Critique author	Ed Whitney

Bibliographic Data	
Authors	Zhang SS, Wu Z, et al
Title	Efficacy and safety of pregabalin for treating painful diabetic peripheral neuropathy: a meta-analysis.
PMID	25328117
Citation	Acta Anaesthesiol Scand. 2015 Feb;59(2):147-59.
Other information if relevant	

Methods	
Aim of study	To assess the safety and efficacy of pregabalin in the treatment of pain associated with diabetic peripheral neuropathy
Design	Meta-analysis of randomized clinical trials

PICOS	
Population from which participants are drawn	Adults with pain attributable to diabetic peripheral neuropathy (DPN)
Intervention being evaluated	Pregabalin at daily doses of 150 mg, 300 mg, and 600 mg
Comparison or control intervention	Placebo Different doses of pregabalin (300 vs 600 mg)
Outcomes	Mean pain score (MPS) at endpoint on a scale from 0-10 Proportion of patients reporting pain reduction of 50% or more Secondary outcomes included: patients' global impression of change (PGIC), mean sleep interference scores, withdrawals due to lack of efficacy, withdrawals due to adverse events, and frequency of common adverse events

Study types	Randomized, placebo-controlled, double blind clinical trials Open-label studies were excluded

Study selection	
Search date of literature review	18 June 2014
Databases in literature search	MEDLINE, EMBASE, CENTRAL, clinicaltrials.gov
How authors assessed study quality (risk of bias and other considerations	- Jadad 5 point scale, which awards points for randomization, double-blinding, and accounting for withdrawals - 3 points or more was considered “high quality”
Additional information if relevant	

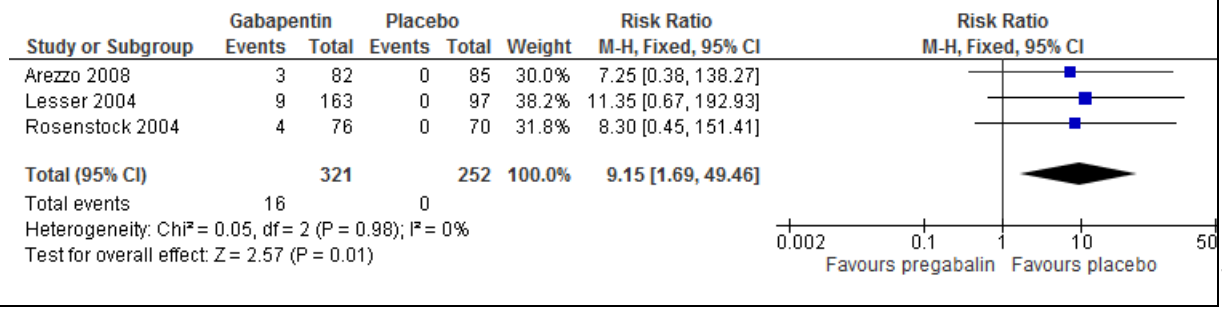
Results	
Number of studies screened	- 85 records were examined after duplicates were removed - 54 records were screened to ensure that a placebo group was included and that they were randomized trials
Number of studies selected for analysis of results	-9 studies included in meta-analysis
Whether authors elected to perform meta-analysis to pool study results statistically and type of meta-analysis done (fixed effect or random effects, heterogeneity, etc)	- Random effects model was used if I^2 was >50% - Fixed effect model was used if I^2 was less than 50%
Quality of studies as assessed by authors	- 4 studies had a Jadad score of 5, 3 had a score of 4, and 2 studies had a score of 3 - Thus, all 9 studies had Jadad scores of at least 3 and were considered high quality

Effect sizes reported for primary outcomes (mean differences, standardized mean differences, response ratios, etc)	- For MPS at endpoint, all 9 studies reported data, and the meta-analysis yielded a mean difference in favor of pregabalin over placebo of 0.79 points (95% CI 1.11 to 0.48) - For MPS at endpoint, 3 studies compared doses of 300 mg with doses of 600 mg, and there were no differences between the two doses - All 9 studies reported data on the proportion of patients with 50% pain reduction, and this also favored pregabalin (36%) over placebo (24%), with a pooled response ratio under a random-effects meta-analysis being 1.54 (95% CI 1.20 to 1.98) - 3 studies reported data on 50% pain relief comparing doses of 300 mg (34.7%) and 600 mg (44.6%), the pooled response rate for 300 mg was 83% that of the 600 mg dose, with a 95% CI from 67% to 103%
Effect sizes reported for additional outcomes (mean differences, standardized mean differences, response ratios, etc)	- In 6 studies which provided data, 73% of patients taking pregabalin reported themselves "improved" on the PGIC, compared to 50% of placebo patients; 51% of pregabalin patients were "much improved," compared to 33% of placebo patients - Withdrawals due to lack of efficacy were less frequent with pregabalin than with placebo; the authors reported a relative risk (RR) of 0.62 in favor of pregabalin but did not report the actual percentages of patients who withdrew - 9 studies reported increased occurrence of withdrawal due to adverse events with pregabalin (10.7%) over placebo (6.0%); the pooled odds ratio was 2.11 for all adverse events, 4.28 for dizziness, 2.72 for peripheral edema, and 4.81 for somnolence
Additional information if relevant	- The authors did a subgroup analysis based on whether the study used an enriched enrollment design - 7 trials did not and 2 trials did use enriched enrollment - The pooled mean pain score reduction from the 7 trials not using enriched enrollment was 0.63 points in favor of pregabalin; for the 2 enriched enrollment the mean pain reduction was 1.37 points; the pooled pain reduction from all 9 studies was 0.79 points in favor of pregabalin, and there was a high degree of heterogeneity between study designs - Data from 3 studies showed that the relative risk of euphoria with pregabalin compared to placebo was 9.15 (95% CI 1.69 to 49.46), but actual percentages were not reported

Conclusions	
Key conclusions of study authors	- Pregabalin showed significant clinical benefit for lowering mean pain score and achieving at least 50% pain reduction in patients with painful DPN - The drug also led more patients to report their status as “improved” on the global impression of change scale - On the other hand, several adverse events were more common with pregabalin: dizziness, somnolence, peripheral edema, weight gain, asthenia, and euphoria - Pregabalin does not increase the risk of headache, diarrhea, amblyopia, accidental injury, or infection - The 600 mg and 300 mg doses were associated with similar pain reduction at the end of the study, but 600 mg was associated with higher dizziness and somnolence - There were some limitations to the study, which included a relatively small number of small-scale studies published in English, and long-term efficacy data was not available
Additional information if relevant	

Comments by DOWC staff

- Although the authors report significant pain reduction with pregabalin, the mean difference between pregabalin and placebo (0.79 points on a scale 0-10) is less than half of the generally accepted clinically important difference of 2 points
- The right hand column of Table I, BOCF/LOCF, presumably refers to the handling of missing data by whether the baseline or the last observation was carried forward; having "yes/no" answers to this either/or question is unexplained and unhelpful
- The primary outcome, differences between pregabalin and placebo in mean pain scores, was influenced by study design; the effect size in studies which used enriched enrollment was twice the effect size in studies which did not use enriched enrollment
- Studies appear not to be reporting on response rates among patients who have and who have not been taking opioids at the time of entry into the study; if pregabalin success is different between these two groups, that would be an important finding
- The authors based the decision whether to use fixed effect or random effects model on the value of I^2 ; if this was >50% they used a random effects model; if less than 50% they used a fixed effect model; this is not the best way to decide that issue
- There were advantages of pregabalin in terms of 50% pain reduction and reported global improvement, but these were modest in absolute size, since this outcome was reported in 36% of pregabalin patients and in 24% of placebo patients
- Functional outcomes for such variables as performance of daily activities were not reported
- Global improvement as perceived by the patient is not a good substitute for a functional scale assessing activities of daily life, and if some of the effect of the drug is mediated through effects on overall mood, this could account for some of the 73% of patients who reported themselves "improved" while only 36% had a 50% pain reduction
- A random effects model was the forest plot for Figure 2, where heterogeneity was observed; however, sources of this heterogeneity were not explored
- One of the studies in that forest plot, Rauck 2012, was an outlier in that the mean difference (0.39) was not statistically significant, but slightly favored placebo; all other studies favored pregabalin
- Rauck differed in one respect from the other studies: it used pregabalin not as the focus of the study, but as one of two control groups for comparison with gabapentin enacarbil, which was the main focus of Rauck's study; it is possible, but far from certain, that this could be a source of the observed but unexplored heterogeneity
- When Rauck is removed from the analysis, the estimate of mean pain difference increases only slightly, to 0.70, and the overall estimate of pregabalin's effectiveness is not changed
- Some of the comparisons were reported in terms of pooled relative risks without reporting of actual risks; for example, withdrawals due to lack of efficacy had a RR of 0.62 in pregabalin compared to placebo, but the percentages of such withdrawals was not reported
- It was possible to find data on euphoria from the three studies used by the authors to report a RR of 9.15, where euphoria was reported in 5% of pregabalin patients and in 0% of placebo patients



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Assessment by DOWC staff	
Overall assessment as suitability of evidence for the guideline x☐ High quality ☐ Adequate ☐ Inadequate	Adequate meta-analysis supporting strong evidence that in the setting of painful diabetic neuropathy, pregabalin as a stand-alone treatment is more effective than placebo in producing a 50% pain reduction, but this goal is realized in only 36% of patients treated with pregabalin compared with 24% of patients treated with placebo. There is an absence of published evidence regarding its effectiveness in improving physical function in this condition.
If inadequate, main reasons for recommending that the article not be cited as evidence	The evidence in favor of pregabalin is high quality, but the meta-analysis is not high quality due to the lack of any exploration of sources of heterogeneity

Additional references if relevant
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