Critique author	**Ed Whitney**

Bibliographic Data	
Authors	Baron R, Freynhagen R, et al
Title	The efficacy and safety of pregabalin in the treatment of neuropathic pain associated with chronic lumbosacral radiculopathy
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Citation	Pain 2010;150:420-427
Other information if relevant	

Methods	
Aim of study	To assess the effectiveness of pregabalin in patients with chronic lumbosacral radiculopathy
Design	Randomized clinical trial with enriched enrolment and randomized withdrawal

Participants	
Population from which participants are drawn	Patients with lumbosacral radiculopathy due to spinal stenosis or herniated disc
Setting (location and type of facility)	46 centers in Belgium, Canada, Germany, Italy, Spain, Sweden, Turkey, and the US
Age	52.6
Sex	183 women, 181 men

Total number of participants for whom outcome data were reported	- 364 patients were treated out of 544 who were screened - 378 of the screened patients met all eligibility criteria - These 378 were placed on 7 days of placebo treatment to remove placebo responders, defined as having a 50% or greater pain reduction on placebo (n=14) - The remaining 364 patients were treated with pregabalin in a single blind fashion for 28 days in order to remove non-responders to pregabalin, defined as having less than a 30% reduction in mean weekly pain scores - Of those 364 patients who entered the 28 day pregabalin treatment phase, 82 were removed for lack of efficacy, 32 for adverse events, and 31 for other reasons, 1 for an inadvertent protocol violation during the placebo run-in, and 1 who did not receive the assigned treatment - This left 217 patients who were had a 30% pain reduction on pregabalin and were randomized into a double blind phase of the study
Inclusion criteria	Age 18 and over with pain consistent with a diagnosis of chronic lumbosacral radiculopathy due to herniated disc or spinal stenosis, radiating to the calf or foot in a distribution consistent with L5 or S1 nerve root involvement, colocalized with sensory or motor findings on clinical examination, with leg pain greater than back pain on a VAS score, lasting at least 6 months, stable for at least 4 weeks, with mean weekly pain score of at least 4 points on a 10 point VAS
Exclusion criteria	Lumbosacral neuropathic pain lasting over 4 years, surgery for L-S radiculopathy in the past 6 months, epidural injection for L-S radiculopathy in the past 6 weeks, or more than one past spinal surgery for L5-S1 pain
Other information if relevant	The “success rate” (>=30% pain reduction) on single blind pregabalin was 57.9% , and 68.8% of patients rated themselves as improved or as very much improved

Intervention Groups

Group 1	
Group name	Pregabalin
Number in group	110
Description of intervention	Double-blind pregabalin for 35 days followed by a 7 day tapering from treatment
Duration of treatment period	42 days

Co-interventions if reported	- Concomitant medication was permitted as long as the dose had been stable for at least 30 days before the study began and was not an antiepileptic or an opioid - Rescue medication (acetaminophen or codeine) had been permitted before the beginning of the double-blind withdrawal phase of the study, but not after the double-blind phase had begun
Additional information if relevant	

Group 2	
Group name	Placebo
Number in group	107
Description of intervention	For the first week of the double-blind phase, the placebo group had its pregabalin dose tapered; then the treatment schedule was parallel to the other group
Duration of treatment period	42 days
Co-interventions if reported	- Concomitant medication was permitted as long as the dose had been stable for at least 30 days before the study began and was not an antiepileptic or an opioid - Rescue medication (acetaminophen or codeine) had been permitted before the beginning of the double-blind withdrawal phase of the study, but not after the double-blind phase had begun
Additional information if relevant	

Primary outcome	
Outcome name and criteria for definition	- Loss of response, defined as a an increase of 1 or more points in weekly mean pain score compared with the pain scores at the time of randomization - Use of any rescue medication for pain during the double-blind phase of the study was also counted as loss of response

Time points measured and/or reported	Loss of response was tracked on a daily basis using a Kaplan-Meier survival curve, but short term fluctuations in pain were not counted as loss of response unless the patient had a weekly mean pain score at the end of the double blind phase which had returned to within 30% of their weekly pain score when the study first began
Differences between groups	- From the start of the double-blind phase, the mean change in pain score was a 0.16 point decrease in the pregabalin group and a 0.05 point increase in the placebo group, a statistically equivalent outcome result - During the double-blind phase, both groups recorded a majority of days in which they reported no pain or mild pain (less than 4/10); this was reported by 61.8% of pregabalin patients and in 62.4% of placebo patients
Additional information if relevant	- Only 28% of patients in each group experienced a loss of response during the double-blind phase of the study - Patients with a higher baseline pain score were more likely to experience a loss of response than patients with lower baseline pain scores

Secondary outcomes	
Outcome name and criteria for definition	- Secondary outcomes included sleep interference, patient global impression of change, Roland-Morris Disability (RMD) scores, Work Productivity and Activity Impairment Questionnaire WPAI) , and quality of life as measured by the DQ-5D - Sleep disturbance and sleep quantity were defined separately from sleep interference - Anxiety and depression scores were measured separately
Time points measured	At the onset of the double blind phase and at the end of 42 days
Differences between groups	Sleep interference, patient global impression of change, RMD scores, WPAI, and quality of life as measured by the DQ-5D; the groups did not differ between groups Sleep disturbance, sleep quantity, anxiety scores, and depression scores were also better in the pregabalin than the placebo group
Additional information if relevant	- The most common adverse events for pregabalin were dizziness (30.5%) and somnolence (12.6%) - 9.9% of the pregabalin patients and 5.6% of the placebo patients withdrew from the study due to adverse events

Conclusions	
Key conclusions of study authors	- The pregabalin and placebo groups were not clearly separated on the primary outcome of a loss of pain response during the randomized withdrawal phase of the study - Several factors could lead to the fact that the treatment responses did not appear to differ between groups - One possible explanation is that the effect of pregabalin carried over from the titration phase into the double-blind phase; the placebo group had its dose of pregabalin tapered for the first week of the double blind phase, and 8 placebo patients had protocol violations by being on the pregabalin taper for more than 10 days - In addition, most patients received concomitant medications during the double blind phase, which could also blunt the separation of the pain scores in the groups - It is possible that the apparent equivalence between pregabalin and placebo is attributable to the pathophysiology of lumbosacral radiculopathy, which could include components of both nociceptive and neuropathic pain; since pregabalin is expected only to work on neuropathic pain, it may address only part of the pain mechanisms for this condition

Risk of bias assessment		
Domain	Risk of bias Low High Unclear	Comments
Random sequence generation *(selection bias)*	Low	
Allocation concealment *(selection bias)*	Low	
Blinding of participants and personnel *(performance bias)*	Low	

Blinding of outcome assessment *(detection bias)*	Low	
Incomplete outcome data *(attrition bias)*	Low	98 of 110 patients allocated to pregabalin for the double blind phase completed the trial; 89 of the 107 patients allocated to placebo completed the trial
Selective outcome reporting? *(reporting bias)*	Unclear	The trial was registered at clinicaltrials.gov with the identifier NCT00159705; however, there is incomplete information on the trial at that site. The primary outcome is not specified, nor are the secondary outcomes. He study is reported to be completed, but no trial results are posted, even though they have been published in this article
Other bias		

Sponsorship if reported		
Study funding sources if reported	Pfizer	
Possible conflicts of interest for study authors	Several of the study authors are consultants for or have received honoraria from Pfizer	
Notes:		

Comments by DOWC staff

- The study is complex and its interpretation is open to several possibilities, and it illustrates several of the problems which can arise in assessing placebo controlled trials
- It is likely from the initial 4-week single-blind pregabalin phase of the study, that about 42% of patients started on pregabalin did not achieve a therapeutic response as defined by a 30% reduction in pain scores, and that pregabalin is not an especially powerful drug for pain arising from lumbosacral radiculopathy
- The authors' explain that the lack of a clear separation between pregabalin and placebo could be due to carryover effects of pregabalin from the single blind phase
- It is also possible that the condition being studied does not invite itself to an assessment of the effect of pregabalin for this kind of pain; intervertebral disc protrusion was the primary cause of pain in 79.7% of patients who entered the study
- Since disc protrusion is likely to have a clinical course which tends to resolve over time, and since the duration of the entire study was 77 days, the low rate of "loss of response" to pregabalin in both groups at the end of the study could be a reflection of the natural history of protruded discs
- That is, an enriched enrollment randomized withdrawal study design is at risk of being unsuitable for treatment of a condition which is likely to resolve during the time frame in which the study is being conducted
- The protocol filed at clinicaltrials.gov is uninformative on several points, especially with respect to the primary and secondary outcomes
- Most common sources of bias were adequately controlled, making the study of generally high methodological quality, but the study does not support clear conclusions that pregabalin lacks a therapeutic effect

Assessment by DOWC staff	
Overall assessment as suitability of evidence for the guideline ☐ High quality ☐ Adequate ☒ Inadequate	
If inadequate, main reasons for recommending that the article not be cited as evidence	Although this industry-sponsored trial controls the risks of bias well, no conclusions can be drawn in favor of or against the likely benefits of pregabalin in the setting of lumbosacral radiculopathy due to numerous factors which could obscure differences between pregabalin and placebo

Additional references if relevant

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