Critique author	**Ed Whitney**

Bibliographic Data	
Authors	Cardenas DD, Nieshoff EC, et al
Title	A randomized trial of pregabalin in patients with neuropathic pain due to spinal cord injury
PMID	23345639
Citation	Neurology 2013;80:533–539
Other information if relevant	

Methods	
Aim of study	To assess the efficacy and tolerability of pregabalin for the treatment of central neuropathic pain after spinal cord injury (SCI)
Design	Randomized parallel group clinical trial

Participants	
Population from which participants are drawn	Patients with neuropathic pain arising from spinal cord injury between C2 and T12
Setting (location and type of facility)	60 medical centers in Chile, China, Colombia, Hong Kong, Czech Republic, India, Japan, the Philippines, Russia, and the US
Age	Mean age 46
Sex	176 men, 43 women
Total number of participants for whom outcome data were reported	219

Inclusion criteria	Age over 18 with SCI due to trauma, ischemia, or surgery between C2 and T12, defined as the most caudal level with normal motor and sensory function, having pain below that level for at least 3 continuous months or at least 6 months in a relapsing, remitting pattern, with an average pain score of at least 4 on an 11 point scale in the week before randomization
Exclusion criteria	Other neurologic disorders, medical conditions, or pain that could confound the assessment of neuropathic pain associated with SCI; previous participation in a trial of, or intolerance to, pregabalin; intolerance to gabapentin; preexisting myelopathy of other causes; traumatic SCI superimposed on congenital canal stenosis; and retinal abnormalities or previous treatment with retinotoxic agents
Other information if relevant	

Intervention Groups

Group 1	
Group name	Pregabalin
Number in group	111
Description of intervention	Pregabalin titrated at a dose of 150 mg for 7 days, increased to 300 mg on day 8, 450 mg on day 15, and 600 mg on day 22, based on tolerability. This was followed by a maintenance period of 12 weeks at the titrated dose, with one dose reduction allowed This was followed by a 1 week taper off pregabalin
Duration of treatment period	16 weeks
Co-interventions if reported	NSAIDs, COX-2 drugs, and acetaminophen were permitted as rescue therapy
Additional information if relevant	Compliance was monitored by tablet counts at each visit, with less than 80% compliance as a cause for discontinuation

Group 2	
Group name	Placebo
Number in group	108
Description of intervention	Identical appearing grey tablets titrated at the same schedule as pregabalin

Duration of treatment period	16 weeks
Co-interventions if reported	NSAIDs, COX-2 drugs, and acetaminophen were permitted as rescue therapy
Additional information if relevant	Identical appearing grey tablets titrated at the same schedule as pregabalin

Primary outcome	
Outcome name and criteria for definition	Duration-adjusted average change in pain (DAAC), which is a weighted average of changes from baseline in pain scores, weighted proportional to the duration of participation, with missing scores counted as 0 (i.e., as if they were equal to baseline pain), derived from diaries in which patients recorded their average pain in the past 24 hours
Time points measured and/or reported	DAAC was measured at baseline and at 16 weeks from daily pain diaries
Differences between groups	DAAC for placebo was -1.07 points; DAAC for pregabalin was -1.66 points; the difference was 0.59 points in favor of pregabalin (95% confidence interval = 0.20 to 0.98 points)
Additional information if relevant	The authors also compared DAAC analyzing only treatment-compliant patients who completed the full study (n=77), and the DAAC difference was 0.69 (95% CI 0.26 to 1.12)

Secondary outcomes	
Outcome name and criteria for definition	- The unadjusted pain score change (baseline minus 16 weeks) was 0.70 points in favor of pregabalin - Responder analysis (30% or more pain reduction) was higher with pregabalin (45.7%) than placebo (31.4%) - Global impression of change favored pregabalin over placebo: “much or very much improved” was 40% versus 27%; no change was 19% versus 40%
Time points measured	Baseline and 16 weeks
Differences between groups	As above

Additional information if relevant	- Change in sleep interference on a scale from 0 to 10 favored pregabalin (-2.10 points over placebo (-1.02 points); group difference =1.08 points - Adverse events were more common with pregabalin than placebo: somnolence 33% vs. 13%, dizziness 17.9% vs 5.6%; peripheral edema 11.6% vs. 2.8%; blurred vision 6.3% vs 0%

Conclusions	
Key conclusions of study authors	- Treatment with pregabalin is more effective than placebo on the primary and secondary outcomes in this population of SCI patients - Adverse events were consistent with the known safety profile of pregabalin, but somnolence (13%) with placebo was higher than usually reported, possibly due to the use of benzodiazepines or other features of SCI such as spasticity - Although a large proportion of pregabalin patients did not have a pain reduction of at least 30%, this is not surprising in a difficult-to-treat patient population such as SCI

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	The use of a weighted average of pain change scores, with missing data scored as 0, preserves more data than many other methods of handling missing data such as baseline observation carried forward and last observation carried forward
Selective outcome reporting? *(reporting bias)*	Low	
Other bias		

Sponsorship if reported		
Study funding sources if reported	Pfizer	
Possible conflicts of interest for study authors	Several authors are consultants for Pfizer or hold stock in the company	
Notes:		

Comments by DOWC staff

- Although rescue medication in the form of NSAIDs, COX-2, and acetaminophen was "permitted" during the study, an online data supplement shows that other pain medication was commonly used during the study (opioids in 30.8% of placebo and in 20.5% of pregabalin patients), which could easily magnify the "placebo response" and obscure a treatment effect of pregabalin; this could bias the treatment effect in favor of placebo and does not undermine the study conclusion
- Although the pain score difference appears to be of little clinical importance (DAAC difference of 0.59 points), the secondary outcomes, especially sleep interference (1.08 points in favor of pregabalin over placebo) and responder rate (45.7% vs 31.4%) suggest that the treatment effect is likely to be clinically relevant
- The fact that the study was conducted in many sites on several continents would be expected to increase the amount of random variation into the estimation of treatment effects, thereby tending to mask differences between pregabalin and placebo; this could result in a conservative estimate of the clinical effectiveness of pregabalin

Assessment by DOWC staff	

Overall assessment as suitability of evidence for the guideline ☐ High quality ☒ Adequate ☐ Inadequate	In the setting of neuropathic pain due to spinal cord injury, there is some evidence that pregabalin is more effective than placebo in reducing pain and in improving sleep interference due to pain
If inadequate, main reasons for recommending that the article not be cited as evidence	The primary outcome effect size is too small to be high quality evidence of the benefits of pregabalin, but the consistency of the secondary outcomes, together with potential biases which would underestimate the effects of pregabalin, qualify the study as meeting DOWC standards of evidence

Additional references if relevant
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