Critique author	Ed Whitney

Bibliographic Data	
Authors	Moore RA, Wiffen PJ, et al
Title	Gabapentin for chronic neuropathic pain and fibromyalgia in adults
PMID	24771480
Citation	Cochrane Database of Systematic Reviews 2014, Issue 4. Art. No.: CD007938
Other information if relevant	

Methods	
Aim of study	To assess the analgesic benefits and the adverse effects of gabapentin when used in the treatment of chronic neuropathic pain and of fibromyalgia
Design	Meta-analysis of randomized clinical trials

PICOS	
Population from which participants are drawn	Adult participants 18 and above with neuropathic pain from a wide variety of conditions, including postherpetic neuralgia (PHN), painful diabetic neuropathy (PDN), trigeminal neuralgia, phantom limb pain, post-traumatic or postsurgical pain, cancer, HIV, and spinal cord injury Studies of the treatment of pain caused by the administration of other drugs were excluded from consideration
Intervention being evaluated	Gabapentin in any dose by any route of administration administered for the relief of neuropathic pain or fibromyalgia Doses generally ranged from 300 mg to 1800 mg per day, but the data was generally too sparse for the authors to undertake a robust dose-response analysis
Comparison or control intervention	Placebo No intervention Any other active comparator

Outcomes	- Primary outcomes were based on the frequency of occurrence of a defined benefit, with emphasis on pain reduction of 50% from baseline, 30% reduction, patient-reported global impression of change of much improved or very much improved - Secondary outcomes were any pain-related outcome indicating some improvement, withdrawals due to lack of efficacy, patients experiencing any adverse event, patients withdrawing from treatment due to adverse events, and specific adverse events such as somnolence or dizziness
Study types	RCTs with double-blind (patient and observers) outcome assessment, following at least two weeks of treatment (but emphasis was on trials lasting six weeks or longer)

Study selection	
Search date of literature review	March 17, 2014
Databases in literature search	Cochrane Central Register, MEDLINE, EMBASE, and clinicaltrials.gov
How authors assessed study quality (risk of bias and other considerations	Three tiers of quality were considered: - First tier evidence met best current standards for control of bias with a parallel design, reporting on numbers of patients with at least 50% pain intensity reduction, reporting intention to treat (ITT) analysis of outcomes, without the use of Last Observation Carried Forward (LOCF) to deal with missing data, lasting at least 8 weeks, and having at least 200 patients (preferably 400) in the comparison - Second tier uses data from at least 200 patients but one or more of the above conditions is not met - Third tier relates to data from fewer than 200 patients, or has significant problems arising from short duration less than 4 weeks or has shortcomings relating to risk of a biased comparison between groups
Additional information if relevant	All studies were evaluated for bias using the standard Cochrane criteria of randomization sequence, allocation concealment, blinding, accounting for dropouts, and selective outcome reporting; the three tiers of evidence were based on the additional criteria above

Results	

Number of studies screened	There were 29 studies included in a 2011 Cochrane Review, all of which were included in the current study; an additional 8 trials (7 of oral and 1 of intrathecal treatment) were included, and one of the earlier studies had been published with more complete information than the original report
Number of studies selected for analysis of results	37 studies were included Fewer than 37 studies were incorporated on analyses of pain conditions because not all reports presented complete data for the outcomes
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)	All meta-analyses were presented as pooled relative "risks" (actually response ratios) between gabapentin and the comparison, and all analyses were done under a fixed effect model, even when significant heterogeneity was present
Quality of studies as assessed by authors	- There was no first tier evidence as defined by the authors - Most studies were satisfactory with respect to reporting quality; most of the shortcomings of the studies were due to inadequate descriptions of the randomization methods and of allocation concealment
Effect sizes reported for primary outcomes (mean differences, standardized mean differences, response ratios, etc)	Although several types of neuropathic pain were considered, only PHN and PDN had two or more trials from which data could be pooled in a meta-analysis - For the outcome of 50% or better pain reduction in PHN, there were 6 studies with a total of 1816 patients, and gabapentin was successful more frequently (395/1143=34%) than placebo (142/673=21%); the pooled response ratio was 1.6 - The RR for 30% reduction was similar (1.4), and a higher percentage of patients reached the 30% benchmark (54% for gabapentin, 38% for placebo) - Other outcomes for PHN had response ratios similar to the RR for 50% pain reduction: "much or very much improved" (RR=1.32), "substantial improvement" (RR=1.63), "at least moderate improvement" (RR=1.59), "at least 30% reduction (RR=1.4) - There was a similar pattern of response with PDN as with PHN - For PDN, there were 6 studies of 1277 patients, and the RR for 50% pain reduction was 1.9 (38% for gabapentin vs. 21% for placebo), the RR for "much or very much improved" was 1.7 (50% for gabapentin and 30% for placebo)

Effect sizes reported for additional outcomes (mean differences, standardized mean differences, response ratios, etc)	Outcomes related to adverse events were more frequent with gabapentin than with placebo: - Dropping out of study due to adverse events: gabapentin 11%, placebo 7.9% - Serious adverse events: gabapentin 3.2%, placebo 2.8% (difference not statistically significant) - Somnolence/drowsiness: gabapentin 14%, placebo 5% - Dizziness: gabapentin 19%, placebo 6.1% - Peripheral edema: gabapentin 7%, placebo 2.2% - Ataxia/gate disturbance: gabapentin 8.8%, placebo 1.2% - Withdrawal due to lack of efficacy was more frequent with placebo (3.1%) than with gabapentin (1.6%)
Additional information if relevant	

Conclusions	
Key conclusions of study authors	- There was no first tier evidence that was unequivocally unbiased, but second tier evidence did support some conclusions - Gabapentin at a dose of 1200 mg daily is a reasonably effective treatment for neuropathic pain conditions, and about 35% of patients achieve a 50% reduction in pain intensity compared with 21% for placebo - There were almost no data for direct comparisons with active treatments other than placebo - There was no way to estimate the timing and consistency of analgesia with gabapentin, but some studies have estimated that around 20 to 40 days may elapse before effects are seen - The dose of gabapentin differed between studies, which also differed on whether the dose was fixed, titrated to effect, or titrated to the maximum dose regardless of beneficial or adverse effects; data were pooled without regard to dose because of a lack of a clear dose-response effect
Additional information if relevant	- The estimates of the efficacy of gabapentin for PHN and PDN were not affected when standard formulations were compared with gabapentin enacarbil or extended release

Comments by DOWC staff

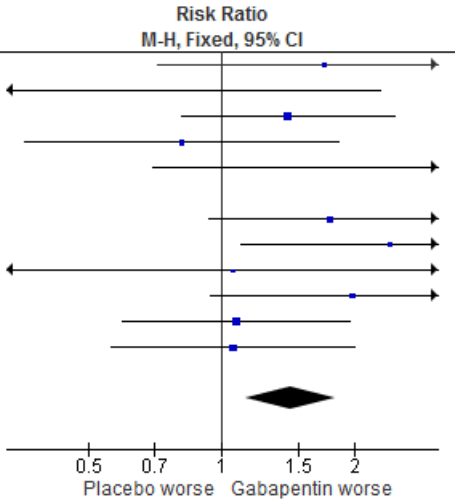
- The specification of a top tier of evidence sets a very high standard which none of the included studies met, but the second tier sets essentially the same standards which are set in other Cochrane reviews, and is capable of supporting a "strong evidence" statement that gabapentin is more effective than placebo for PHN and PDN
- Only two conditions, PHN and PDN, had more than two studies from which data could be pooled, and mixed neuropathic pain had exactly two studies for only one outcome (having at least moderate improvement)
- There is insufficient evidence to draw conclusions about the effectiveness of gabapentin for neuropathic pain from other causes, and the external validity of the data will need to be a matter for clinical judgment based on other considerations
- The optimal starting dose and titration schedule are not analyzed in the meta-analysis, but it is clear that these decisions need to be individualized based on the patient and the situation
- Two of the included studies, Gilron 2005 and Gilron 2009, were previously reviewed in the last guideline update
- Gilron 2005 enrolled patients with mixed neuropathic pain (PHN and PDN), comparing the effects of gabapentin and morphine separately, followed by a combination of both drugs, and reported that the combination of both drugs allowed the use of lower doses of each drug with equal analgesic efficacy
- Gilron 2009 enrolled patients with PHN and PDN, and reported that a combination of gabapentin and nortriptyline provided more effective pain relief than monotherapy with either drug alone
- Studies of both standard formulations were included in the meta-analysis, and the authors reported that there appeared to be no differences in efficacy when extended-release gabapentin and gabapentin enacarbil were analyzed separately from the standard doses
- Because the newer formulations of the drug were developed partly for a more favorable side-effect profile, it may be useful to look at the studies of PHN and PDN with respect to withdrawal due to adverse events, modeled after Analysis 2.2 on page 94 (next box); the two relative risks are nearly the same

Additional comments by DOWC staff

- Twelve of the studies in Analysis 2.2 dealt with PHN and PDN, and for these 12 studies combined, the relative risk of adverse event withdrawal was 1.44 with 95% confidence interval from 1.14 to 1.81 :

	Gabapentin		Placebo			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Backonja 1998	12	75	7	75	6.2%	1.71 [0.71, 4.11]
Backonja 2011	0	47	4	54	3.7%	0.13 [0.01, 2.30]
CTR-945-1008	27	200	18	189	16.3%	1.42 [0.81, 2.49]
CTR-945-224	14	166	8	77	9.6%	0.81 [0.36, 1.85]
Irving 2009	10	96	1	51	1.2%	5.31 [0.70, 40.34]
Perez 2000	0	17	0	15		Not estimable
Rauck 2013a	38	235	11	120	12.8%	1.76 [0.94, 3.33]
Rice 2001	34	223	7	111	8.2%	2.42 [1.11, 5.28]
Sandercock 2012	4	96	2	51	2.3%	1.06 [0.20, 5.61]
Sang 2013	19	221	10	231	8.6%	1.99 [0.94, 4.18]
Wallace 2010	31	269	14	131	16.6%	1.08 [0.59, 1.96]
Zhang 2013	34	276	11	95	14.4%	1.06 [0.56, 2.01]
Total (95% CI)		**1921**		**1200**	**100.0%**	**1.44 [1.14, 1.81]**
Total events	223		93			

Heterogeneity: Chi² = 10.99, df = 10 (P = 0.36); I² = 9%
Test for overall effect: Z = 3.05 (P = 0.002)



- When only the seven studies with newer formulations of gabapentin were included, the RR was 1.38 with 95% CI from 1.01 to 1.87

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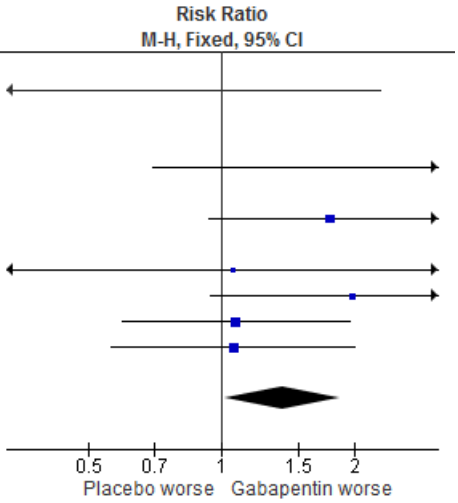
Total (95% CI)		**1240**		**733**	**100.0%**	**1.38 [1.01, 1.87]**
Total events	136		53			

Heterogeneity: Chi² = 7.19, df = 6 (P = 0.30); I² = 17%
Test for overall effect: Z = 2.05 (P = 0.04)



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 gabapentin is more effective than placebo in the relief of painful diabetic neuropathy and postherpetic neuralgia

If inadequate, main reasons for recommending that the article not be cited as evidence	

Additional references if relevant
Gilron I, Bailey JM, et al. Morphine, Gabapentin, or their Combination for Neuropathic Pain. N Engl J Med 2005;352:1324-34. Gilron I, Bailey JM, et al . Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind randomized controlled crossover trial. Lancet 2009;374:1252-61.