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Can tramadol help adults with osteoarthritis? A Cochrane Review summary with commentary

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The aim of this commentary is to discuss in a rehabilitation perspective the published Cochrane Review "Tramadol for osteoarthritis"[1] by Toupin April et al.[a], under the direct supervision of Cochrane Musculoskeletal Group. This Cochrane Corner is produced in agreement with *Journal of Musculoskeletal and Neuronal Interactions (JMNI)* by Cochrane Rehabilitation.

Background

Osteoarthritis (OA) is highly prevalent across the globe, and the single most common cause of disability in older adults. Its incidence is increasing due to ageing of population[2]. OA also accounts for major portion of healthcare costs; medical cost of OA in various high-income countries is ranging from 1% to 2.5% of the gross domestic product, whereas the majority of those costs are spent on hip and knee joint replacements[3]. Rehabilitation is the key part of the treatment of individuals suffering from OA[4], and specialists in the field of physical medicine and rehabilitation need high-quality information about adequate management of multifaceted symptoms of OA. In the absence of therapies that would enable cure of OA, current symptomatic focus is on alleviation of pain, and improvement of physical function. While opioids, including tramadol, have been prescribed to adults suffering from OA, it is important to carefully assess potential benefits and harms of such interventions due to multiple potential adverse events, including potential for addiction and abuse. An update of a Cochrane Review (first published in 2006[5]) evaluated further evidence regarding the use of tramadol either alone or in combination with other medications in OA[1].

Tramadol for osteoarthritis

(Toupin April et al, 2019)

What is the aim of this Cochrane review?

The aim of this Cochrane Review was to synthesize evidence about benefits and harms of oral tramadol or tramadol combined with acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs) in adults with osteoarthritis.

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[a] This summary is based on a Cochrane Review previously published in the Cochrane Database of Systematic Reviews 2019, Issue 5. Art. No.: CD005522. DOI: 10.1002/14651858.CD005522.pub3. (see www.cochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review.
The views expressed in the summary with commentary are those of the Cochrane Corner author and do not represent the Cochrane Library or Wiley.

What was studied in the Cochrane review?

The population addressed in this review were adults aged 18 years and over suffering from osteoarthritis in any joint. The interventions studied were oral tramadol alone or tramadol combined with acetaminophen or NSAIDs. The intervention was compared to placebo or any active comparator. The primary outcomes studied were pain, physical function, number of participants experiencing any adverse event (AE), number of withdrawals due to AE, number of participants experiencing any serious AE. For pain and physical function, improvement was defined as reaching a minimal clinically important difference (MCID) of 20% on the given scale. The secondary outcome studied was opioid dependence symptoms.

Search methodology and up-to-dateness of the Cochrane review?

The review authors searched for randomized controlled trials (RCTs) that had been published up to February 2018.

What are the main results of the Cochrane review?

The review included 22 randomized controlled trials (RCTs) using daily doses of tramadol in a range between 37.5 mg and 400 mg. 11 new RCTs were added in the current update. 21 RCTs involving 6496 participants were used for metaanalysis. OA patients were mostly women (mean age: 63 years) diagnosed as having knee or hip OA which caused moderate to severe pain.

The review shows that:

- **Pain:** Tramadol alone and in combination with acetaminophen did not lead to important alleviation of pain compared to placebo. Pain was rated with a visual-analogue scale (VAS) from 0 to 100, where lower score is better. Participants who took tramadol alone rated their pain with 50.3 points; people who took a placebo rated their pain with 54.3 points [4% absolute improvement with tramadol; 95% confidence interval (CI) 3% to 5% improvement; 8 trials with 3972 participants]. Participants who took tramadol in combination with acetaminophen rated their pain with 48.3 points; which was 4% absolute improvement compared to placebo (95% CI 2% to 6%; 2 trials with 614 participants).
  Ten out of 100 participants who took placebo experienced an MCID of 20% in pain, compared to 15 out of 100 with tramadol (5% more people with tramadol; 95% CI 3% to 6% improvement). Similarly, in the comparison of placebo and combination of tramadol and acetaminophen, 7 people with placebo experienced 20% MCID in pain, compared to 12 who took the combination (5% improvement; 95% CI 2% to 9 % improvement).
  Quality of evidence about pain was moderate; it was downgraded due to risk of bias.
- **Physical function:** Tramadol alone and in combination with acetaminophen did not lead to important improvement in physical function compared to placebo. Using a WOMAC physical function scale ranging from 0 to 1700 (where lower score is better), participants who took tramadol alone rated their physical function with 991 points, while those with placebo rated it with 1059 points. This corresponds to 4% absolute improvement with tramadol alone compared to placebo (4% absolute improvement; 95% CI 2% to 6% improvement; 5 trials with 2550 participants).
  Using rating of WOMAC physical function from 0 to 10 (where 0=no limitation), participants who took a combination of tramadol and acetaminophen scored their physical function with 5.5 points, while those with placebo scored it with 5.9 points. This corresponds to 4% absolute improvement with the combination (95% CI 2% to 7% improvement; 2 trials with 614 participants).
  Twenty-one out of 100 participants who took tramadol had a 20% MCID in physical function, compared to 16 of 100 who took placebo (5% absolute improvement with tramadol; 95% CI 3% to 8% improvement; 5 trials with 2550 participants).
  Fifteen out of 100 participants who took a combination of tramadol and acetaminophen experienced 20% MCID, compared to 10 out of 100 who took placebo (5% absolute improvement with the combination; 95% CI 2% to 9% improvement; 2 trials with 614 participants).
  Quality of evidence about physical function was moderate; it was downgraded due to risk of bias.
- **Adverse events:** Higher risk of developing adverse events was reported in participants taking tramadol alone [17% (95% CI 12% to 23%) increase; 4 trials with 2039 participants] and tramadol combined with acetaminophen [22% increase (95% CI 8% to 41%); 1 trial with 308 participants], compared to placebo. The most commonly reported AEs were nausea, dizziness and tiredness. Quality of evidence about AEs was moderate; it was downgraded due to risk of bias.
- **Withdrawals due to adverse events:** Higher risk of withdrawals due to AEs was reported in participants taking tramadol alone compared to placebo [12% increase (95% CI 9% to 16%); 9 trials with 4533 participants]; quality of evidence was moderate. Higher risk of withdrawals due to AEs was reported in participants taking tramadol combined with acetaminophen compared to placebo [8% increase (95% CI 2% to 19%); 2 trials with 614 participants]; quality of evidence was low.
- **Serious adverse events:** Higher risk of serious AEs was reported in participants taking tramadol alone in comparison with placebo [1% increase (95% CI 0% to 4%); 7 trials with 3612 participants]. In one small study, with 15 participants, that compared tramadol combined with acetaminophen to placebo, there were no serious AEs. Serious AEs reported among participants who took tramadol groups included unstable angina, chest pain, breast cancer, diverticulitis, grand mal convulsions, prostate cancer, popliteal bursitis, small intestinal

obstruction, cholelithiasis, pancreatitis and abdominal pain. Evidence for this outcome was of low quality; it was downgraded due to risk of bias and imprecision.

- **Symptoms of opioid dependence:** Considering that tramadol is opioid medicine, it is concerning that only four out of 22 trials have reported withdrawal symptoms or propensity for abuse, or both, and only one of them reported data that could contribute to the systematic review.

How did the authors conclude?

The authors concluded that tramadol alone or combined with acetaminophen, compared to placebo, has no important effect on alleviation of pain and improvement of physical function in adults suffering from OA. There were 5% more patients who took tramadol and experienced clinically important improvement in pain and physical function, compared to placebo. Adverse events were more common in patients receiving tramadol, either alone (17% increase) or combined with acetaminophen (22% increase). Low quality evidence indicated that risk of withdrawals due to AEs and risk of serious AEs was higher in patients taking tramadol. The potential of tramadol abuse needs to be studied in future trials because it was rarely reported in RCTs included within this review.

What are the implications of the Cochrane evidence for practice in rehabilitation?

Few adults suffering from OA will benefit from therapy with tramadol, either alone or combined with acetaminophen. Few patients will achieve clinically important benefit in alleviation of pain and improvement of physical function, while risk of AEs, serious AEs and withdrawals due to AEs are higher in patients receiving tramadol. Therefore, any potential benefit that could be achieved in those few patients needs to be weighed in terms of potential risks, particularly potential for opioid dependence and abuse. To note, the results may be applicable mostly to women and those with knee or hip OA. The trials evaluated in the review[1] had a duration of no longer than 13 weeks; however, the results presented in this review indicated small benefits that are probably outweighed by harms, and for this reason longer trials may not be needed. In longer trials there could be more harms reported. To better understand the effect of interventions in general in OA trials and to increase reproducibility/replicability/comparability, future studies should use of Outcome Measures in Rheumatology (OMERACT) core outcome set[6].

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References

1. Toupin April K, Bisaillon J, Welch V, Maxwell LJ, Jüni P, Rutjes AWS, Husni ME, Vincent J, El Hindi T, Wells GA, Tugwell P. Tramadol for osteoarthritis. Cochrane Database Sys Rev 2019;5. CD005522. DOI: 10.1002/14651858.CD005522.pub3.
2. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. Lancet. 2019;393(10182):1745-1759. doi: 10.1016/S0140-6736(19)30417-9.
3. Hunter DJ, Schofield D, Callander E. The individual and socioeconomic impact of osteoarthritis. Nat Rev Rheumatol 2014; 10: 437–441.
4. Ilieva EM, Oral A, Küçükdeveci AA, Varela E, Valero R, Berteanu M, Christodoulou N. Osteoarthritis. The role of physical and rehabilitation medicine physicians. The European perspective based on the best evidence. A paper by the UEMS-PRM Section Professional Practice Committee. Eur J Phys Rehabil Med 2013;49(4):579-593.
5. Cepeda MS, Camargo F, Zea C, Valencia L. Tramadol for osteoarthritis. Cochrane Database Syst Rev 2006;3:CD005522.
6. Krsticevic M, Dosenovic S, Dimcea DA, Jedrzejewska D, Marques Lameirão AC, Almeida ES, Jelicic Kadic A, Jeric Kegalj M, Boric K, Puljak L. Outcome Domains, Outcome Measures, and Characteristics of Randomized Controlled Trials Testing Nonsurgical Interventions for Osteoarthritis. J Rheumatol 2020;47(1):126-131.