Critique author	Ed Whitney

Bibliographic Data	
Authors	Lunn MPT, Hughes RAC, Wiffen PJ
Title	Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia
PMID	24385423
Citation	Cochrane Database of Systematic Reviews 2014, Issue 1. Art # CD007115
Other information if relevant	

Methods	
Aim of study	To assess the benefits and harms of duloxetine for painful neuropathy and other kinds of pain
Design	Meta-analysis of randomized clinical trials

PICOS	
Population from which participants are drawn	People with any form of painful peripheral neuropathy, chronic neuropathic pain, chronic pain without identified cause, or fibromyalgia
Intervention being evaluated	Duloxetine in any formulation or dose
Comparison or control intervention	-Placebo - Other active drug control
Outcomes	- Primary outcome was short-term (up to 12 weeks) improvement of pain using validated pain scales. Preferred measurement was the proportion of patients experiencing a 50% or greater reduction in pain compared to baseline - Secondary outcomes included long-term (more than 12 weeks) pain improvement, proportion of patients with 30% pain reduction, 30% improvement in any validated quality of life score, and adverse events during treatment

Study types	Only randomized double-blind trials in which duloxetine was administered for at least 8 weeks

Study selection	
Search date of literature review	November 2013
Databases in literature search	MEDLINE, CENTRAL, EMBASE, and others
How authors assessed study quality (risk of bias and other considerations	Cochrane risk of bias tool whose main criteria were random sequence generation, allocation concealment, blinding of participants and outcome assessment, attrition bias, selective reporting bias, and other bias
Additional information if relevant	

Results	
Number of studies screened	310 references were screened in a 2009 version of this Cochrane review, and 150 additional references were screened for this edition
Number of studies selected for analysis of results	- 6 trials were selected for the 2009 version, and 12 references were added for this version, for a total of 18 studies with 6407 participants to be included in the analysis of all studies - 8 studies with 2728 participants were of diabetic peripheral neuropathy, and the remaining 10 studies were of fibromyalgia and other conditions - Only the 8 studies of neuropathic pain are relevant to the chronic pain guideline - 6 of the 8 studies compared duloxetine with placebo; 1 compare duloxetine with amitriptyline, and 1 study compared duloxetine with pregabalin - The amitriptyline study was not included in the meta-analysis; and only one phase of the pregabalin study was included in the meta-analysis

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)	- Meta-analysis methods depended on the outcome under consideration - For the dichotomous (50% pain reduction) outcomes, the response ratio (called a "risk ratio") was sometimes estimated with a random effects model and sometimes with a fixed effect model - For the pain score reductions, the preferred measure of effect was the mean difference between treatment groups, which was sometimes done with a random effects and sometimes with a fixed effect model
Quality of studies as assessed by authors	- 2 of the 8 studies involving peripheral neuropathic pain had a low risk of bias in all domains - 6 of these 8 studies had high attrition (>20% of patients), which was the most common problem creating potential bias
Effect sizes reported for primary outcomes (mean differences, standardized mean differences, response ratios, etc)	- For the primary outcome of 50% pain reduction, duloxetine 20 mg daily was not shown to be better than placebo, but at 40, 60, or 120 mg, it was more favorable - Interestingly, the response *ratio* did not increase as the dose went from 40 to 60 to 120 mg; the respective response ratios were 1.91, 1.73, and 1.46 - The actual response *rates* for these three doses were: 37.6% at 40 mg, 46.6% at 60 mg, and 49.2% at 120 mg - For mean improvement at 12 weeks, duloxetine 20 mg was not better than placebo, no study reported this outcome for the 40 mg dose, and the mean difference on a 0-10 point scale was better than placebo for the 60 mg dose (0.96 points) and for 120 mg (0.93 points)
Effect sizes reported for additional outcomes (mean differences, standardized mean differences, response ratios, etc)	- For the 30% pain reduction outcome, the response ratios favoring duloxetine over placebo for the 40, 60, and 120 mg doses were 1.57, 1.53, and 1.38 respectively; the actual response rates were 55.3%, 64.4%, and 67.6% respectively - The authors analyzed adverse events across all included studies, and did not analyze them separately for peripheral neuropathy - Serious adverse events were rare and occurred with about equal frequency for duloxetine (1.5%) and placebo (1.8%) - Adverse events of any sort, however, were common with both duloxetine and placebo, and were slightly more common across all doses of duloxetine 72.7% than placebo (62%); the most common side effect with duloxetine was nausea (29.8%), dry mouth (17.3%), dizziness (14.9%), and somnolence (21.7%) - Of these adverse events, most did not lead to cessation of treatment, but this did occur in 12.6% of duloxetine patients and in 5.8% of placebo patients

Additional information if relevant	- Only one trial compared duloxetine with pregabalin, where the 50% pain reduction rate was higher with duloxetine (37.7%) than with pregabalin (25.8%), and the mean improvement for duloxetine (2.3 points on a 10 point scale) was better than for pregabalin (1.7 points) - Only one trial compared duloxetine with amitriptyline, and this study did not meet the authors' inclusion criterion of having at least 8 weeks of treatment

Conclusions	
Key conclusions of study authors	- There is moderate quality evidence from 4 studies performed by the drug maker that duloxetine in doses of 60 or 120 mg daily is effective in the treatment of painful diabetic peripheral neuropathy but that lower daily doses are not - Minor adverse events are common with duloxetine but serious adverse events are rare - No further trials are required to indicate the efficacy of duloxetine at 60 mg for diabetic peripheral neuropathic pain
Additional information if relevant	- In the trial of duloxetine versus pregabalin, the response rate for duloxetine was superior, but the pregabalin response rate in that study was at the level of a placebo response in other trials; pregabalin is probably effective and the superiority of duloxetine is unclear

Comments by DOWC staff

- The authors searched for studies of duloxetine in the setting of postherpetic neuralgia, but did not find any studies which met inclusion criteria
- Both mean pain differences and percentages of patients responding to treatment with a 50% pain reduction were reported, but the authors strongly prefer the latter measure of effectiveness due to the non-linear distribution of the mean pain difference in the pain literature
- As occurs with other Cochrane reviews, this meta-analysis considered duloxetine as a stand-alone drug and not as a component of a drug combination
- The success rates (50% pain reduction) with duloxetine were recorded in only about half of patients taking the 60 mg or the 120 mg dose, and the fact that the studies were of duloxetine monotherapy should be considered in assessing its effectiveness
- In their conclusion, the authors assert that for painful diabetic neuropathy, no further studies of 60 mg duloxetine are needed, based on trial sequential analysis (TSA) which was displayed in Figure 7
- However, in the "Summary of findings" table on page 4, the evidence for duloxetine in diabetic neuropathy is rated as "moderate," which is interpreted as meaning that further research is likely to have an important impact on their confidence in the estimate and mah change the estimate
- This means that the conclusion from the TSA, that no further studies are needed, appears to stand in contrast to the meaning of "moderate" quality evidence
- It may be the case that while the TSA provides strong evidence that duloxetine is more effective than placebo, and further studies are not needed to prove this, additional studies may change the size of the treatment effect to be greater or lesser, even if those studies will not reduce the effect size to zero
- Although the global impression of change (very much improved, etc) may reflect on function in addition to pain, no validated function scores were reported for the meta-analysis

Comments by DOWC staff concerning trial sequential analysis

- TSA is done when trials are sequentially added to a meta-analysis, and the purpose of TSA is to reduce the risk of spurious conclusions
- TSA has shown that many Cochrane meta-analyses which appeared to be conclusive enough to recommend treatment interventions were actually inconclusive because the statistical criteria for efficacy ($p<0.05$ for a treatment effect) were insufficiently stringent (Brok 2008, 2009)
- TSA is analogous to what is done in clinical trials whose monitoring committees conduct interim analyses of outcome data as participants are sequentially accrued, and apply stringent statistical criteria to avoid biases when trials are stopped early for benefit
- TSA uses dedicated software to estimate the number of patients who would need to be included in the trials in a meta-analysis in order to have adequate power to detect a treatment effect of a given size with specified levels of type I and type II error (at least as large as an optimally powered single RCT)
- TSA also uses the same software to calculate monitoring thresholds as new RCTs are added to a meta-analysis, analogous to the monitoring thresholds used in RCTs
- The studies of duloxetine for diabetic painful neuropathy were subjected to TSA, and figure 7 on page 19 shows the display of the TSA
- On the vertical axis, "Favors Duloxetine: has a horizontal line for the cumulative Z score of 1.96; this is the value of Z when $p=0.05$, which is the nominal level of statistical significance to declare that a treatment is more effective than placebo
- If that nominal value of $Z=1.96$ were made to be the basis of conclusions of treatment effect, the first study on the solid line for the Z-curve (Goldstein 2005), which crosses the horizontal line where $Z=1.96$, would be good enough to conclude that duloxetine is more effective than placebo
- However, the position of the Z-curve for that first study falls below the downward sloping broken line which represents the monitoring boundary, indicating that it would be premature to declare an effect of duloxetine at that time
- The second point on the Z-curve, for Raskin 2005, crosses the monitoring boundary, and that curve continues to rise with the later studies as the monitoring boundary continues to slope downward
- The vertical broken line at the right of Figure 7 represents the optimal information size (total number of patients) for a conclusive meta-analysis, and is especially useful if the Z-curve crosses the optimal information size line while remaining below the monitoring boundary; when that happens, it is justified to declare that the treatment does not work (evidence of absence)
- If the Z-curve is below the monitoring boundary but has not yet crossed the optimal information size, the evidence is inconclusive (absence of evidence)
- The optimal information size is not specified, but it appears from the Figure 7 that the OIS would be reached if there were 1078 more patients than the number which were included in the meta-analysis
- The advocates of TSA think that it has the potential to tell the difference between conclusive and inconclusive evidence based on the position of the Z-curve in relation to the monitoring boundary and the optimal information size
- This is the first Cochrane review in the cumulative guideline bibliographies to display a TSA, which appears to be a fairly new and infrequently used tool for assessing the strength of evidence for an intervention

Assessment by DOWC staff	
Overall assessment as suitability of evidence for the guideline x☐ High quality ☐ Adequate ☐ Inadequate	High quality meta-analysis supporting strong evidence that duloxetine monotherapy is more effective than placebo in relieving the pain of diabetic peripheral neuropathy However, monotherapy leads to a 50% pain reduction in only half of patients who receive a therapeutic dose
If inadequate, main reasons for recommending that the article not be cited as evidence	

Additional references if relevant
- Brok J, Thorlund K, et al. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. J Clin Epidemiol 2008;61:763–9. - Brok J, Thorlund K, et al. Apparently conclusive meta-analyses may be inconclusive—trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. Int J Epidemiol 2009;38:287–98.