Critique author	Ed Whitney

Bibliographic Data	
Authors	Santos J, Alarcão J, et al.
Title	Tapentadol for chronic musculoskeletal pain in adults.
PMID	26017279
Citation	Cochrane Database of Systematic Reviews 2015, Issue 5. Art. No.: CD009923
Other information if relevant	

Methods	
Aim of study	To determine the safety, efficacy, and tolerability for extended release tapentadol in the setting of moderate to severe musculoskeletal lasting three months or more
Design	Meta-analysis of randomized clinical trials

PICOS	
Population from which participants are drawn	Adults age 18 or over with moderate to severe chronic musculoskeletal pain of any cause
Intervention being evaluated	Tapentadol extended release in doses of 100 to 500 mg per day
Comparison or control intervention	- Placebo - Oxycodone
Outcomes	- Pain control assessed by change in pain intensity and responder rate (at least 50% relief) - Pain control assessed by patient global impression of change (much or very much improved) - Safety as assessed by withdrawal from study due to any adverse events, including lack of efficacy

Study types	Randomized trials, both parallel and crossover, where randomization was explicit and appropriate

Study selection	
Search date of literature review	Through March 2014
Databases in literature search	Cochrane Central Register, MEDLINE, EMBASE, Web of Science, and trial registries such as clinicaltrials.gov
How authors assessed study quality (risk of bias and other considerations	Cochrane Risk of Bias tool for - Random sequence generation - Allocation concealment - Blinding of participants and personnel delivering care - Blinding of outcome assessment - Incomplete outcome data (attrition and withdrawal from study) - Selective outcome reporting
Additional information if relevant	

Results	
Number of studies screened	291 records screened
Number of studies selected for analysis of results	4 studies in qualitative synthesis (32 reports)
Whether authors elected to perform meta-analysis to pool study results statistically and type of meta-analysis done (fixed effect or random effects, heterogeneity, etc)	Yes Random effects for some outcomes Fixed effect for most outcomes
Quality of studies as assessed by authors	- Two trials were considered to be at low risk of bias - Two trials were considered to be at high risk of bias due to being open-label (one study) or unclear allocation concealment (one study)

Effect sizes reported for primary outcomes for **tapentadol versus placebo** (mean differences, standardized mean differences, response ratios, etc)	- For tapentadol versus placebo, pain control data were obtained from three studies with 1973 participants for reduction in pain intensity from baseline to week 12 - For pain reduction at week 12, tapentadol was better than placebo; the difference on a numerical rating scale from 0-10 was 0.56 (95% CI from 0.92 to 0.22) - For responder rate of 50% pain reduction, tapentadol was better than placebo with a response ratio 1.36 (95% CI 1.13 to 1.64) - Withdrawal from the study due to any adverse effect was more common with tapentadol than with placebo (risk ratio 2.68, 95% CI from 2.05 to 3.52)
Effect sizes reported for primary outcomes for **tapentadol versus oxycodone** (mean differences, standardized mean differences, response ratios, etc)	- Tapentadol was compared to oxycodone in 4 trials - Tapentadol was slightly more effective than oxycodone for reduction in pain intensity; ; the difference on a numerical rating scale from 0-10 was 0.24 (95% CI from 0.05 to 0.43) - For responder rate of 50% pain reduction, tapentadol was equal to oxycodone - Withdrawal from the study due to any adverse effect was less common with tapentadol than with oxycodone (risk ratio 0.50, 95% CI 0.42 to 0.60)
Effect sizes reported for additional outcomes (mean differences, standardized mean differences, response ratios, etc)	- For patient global impression of change (much or very much improved), the response ratio of 1.53 (95% CI 1.28 to 1.82) also favored tapentadol over placebo - The occurrence of serious adverse events was equal between tapentadol and placebo - For patient global impression of change (much or very much improved), there was no difference between tapentadol and oxycodone - The occurrence of serious adverse events was equal between oxycodone and tapentadol - Constipation was less frequent with tapentadol than with oxycodone (risk ratio 0.55) but constipation was more frequent with tapentadol than placebo (RR 2.43)
Additional information if relevant	- A subgroup analysis examined whether the estimated benefits of tapentadol over placebo was different between high and low quality studies; the analysis appeared to show that the outcomes for tapentadol were better in the higher quality studies

Conclusions	
Key conclusions of study authors	- Four trials provided moderate quality data concerning tapentadol in comparison with both placebo and oxycodone - There was insufficient evidence to support or not support the use of tapentadol for moderate to severe chronic musculoskeletal pain at doses of 200 to 500 mg per day - Tapentadol improved pain control slightly in comparison to placebo and oxycodone, but the difference was small in terms of pain reduction - Tapentadol had high dropout rates (17.5%), and this may be responsible for some overestimation of its effectiveness - The available evidence did not allow an assessment of the functional benefits, if any, of tapentadol - The safety profile of tapentadol may be advantageous, but its overall clinical benefit for pain reduction may be small
Additional information if relevant	- The authors did not have access to the full research data, and therefore found it difficult to determine what kinds of investments should be made for further research - The authors recommend that future studies report responder rates (50% pain relief) and use baseline observation carried forward, rather than last observation carried forward to deal with missing data, since the dropout rates are fairly high

Comments by DOWC staff

- "Serious adverse events" were reported as an outcome, but the term was not defined
- At clinicaltrials.gov, "serious" adverse events include congestive heart failure, myocardial infarction, anemia, stroke, confusional state, and other effects
- Although there were only four trials of tapentadol, there were 32 reports, since most of the trials were used to generate multiple separate reports (tapentadol vs placebo and tapentadol vs oxycodone for osteoarthritis knee pain and chronic low back pain in patients with or without prior opioid experience, etc)
- Studies on neuropathic pain were excluded from the study selection
- The overall responder rate, defined as a 50% pain intensity reduction, was reported in only two studies, where it was 195/659 (29.6%)
- All studies were sponsored by the manufacturer
- More than 4000 participants were enrolled in the four studies, and large treatment effects were not likely to be missed

Assessment by DOWC staff	
Overall assessment as suitability of evidence for the guideline ☐ High quality x☐ Adequate ☐ Inadequate	The systematic review is high quality methodologically. The evidence to support tapentadol to treat chronic pain is inadequate. The evidence that tapentadol causes less constipation than oxycodone is adequate.
If inadequate, main reasons for recommending that the article not be cited as evidence	The authors had access to a small number of trials, and the effect of tapentadol was small in comparison to placebo

Additional references if relevant
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