>
<tr>
<td>Silverfield 2002</td>
<td>159/197</td>
<td>62/111</td>
<td>41.1 %</td>
<td>1.44</td>
<td>[ 1.21, 1.73 ]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>282</strong></td>
<td><strong>223</strong></td>
<td></td>
<td><strong>71.0 %</strong></td>
<td><strong>1.38 [ 1.21, 1.58 ]</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long follow up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emkey 2004</td>
<td>54/91</td>
<td>34/71</td>
<td>19.8 %</td>
<td>1.24</td>
<td>[ 0.92, 1.67 ]</td>
</tr>
<tr>
<td>Fleischmann 2001</td>
<td>28/62</td>
<td>18/64</td>
<td>9.2 %</td>
<td>1.61</td>
<td>[ 1.00, 2.59 ]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>153</strong></td>
<td><strong>135</strong></td>
<td></td>
<td><strong>29.0 %</strong></td>
<td><strong>1.36 [ 1.05, 1.75 ]</strong></td>
</tr>
</tbody>
</table>

Total (95% CI) 435 358 100.0 % 1.37 [ 1.22, 1.55 ]

**Heterogeneity:** Chi$^2 = 0.66$, df = 1 ($P = 0.42$); $I^2 = 0.0$

**Test for overall effect:** Z = 4.85 ($P < 0.00001$)

**Heterogeneity:** Chi$^2 = 0.83$, df = 1 ($P = 0.36$); $I^2 = 0.0$

**Test for overall effect:** Z = 2.34 ($P = 0.019$)

**Heterogeneity:** Chi$^2 = 1.53$, df = 3 ($P = 0.68$); $I^2 = 0.0$

**Test for overall effect:** Z = 5.26 ($P < 0.00001$)
## Analysis 6.1. Comparison 6 Proportion of subjects with minor adverse events, Outcome 1 Proportion of subjects with minor adverse events.

### Review: Tramadol for osteoarthritis

### Comparison: 6 Proportion of subjects with minor adverse events

### Outcome: 1 Proportion of subjects with minor adverse events

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 Proportion of subjects developing minor adverse events in placebo-controlled studies</strong></td>
<td>Babul 2004</td>
<td>80/124</td>
<td>39/122</td>
<td>47.8 %</td>
<td>2.02 [ 1.51, 2.70 ]</td>
</tr>
<tr>
<td></td>
<td>Emkey 2004</td>
<td>20/153</td>
<td>6/154</td>
<td>7.3 %</td>
<td>3.36 [ 1.39, 8.12 ]</td>
</tr>
<tr>
<td></td>
<td>Malonne 2004</td>
<td>50/51</td>
<td>23/41</td>
<td>31.0 %</td>
<td>1.75 [ 1.33, 2.30 ]</td>
</tr>
<tr>
<td></td>
<td>Silverfield 2002</td>
<td>48/197</td>
<td>9/111</td>
<td>14.0 %</td>
<td>3.01 [ 1.53, 5.89 ]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>525</td>
<td>428</td>
<td>100.0 %</td>
<td>2.17 [ 1.77, 2.66 ]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 198 (Treatment), 77 (Control)

Heterogeneity: Chi² = 4.47, df = 3 (P = 0.21); I² = 33%

Test for overall effect: Z = 7.38 (P < 0.00001)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2 Proportion of subjects developing minor adverse events in active-controlled studies</strong></td>
<td>Bird 1995</td>
<td>18/34</td>
<td>28/36</td>
<td>38.2 %</td>
<td>0.68 [ 0.47, 0.98 ]</td>
</tr>
<tr>
<td></td>
<td>Jensen 1994</td>
<td>75/135</td>
<td>41/129</td>
<td>58.9 %</td>
<td>1.75 [ 1.30, 2.35 ]</td>
</tr>
<tr>
<td></td>
<td>Pavelka 1998</td>
<td>12/54</td>
<td>2/54</td>
<td>2.8 %</td>
<td>6.00 [ 1.41, 25.54 ]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>223</td>
<td>219</td>
<td>100.0 %</td>
<td>1.46 [ 1.16, 1.83 ]</td>
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</tr>
</tbody>
</table>

Total events: 105 (Treatment), 71 (Control)

Heterogeneity: Chi² = 22.17, df = 2 (P = 0.00002); I² = 91%

Test for overall effect: Z = 3.25 (P = 0.0011)
Analysis 7.1. Comparison 7 Proportion of subjects with major adverse events, Outcome 1 Proportion of subjects with major adverse events.

Review: Tramadol for osteoarthritis

Comparison: 7 Proportion of subjects with major adverse events

Outcome: 1 Proportion of subjects with major adverse events

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>1 Proportion of subjects having major adverse events in placebo-controlled studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Babul 2004</td>
<td>33/124</td>
<td>9/122</td>
<td>17.9 %</td>
<td>3.61 [ 1.80, 7.22 ]</td>
<td></td>
</tr>
<tr>
<td>Bianchi 2003</td>
<td>2/8</td>
<td>0/10</td>
<td>0.9 %</td>
<td>6.11 [ 0.33, 111.71 ]</td>
<td></td>
</tr>
<tr>
<td>Emkey 2004</td>
<td>20/153</td>
<td>6/154</td>
<td>11.8 %</td>
<td>3.36 [ 1.39, 8.12 ]</td>
<td></td>
</tr>
<tr>
<td>Fleischmann 2001</td>
<td>14/63</td>
<td>10/66</td>
<td>19.3 %</td>
<td>1.47 [ 0.70, 3.06 ]</td>
<td></td>
</tr>
<tr>
<td>Malonne 2004</td>
<td>24/51</td>
<td>2/41</td>
<td>4.4 %</td>
<td>9.65 [ 2.42, 38.45 ]</td>
<td></td>
</tr>
<tr>
<td>Schnitzer 1999</td>
<td>25/114</td>
<td>16/122</td>
<td>30.5 %</td>
<td>1.67 [ 0.94, 2.97 ]</td>
<td></td>
</tr>
<tr>
<td>Silverfield 2002</td>
<td>25/197</td>
<td>6/111</td>
<td>15.2 %</td>
<td>2.35 [ 0.99, 5.55 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>710</td>
<td>626</td>
<td>100.0 %</td>
<td>2.67 [ 1.96, 3.63 ]</td>
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<tr>
<td>Total events: 143 (Treatment), 49 (Control)</td>
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<tr>
<td>Heterogeneity: Ch² = 9.81, df = 6 (P = 0.13); I² =39%</td>
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<tr>
<td>Test for overall effect: Z = 6.26 (P &lt; 0.00001)</td>
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<tr>
<td>2 Proportion of subjects having major adverse events in active-controlled studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bird 1995</td>
<td>9/30</td>
<td>11/30</td>
<td>41.8 %</td>
<td>0.82 [ 0.40, 1.68 ]</td>
<td></td>
</tr>
<tr>
<td>Jensen 1994</td>
<td>48/135</td>
<td>14/129</td>
<td>54.4 %</td>
<td>3.28 [ 1.90, 5.65 ]</td>
<td></td>
</tr>
<tr>
<td>Pavelka 1998</td>
<td>5/54</td>
<td>1/54</td>
<td>3.8 %</td>
<td>5.00 [ 0.60, 41.39 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>219</td>
<td>213</td>
<td>100.0 %</td>
<td>2.31 [ 1.53, 3.50 ]</td>
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<tr>
<td>Total events: 62 (Treatment), 26 (Control)</td>
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<tr>
<td>Heterogeneity: Ch² = 10.06, df = 2 (P = 0.01); I² =80%</td>
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</tr>
<tr>
<td>Test for overall effect: Z = 3.99 (P = 0.000067)</td>
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</tr>
</tbody>
</table>

Favors treatment | Favors control
Appendix 1. MEDLINE search strategy

1. exp osteoarthritis/
2. osteoarthr$.tw.
3. degenerative arthritis.tw.
4. tramadol.tw or tramadol.sh
5. ultracet.tw or ultracet.nm
6. or/1-5
7. randomized controlled trial.pt.
8. controlled clinical trial.pt.
9. randomized controlled trials.sh.
10. random allocation.sh.
11. double blind method.sh.
12. single-blind method.sh.
13. clinical trial.pt.
14. clinical trials.sh.
15. clinical trial.tw.
16. ((singl$ or doubl$ or trebl$ or tripl$) and (mask$ or blind$)).tw.
17. placebos.sh.
18. placebo$.tw.
19. random$.tw.
20. Research Design/
22. evaluation studies.sh.
23. follow-up studies.sh.
24. prospective studies.sh.
25. control$.tw.
26. prospectiv$.tw.
27. volunteer$.tw.
28. or/7-27
29. (animal not human).mp.
30. 28 not 29
31. and/6-30

What's New

Last assessed as up-to-date: 22 May 2006.

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
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<td>10 November 2008</td>
<td>Amended</td>
<td>Converted to new review format.</td>
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HISTORY
Protocol first published: Issue 4, 2005
Review first published: Issue 3, 2006

CONTRIBUTIONS OF AUTHORS
M. Soledad Cepeda: Conceived and designed the study, performed the literature search, contacted the authors of original clinical trials, performed the analysis and wrote the manuscript.
Francisco Camargo: Co-designed the study, appraised the clinical study reports and revised the final version of the manuscript.
Carlota Zea: Co-designed the study, appraised the clinical study reports and revised the final version of the manuscript.
Lina Valencia: Co-designed the study, generated the database for analysis and revised the final version of the manuscript.

DECLARATIONS OF INTEREST
None known

INDEX TERMS
Medical Subject Headings (MeSH)
Acetaminophen [therapeutic use]; Analgesics, Non-Narcotic [*therapeutic use]; Osteoarthritis [*drug therapy]; Randomized Controlled Trials as Topic; Tramadol [*therapeutic use]

MeSH check words
Humans