Tramadol versus placebo for chronic pain: a systematic review with meta-analysis and trial sequential analysis

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Abstract

Objectives The objective of our study was to assess the benefits and harms of tramadol vs placebo in adults with chronic pain.

Design The research method was a systematic review of randomised clinical trials with meta-analysis. The review followed the Trial Sequential Analysis and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Data sources The Cochrane Library, MEDLINE, Embase, Science Citation Index and BIOSIS were searched for trials published from inception to 6 February 2025.

Eligibility criteria for selecting studies Studies were eligible for inclusion if they were published and unpublished randomised clinical trials comparing tramadol vs placebo in adults with any type of chronic pain. Risk of bias was assessed according to the Cochrane Handbook for Systematic Reviews of Interventions.

Main outcome measures The main outcome measures were pain level, adverse events, quality of life, dependence, abuse and depressive symptoms.

Results We included 19 randomised placebo-controlled clinical trials enrolling 6506 participants. All outcome results were at high risk of bias. Meta-analysis and Trial Sequential Analysis showed evidence of a beneficial effect of tramadol on chronic pain (mean difference numerical rating scale (NRS) −0.93 points; 97.5% CI −1.26 to −0.60; p<0.0001; low certainty of evidence). However, the effect size was below our predefined minimal important difference of 1.0 point on NRS. Beta binomial regression showed evidence of a harmful effect of tramadol on serious adverse events (OR 2.13; 97.5% CI 1.29 to 3.51; p=0.001; moderate certainty of evidence), mainly driven by a higher proportion of cardiac events and neoplasms. It was not possible to conduct a meta-analysis of the quality of life due to a lack of data. Meta-analysis and Trial Sequential Analysis showed that tramadol increased the risk of several non-serious adverse events including nausea (number needed to harm (NNH) 7), dizziness (NNH 8), constipation (NNH 9), and somnolence (NNH 13) (all very low certainty of evidence).

Conclusion Tramadol may have a slight effect on reducing chronic pain levels (low certainty of evidence) while likely increasing the risk of both serious (moderate certainty of evidence) and non-serious adverse events (very low certainty of evidence). The potential harms associated with tramadol use for pain management likely outweigh its limited benefits.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Tramadol is widely prescribed for chronic pain and considered safer than other opioids. Prior reviews have been condition-specific or grouped opioids, leaving tramadol's overall benefits and harms unclear.

WHAT THIS STUDY ADDS

⇒ This first comprehensive systematic review, with meta-analysis and trial sequential analysis, finds low-certainty evidence that tramadol may reduce chronic pain below the minimal important difference threshold. Moderate-certainty evidence shows it likely increases serious adverse events, particularly cardiac events.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Given the limited analgesic benefits and increased risk of harm, tramadol use for chronic pain should be reconsidered, with preference for safer alternatives and further high-quality trials to clarify its risk–benefit profile.

Introduction

Pain is the most frequently reported symptom in the general population and in clinical settings.[1–3] Pain is one of the most common causes of temporary or permanent work disability and is associated with reduced health-related quality of life, contributing

to psychosocial distress, insomnia and depressive symptoms.[4–12] Tramadol (tramadol hydrochloride) is a widely used dual-action analgesic opioid with monoaminergic properties.[13] According to manufacturer records, from 1990 to 2009, 11 758 million defined daily doses (DDD) of tramadol (1 DDD=300 mg) were consumed worldwide.[14] Tramadol is indicated for the treatment of moderate to severe pain.[15 16] It is available globally and is used for both acute (eg, postoperative, trauma) and chronic pain (including cancer and non-cancer pain).[14 16–21] Tramadol is recommended in several medical guidelines for pain management,[22] and the WHO guidelines recommend it as a step 2 analgesic for cancer pain relief.[23]

Tramadol use has surged in recent years[24] and is now among the most commonly prescribed opioids in the US.[25] This increase is likely driven by its perceived benefits, including what physicians may view as a favourable adverse effects profile and the widespread belief that it is safer and less addictive than other short-acting opioids.[26] However, evidence indicates that tramadol carries a comparable or even greater risk of transitioning from acute to prolonged use compared with other short-acting opioids.[27]

Although tramadol has been included in previous systematic reviews, these have either assessed opioids as a class or focused on specific conditions. Busse *et al,* conducted a systematic review on opioids for chronic non-cancer pain, which included trials with tramadol as the intervention but did not report drug-specific outcomes.[28] Toupin-April *et al*, evaluated tramadol for osteoarthritis[29] and Duehmke *et al,* assessed tramadol's use for neuropathic pain.[13] However, these reviews were condition-specific and limited in scope, and none provided a comprehensive evaluation of tramadol's efficacy and safety across chronic pain conditions.

To our knowledge, this is the first systematic review related to the usage of tramadol for any type of chronic pain with a thorough investigation of adverse events.

Objective

The objective of this review was to evaluate the beneficial and harmful effects of tramadol compared with placebo in adults with chronic pain.

Methods

Our protocol, published before the literature search, described our predefined methodology in detail.[30] In short, our systematic review aimed to assess the benefits and harms of tramadol vs placebo in adults with chronic pain.

The literature review followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[31 32] We included all randomised clinical trials comparing tramadol vs placebo for patients with chronic pain. Two authors (JB, MM) independently searched for trials published from inception to 6 February 2025 (supplement 1–3). Randomised trials were included regardless of design, setting, publication status, year and reporting of outcomes. Adult participants with any type of chronic pain, that is, chronic neuropathic pain, chronic nociceptive pain, chronic cancer-related pain or any other types of chronic pain (as defined by the trialists) were included. Five authors (JB, MM, EI, JJP and YB) working in pairs independently extracted data and assessed the risks of bias in the included trials. We contacted trial authors by email if data were unclear or missing. Disagreements were resolved through discussion or consulting a third author (JCJ).

Outcomes

Primary outcomes

- Pain level assessed on visual analogue scale (VAS) or numerical rating scale (NRS)
- Serious adverse events (according to International Committee of Harmonization-Good Clinical Practice (ICH-GCP))[33]
- Quality of life (any valid continuous scale)

Secondary outcomes

- Non-serious adverse events (according to ICH-GCP)[33]
- Depressive symptoms (eg, Hamilton Depression Rating Scale)
- Dependence (as defined by trialists)
- Abuse (as defined by trialists)

For all outcomes, we used the trial results reported at maximal follow-up.

During data extraction, we extracted data on serious adverse events and non-serious adverse events. We extracted data on the overall proportion of participants experiencing an event and the proportion of participants experiencing individual adverse events. Serious adverse events were defined according to the ICH-GCP recommendations.[33] If the trial used a different definition, the events were included as serious adverse events if the trialists either (1) used the term 'serious adverse event' but did not refer to ICH-GCP or (2) reported the proportion of participants with an event we considered to fulfil the ICH-GCP definition (eg, myocardial infarction or hospitalisation). Non-serious adverse events were defined as any adverse event not fulfilling the criteria for serious adverse events.[33] When all individual adverse events had been extracted, they were grouped into categories (eg,'vascular disorders') in a blinded manner. If one trial reported more individual non-serious adverse events in the same category, the event with the highest proportion was used. Data on adverse events were extracted from primary publications, secondary publications and study registries. If the trials presented only an overall count of adverse events combined in both groups, the data were not included.

Patient and public involvement

We conducted email correspondence with several patient associations in Denmark to select the most patient-relevant outcomes. The associations were the Danish Diabetes Association, the Danish Rheumatism Association, the Danish Multiple Sclerosis Society and the Danish Cancer Society.

Sub-group analyses

We performed several subgroup analyses when analysing the primary outcomes (pain level assessed on visual analogue scale (VAS) or numerical rating scale (NRS), serious adverse event and quality of life).[30]

1. Trials at a high risk of bias/ trials at a low risk of bias
2. Trials at risk of vested interests/ trials at no risk of vested interests
3. Types of chronic pain
4. Dosage of tramadol used (below median/ median or above)
5. Duration of tramadol administration (below median/ median or above)
6. Age of participants: 18 to 59 years/ 60 to 79 years/ above 80 years

For the daily dosage of tramadol administered, we used the stated fixed dose for trials with prespecified regimens, treating each intervention arm separately where dosing differed.

In studies employing flexible titration to a maximum dose, we extracted the mean dose received during the double-blind

phase—calculated from the authors' own description of the doses administered and the number of participants at each level—thereby deriving a mean cumulative daily dose for subgroup allocation.

Assessment of risk of bias

We assessed the risks of bias according to the Cochrane Handbook for Systematic Reviews of Interventions 5.1.[34] (See supplement 4.1' for more details).

Overall risk of bias was assessed in the following manner:

- Low risk of bias: The trial was classified at overall 'low risk of bias' only if all of the bias domains were classified at 'low risk of bias'.
- High risk of bias: The trial was classified at 'high risk of bias' if any of the bias risk domains were classified at 'unclear' or 'high risk of bias'.

Assessment of statistical and clinical significance

All meta-analyses were conducted using STATA version 18.1.[35] The intervention effects were evaluated using both random effects meta-analyses, following the Hartung-Knapp and Sidik-Jonkman method,[36] and fixed effect meta-analyses, employing the inverse-variance approach.[37] The random effects estimate was primarily reported, while the fixed effects estimate was presented as part of a sensitivity analysis.[38] Beta-binomial regression was employed as the meta-analytic method in instances where zero events or rare events were encountered. The beta binomial models were frequentist (no priors) and incorporated random effects with study level beta distributions. Clustered trials were analysed within the Hartung–Knapp and Sidik-Jonkman framework. Double zero events were not included in the beta-binomial regression. To address random errors in the analysis of primary outcomes, the threshold for statistical significance was adjusted in accordance with the procedure proposed by Jakobsen *et al*.[38]

We converted all pain measures to NRS (VAS scores were divided by 10), giving a value between 0 and 10 points.[39 40]

Given the inclusion of three primary outcomes, a p value threshold of 0.025 was employed for statistical significance.[38] For secondary outcomes, which were considered exploratory, a p value threshold of 0.05 was used.[38] Trial sequential analysis (TSA) was applied to mitigate the risks associated with random errors.[41] We used Grading Recommendations Assessment Development Evaluation (GRADE) to assess the certainty of evidence.[42]

We assessed imprecision by TSA and by methods and recommendations described in chapter 8 (Sect. 8.5) and chapter 12 of the Cochrane Handbook for Systematic Reviews of Interventions[34 43] using the GRADEpro software. We downgraded imprecision in GRADE by two levels if the accrued number of participants was below 50% of the diversity-adjusted required information size (DARIS) and one level if it was between 50% and 99% of DARIS. We did not downgrade if the cumulative Z-curve crossed the monitoring boundaries for benefit, harm, or futility, or DARIS was reached.

A systematic review conducted by Olsen *et al*, on minimal important difference (MID) in patients with chronic pain, and the results suggested a MID of 23 mm on VAS (IQR 12 to 39 mm) when using the within-patient anchor-based method, while the median in studies using the sensitivity and specificity based method was 20 mm on VAS (IQR 15–30 mm).**44**

In this systematic review, we chose a minimal important difference equivalent of 1.0 point on the numerical rating scale. Thereby, we are in close agreement with the lower IQR boundary of 12 mm or 1.2 cm of previous findings.[44] This MID is considered lenient compared with a recent comparable systematic review,[45] and we thereby avoid missing a clinically important effect.

Assessment of heterogeneity

We primarily investigated forest plots visually to assess heterogeneity.

We then measured heterogeneity by the estimate of Tau^2 and the proportion of total variation due to between-study variability by the I^2-statistic. We investigated the reasons for heterogeneity through subgroup analyses.

Assessment of reporting biases

We used funnel plots to assess reporting bias if 10 or more trials were included. We visually inspected the funnel plots to assess the risk of bias. From this information, we assessed the possible reporting bias. For dichotomous outcomes, we tested asymmetry with the Harbord test[46] if τ^2 was less than 0.1 and with the Rücker test if τ^2 was more than 0.1. For continuous outcomes, we used the regression asymmetry test.[47]

Differences between protocol and review

On the editors' and peer reviewers' recommendation, we reported meta-analysis results using random-effects models rather than the previously planned 'most conservative' estimate. This was due to the included trials exhibiting considerable clinical heterogeneity.

Results

We included 19 randomised placebo-controlled clinical trials enrolling 6506 participants with chronic pain. Five trials investigated tramadol on neuropathic pain,[48–52] nine trials on osteoarthritis,[53–61] four trials on chronic low back pain[62–65] and one trial on fibromyalgia.[66] All trials except two[48 62] were at high risk of bias(supplement 4).

See figure 1 for PRISMA flow diagram of included trials.

The mean age of the participants was 58 years ranging from 47 years[63] to 69 years.[51] All 19 trials compared tramadol vs placebo with all trials using peroral tramadol as the administration form, except one trial which used topical administration.[53] Treatment duration ranged between 2 weeks[61] and 16 weeks[62] (see table 1 for more details). Missing data constituted ≤5% of the overall data, and we deemed the impact of missing data to be low; therefore, we did not conduct our predefined sensitivity analyses.

Chronic pain

Thirteen trials randomising 3455 participants assessed chronic pain levels using either VAS (eight trials)[49 53 54 61 63 65–67] or NRS (five trials).[50 51 55 57 60] Follow-up duration for trials assessing chronic pain levels ranged between 3 weeks[53] and 15 weeks.[65]

Meta-analysis showed evidence of a beneficial effect of tramadol (mean difference NRS −0.93 points; 97.5% CI −1.26 to −0.60; p<0.0001; figure 2, figure S5.1), but the effect size was below our predefined MID of 1.0 point on the NRS.[30] Visual inspection of the forest plot, I^2-statistic (I^2=67.8%) and Tau^2 statistic (τ^2=0.16; τ=0.4) showed no clear signs of heterogeneity. TSA showed the meta-analysis was sufficiently powered (figure S5.2). We assessed this outcome result at high risk of bias, and the certainty of the evidence was low (table 2, supplement 8).

The subgroup analyses comparing different types of chronic pain (p=0.22) (figure S5.3), dosages of tramadol administration (p=0.31) (figure S5.4), durations of tramadol administration (p=0.84) (figure S5.5), and different age groups (p=0.79) (figure S5.6) did not explain the heterogeneity.

All remaining planned subgroup analyses were not possible due to a lack of relevant data.

The funnel plot showed signs of small-study effects (figure S5.7).

Assuming a normal distribution of treatment effects and based on the estimated pooled SD derived from the individual studies, approximately 48.6% of participants receiving tramadol achieved ≥1.0 NRS point pain reduction (our MID) vs 41.1% on placebo, indicating that an additional 7.5% of patients experienced meaningful pain relief with tramadol compared with placebo.

Serious adverse events

Eight trials randomising 4583 participants reported the proportion of serious adverse events.[55–58 62 63 67] Follow-up duration for trials assessing serious adverse events ranged between 7 weeks[63] and 16 weeks.[62]

Beta binomial regression showed evidence of a harmful effect of tramadol (OR 2.12; 97.5% CI 1.29 to 3.51; p=0.001; figure S6.1), mainly driven by a higher proportion of 'cardiac events' (eg, chest pain, coronary artery disease, and congestive heart failure) and 'neoplasm' events (eg, prostate cancer, breast cancer, and thyroid neoplasm) in the tramadol groups (online supplemental file S2). We assessed this outcome result at high risk of bias, and the certainty of evidence was moderate (table 2, supplement 8).

One trial[55] reported data on seizures with 1 in 432 participants receiving tramadol and 0 in 214 participants receiving placebo experiencing a seizure. Another trial[57] reported no seizures in either group. During the analyses, data on seizures were analysed along with data on Meniere's disease in the overall category named 'Vestibular and neurological disorders' (online supplemental file S2).

No evidence of differences was found when analysing each specific serious adverse event separately (online supplemental file S2).

Quality of life

Five trials assessing tramadol's impact on quality of life yielded mixed results. Two trials found improvements in quality of life measures,[48 50] while three trials reported no significant differences between tramadol and placebo groups.[49 56 59] Meta-analysis was not conducted due to the substantial heterogeneity among the scales utilised in the trials, which measured different aspects of quality of life.

Non-serious adverse events

Fourteen trials randomising 5070 participants reported non-serious adverse events.[48 49 51 52 54 56 58–62 64–66] Follow-up duration for trials assessing non-serious adverse events ranged between 4 weeks[52 61] and 16 weeks.[62] See figure 3 for the forest plot of the meta-analysis of non-serious adverse events. The certainty of evidence was very low (table 2, supplement 8).

Meta-analysis indicated a harmful effect of tramadol regarding 'nausea' RR 2.85; 95% CI 2.08 to 3.92 (number needed to harm (NNH) 7); 'dizziness' 2.98; 95% CI 2.15 to 4.12 (NNH 8); 'constipation' RR 3.12; 95% CI 2.04 to 4.79 (NNH 9); 'somnolence' 4.40; 95% CI 2.27 to 8.53 (NNH 13); 'pruritus' RR 4.10; 95% CI 1.52 to 11.03 (NNH 17); 'vomiting' RR 4.41; 95% CI 2.17 to 8.97 (NNH 18); 'flushing' RR 2.16; 95% CI 1.34

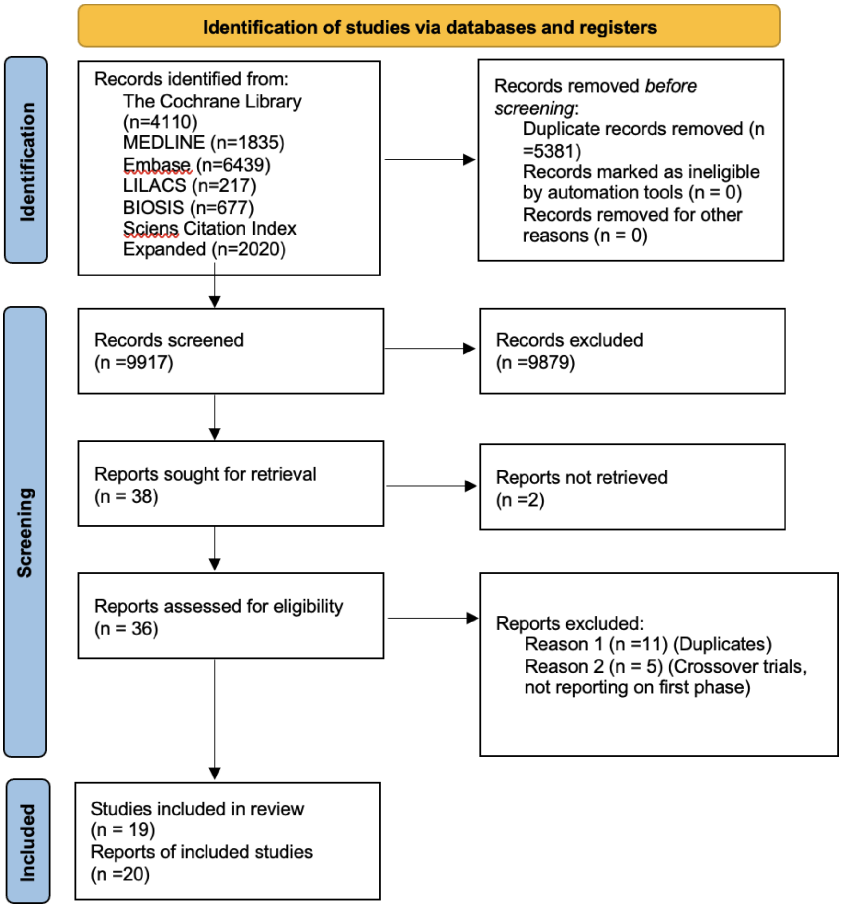

Figure 1 PRISMA flow diagram.

Table 1 Summary and characteristics of included trials

Trial	Sample size calculation / number of participants included / number of participants in primary outcome analyses	Medical condition	Mean age (years)	Proportion males (%)	Type of tramadol administration	Treatment duration in weeks	Follow-up period in weeks
Arbaiza 2007	36/36/36	Neuropathic pain (in cancer participants)	50	40%	Peroral tramadol	6.5	6.5
Babul 2003	140/246/246	Osteoarthritis	61	40%	Peroral tramadol	12	12
Boureau 2003	140/127/125	Post-herpetic neuralgia (neuropathic pain)	66	30%	Peroral tramadol	6	6.15
Burch 2007	440/646/589	Osteoarthritis	63	40%	Peroral tramadol	12	12
Delemos 2011	800/808/799	Osteoarthritis	60	40%	Peroral tramadol	12	12
Fleischmann 2001	118/129/129	Osteoarthritis	62.5	35%	Peroral tramadol	13	13
Fishman 2009	520/552/552	Osteoarthritis	60	35%	Peroral tramadol	12	12
Gana/Kosinski 2006	1000/1020/1011	Osteoarthritis	58	40%	Peroral tramadol	12	13
Harati 1998	112/131/131	Diabetic neuropathic pain	59	60%	Peroral tramadol	6	6
Kawai 2022	160/160/159	Osteoarthritis	67	35%	Peroral tramadol	4	10
Kawai 2023	160/173/171	Post-herpetic neuralgia (neuropathic pain)	69	45%	Peroral tramadol	4	11
Malonne 2004	? / 231/230	Osteoarthritis	66.8	27%	Peroral tramadol	2	4
Markman 2020	1017/1011/1011	Chronic low back pain	48.6	43%	Peroral tramadol	16	16
Norrbrink 2009	? / 35/35	Neuropathic pain (spinal cord injury)	51.3	77%	Peroral tramadol	4	4
Russel 2000	60/69/69	Fibromyalgia	48.8	6%	Peroral tramadol	6	9
Schnitzer 2000	240/254/254	Chronic low back pain	47.1	50%	Peroral tramadol	4	7
Shahram 2024	? / 60/60	Osteoarthritis	62	23%	Topical tramadol	3	3
Überall 2012	240/240/217	Chronic low back pain	58.4	42%	Peroral tramadol	4	5.3
Vorsanger 2008	360/386/384	Chronic low back pain	47.8	50%	Peroral tramadol	12	15

to 3.48 (NNH 18); 'dry mouth' RR 2.99; 95% CI 1.63 to 5.50 (NNH 19); 'insomnia' RR 2.25; 95% CI 1.36 to 3.70 (NNH 21); 'fatigue' RR 3.02; 95% CI 1.73 to 5.28 (NNH 23); 'increased sweating' RR 3.95; 95% CI 1.42 to 10.95 (NNH 26); 'nervousness' RR 4.51; 95% CI 1.08 to 18.79 (NNH 28); and 'anorexia' RR 8.07; 95% CI 1.59 to 40.92 (NNH 36) (online supplemental file S3).

No evidence of differences was found when analysing each specific remaining non-serious adverse event separately (online supplemental file S3).

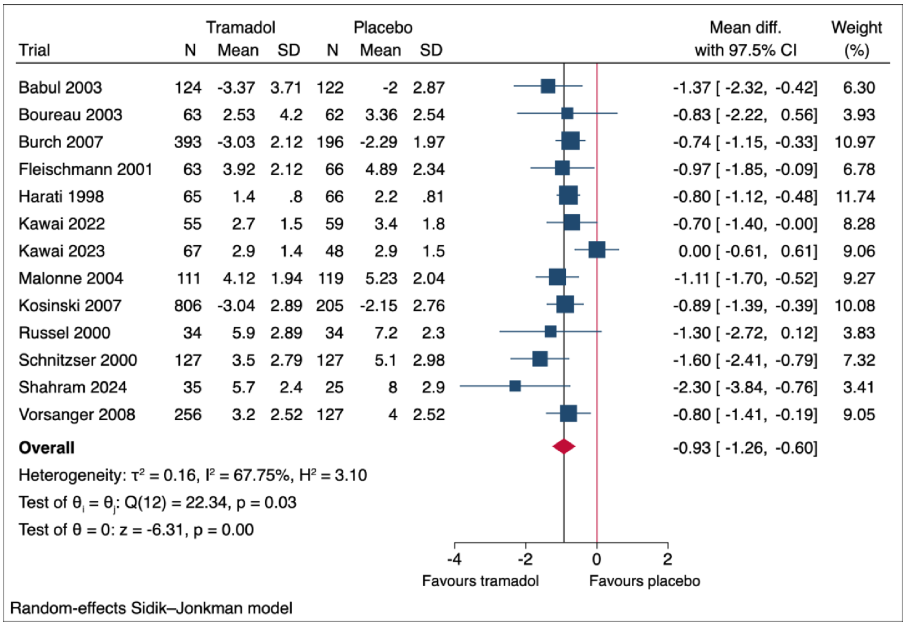

Figure 2 Forest plot of the meta-analysis of chronic pain with 97.5% CI.

Table 2 Summary of findings table with explanations

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tramadol	Placebo	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Pain score (assessed with: NRS)												
13	Randomised trials	Serious*	Not serious	Not serious	Not serious†	Publication bias strongly suspected‡	2199	1256	–	MD **0.93 NRS lower**(1.22 lower to 0.64 lower)	⨁⨁◯◯ Low*†‡	CRITICAL
Serious adverse events (assessed with: Number of participants with at least one event)												
8	Randomised trials	Serious*	Not serious	Not serious	Serious§	Strong association¶	130/3050 (4.3%)	26/1533 (1.7%)	**OR 2.12** (1.37 to 3.29)	**18 more per 1.000**(from 6 more to 37 more)	⨁⨁⨁◯ Moderate*§¶	CRITICAL
Non-serious adverse events (assessed with: Number of participants with at least one event)												
14	Randomised trials	Serious*	Serious**	Not serious	Not serious†	Publication bias strongly suspected‡	1975/3249 (60.8%)	739/1821 (40.6%)	**RR 1.40** (1.15 to 1.70)	**162 more per 1.000** (from 61 more to 284 more)	⨁◯◯◯ Very low*†‡**	IMPORTANT

*Downgraded one level for risk of bias due to Incomplete outcome data or selective reporting. Several trials excluded patients during open-label run-in phases, leading to potential overestimation of treatment effects.

†The cumulative Z-curve crosses the monitoring boundaries for benefit, harm, or futility, or DARIS is reached. Therefore, we did not downgrade.

‡Downgraded one level for publication bias because visual inspection of funnel plots and Harbord regression tests suggested asymmetry indicating small study effects.

§Downgraded one level for imprecision due to wide CIs reflecting uncertainty about the magnitude of harm.

¶Upgraded one level for strong association due to large effect size (OR ›2).

**Downgraded one level for inconsistency because of moderate to high heterogeneity (I^2 › 50%), prediction interval including no difference and Tau2 statistic ($\tau 2 = 0.1$; $\tau = 0.32$).

MD, mean difference; NRS, numerical rating scale; RR, risk ratio.

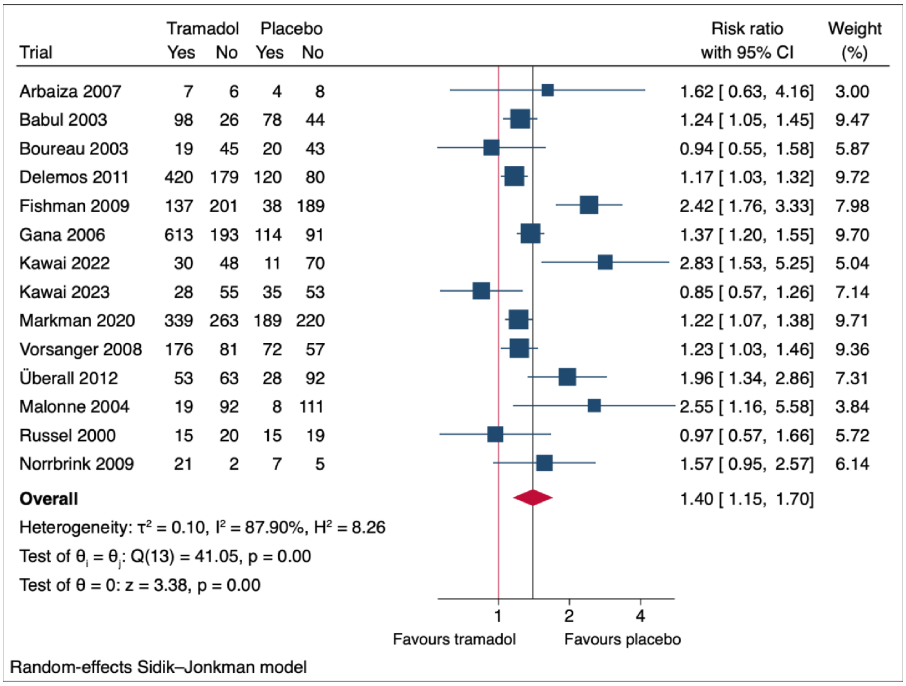

Figure 3 Forest plot of the meta-analysis of non-serious adverse events with 95% CI.

Depressive symptoms, dependence and abuse

Two trials assessed tramadol's effect on depression, with no significant differences observed between tramadol and placebo groups.[48 52]

Three trials examined dependence-related effects of tramadol, identifying increased symptoms following treatment discontinuation. This was measured using primarily the physical dependence questionnaire (PDQ).[56 59 65]

Two trials assessed abuse potential and found no significant differences observed between tramadol and placebo groups.[56 65]

Discussion

The objective of this review was to systematically evaluate the beneficial and harmful effects of tramadol compared with placebo for any type of chronic pain. Nineteen randomised placebo-controlled clinical trials randomising 6506 participants were included. All outcome results were at high risk of bias. Tramadol may slightly reduce chronic pain levels, but the effect size was below our predefined MID. Tramadol appeared to increase the risks of serious adverse events, mainly driven by a higher proportion of cardiac events and neoplasms. 'Neoplasms' were defined as the emergence of newly diagnosed cancer disease during the follow-up period of the trial. Trials reporting on neoplasms did not exceed 12 weeks of follow-up. A causality between the use of tramadol and the risk of new cancer disease, based on our results, is questionable at this point. Tramadol increased the risks of several non-serious adverse events, including nausea, dizziness, constipation and somnolence.

Our review has several strengths. First, to our knowledge, this is the first systematic assessment of tramadol's adverse effects. The incidences of serious adverse events, including cardiac events, have been mostly described qualitatively in previous systematic overviews concerning the safety profile of tramadol.[68 69] Second, compared with earlier reviews on chronic pain, our analysis includes more trials, enhancing statistical power, precision and the robustness of our findings. Third, the methodology was predefined and described comprehensively and in detail in our published protocol.[30] Fourth, to mitigate the risk of random errors, we employed TSA[41] and adjusted the thresholds for statistical significance accordingly.[38] In frequentist statistical analyses on accumulating data, it has been recommended since the 1950s that such analyses should take into account the number of repeated analyses.[70] TSA can control the risks of type I and type II errors in meta-analyses.[41] With the number of trials as well as the large number of meta-analyses and systematic reviews on tramadol, the risks of type I errors are substantial.

Fifth, we systematically assessed the risk of bias in all included trials to evaluate the potential for systematic errors[71 72] and applied our 8-step procedure to determine whether the statistical and clinical significance thresholds were met.[38] Sixth, we predefined MIDs for pain outcomes to evaluate the clinical relevance of our findings for patients.[30] Pain level thresholds for chronic pain were established based on Olsen *et al*.[44] The MID of 1.0 point on the NRS is relatively lenient compared with previous reviews; this predefined lenient threshold minimises the risk of incorrectly dismissing tramadol's beneficial effects on chronic pain.[13 45 73 74]

Our review also had some limitations. All included trials were at high risk of bias except two, which increasesd the likelihood that our findings overestimate the beneficial effects and underestimate the harmful effects of tramadol (online supplemental file 4).[75–81] Furthermore, we found that several trials did not report the specific type of serious adverse events, which may be why no statistically significant difference was found when investigating the individual events. Follow-up length also varied between trials, especially concerning the outcomes 'chronic pain' and 'non-serious adverse events'. Although it remains a limitation of the results, this was partially accommodated by our predefined subgroup analyses.

To ensure relevant outcomes for the patient groups addressed in our review, we consulted several Danish patient organisations and selected the outcomes they considered most important. However, the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) has recommended several

patient-important outcomes in patients with chronic pain.[82 83] As it is not feasible to include an unlimited number of outcomes, we had to prioritise after thorough discussion within the author group, which inevitably is a limitation of this systematic review.

Approximately 60 million individuals worldwide experience the addictive effects of opioids.[84] In 2019, drug use was responsible for approximately 600 000 deaths, with nearly 80% of these fatalities associated with opioids and approximately 25% resulting from opioid overdose.[85] In the United States, the number of opioid-related overdose deaths increased from 49 860 in 2019 to 81 806 in 2022.[86] Given these trends and the present findings, the use of tramadol and other opioids should be minimised to the greatest extent possible.

Conclusions

Tramadol may have a slight effect on reducing chronic pain (low certainty of evidence) while likely increasing the risk of both serious (moderate certainty of evidence) and non-serious adverse events (very low certainty of evidence). The potential harms associated with tramadol use for pain management likely outweigh its limited benefits.

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Contributors JB and JCJ conceived the study idea; SK designed the search strategy; JB and MM screened studies for eligibility; JB, MM, YB, EI and JJP extracted data and assessed the credibility; JB wrote the first draft of the manuscript; CG, JJB, YB, OM and JCJ interpreted the data analysis and critically revised the manuscript. JB is the guarantor.

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