Critique author	**Ed Whitney**

Bibliographic Data	
Authors	Kalita J,,Kohat AK, et al
Title	An open labeled randomized controlled trial of pregabalin versus amitriptyline in chronic low backache.
PMID	24857356
Citation	J Neurol Sci. 2014 Jul 15;342(1-2);127-32.
Other information if relevant	

Methods	
Aim of study	To compare the effectiveness and safety of amitriptyline versus pregabalin in chronic back pain with or without radiculopathy
Design	Open label parallel randomized clinical trial

Participants	
Population from which participants are drawn	Consecutive patients with chronic low back pain of three or more months duration
Setting (location and type of facility)	A neurological clinic in a medical sciences institute in Lucknow, India
Age	Mean age 41.5
Sex	91 women, 109 men
Total number of participants for whom outcome data were reported	200
Inclusion criteria	Age 15 to 65 with three months of low back pain but without severe neurological deficits due to radiculopathy or spinal stenosis

Exclusion criteria	Low back pain due to specific causes such as injury, infection, malignancy, collagen vascular disease, rheumatoid or seronegative arthritis, spinal tumors, vascular malformation, taking immunosuppression therapy, anticancer drugs, post-organ transplantation, and post-spinal surgery;
Other information if relevant	Patients were categorized on the basis of clinical examination as (1) localized back pain, (2) back pain with radiculopathy, and (3) back pain with lumbar canal stenosis; this was done for a planned subgroup analysis Prior to starting the trial treatment, pain medication was discontinued for one month, during which patients were permitted to take ibuprofen or piroxicam if needed Baseline VAS was 6.7 for both drugs (standard deviations were unequal but similar) Baseline Oswestry was 42.2 for both drugs (standard deviations were unequal but similar)

Intervention Groups

Group 1	
Group name	Amitriptyline group
Number in group	103
Description of intervention	Amitriptyline for 14 weeks, with a starting dose of 12.5 mg at bedtime, increased after two weeks to 25 mg for 4 weeks and then increased to 50 mg
Duration of treatment period	14 weeks
Co-interventions if reported	All patients were advised to do back extension exercises for 10 to 15 minutes daily, were advised to avoid heavy lifting, and were taught proper technique in lifting weight
Additional information if relevant	Drug titration schedule was flexible and guided by pain response and by the emergence of adverse effects

Group 2	
Group name	Pregabalin group
Number in group	97
Description of intervention	Pregabalin at a starting dose of 75 mg bid for 2 weeks, followed by 150 mg bid for 4 weeks, followed by 300 mg bid
Duration of treatment period	14 weeks

Co-interventions if reported	All patients were advised to do back extension exercises for 10 to 15 minutes daily, were advised to avoid heavy lifting, and were taught proper technique in lifting weight
Additional information if relevant	Drug titration schedule was flexible and guided by pain response and by the emergence of adverse effects

Primary outcome	
Outcome name and criteria for definition	- Pain response defined as 50% reduction in VAS pain score - Functional response defined as a 20% improvement on the Oswestry score
Time points measured and/or reported	6 weeks for an interim score; main analysis was at 14 weeks
Differences between groups	- At 14 weeks, the amitriptyline group had a superior response defined by a 50% pain reduction: 57.3% versus 39.2% for pregabalin - At 14 weeks, the amitriptyline group also had a superior response defined by a 20% Oswestry score reduction: 65.0% versus 49.5% for pregabalin
Additional information if relevant	Discontinuation due to side effects were equal: 11 for amitriptyline and 12 for pregabalin

Secondary outcomes	
Outcome name and criteria for definition	Adverse effects reported by the patient
Time points measured	14 weeks
Differences between groups	The composite side effects were not statistically different between groups: 18 patients for amitriptyline and 21 patients for pregabalin - Most common side effects for amitriptyline were sedation (n=10) and dry mouth (n=3) - Most common side effects for pregabalin were vertigo (n=6) and sedation (n=4)
Additional information if relevant	The planned subgroup analysis based on localized back pain, back pain with radiculopathy, and back pain with lumbar canal stenosis showed similar responses on pain relief and disability

Conclusions	
Key conclusions of study authors	- Although both drugs reduced pain and disability at 14 weeks, amitriptyline was more effective on both outcomes - The study was limited by being open label and by not having a placebo group; the use of placebo was considered ethically questionable in patients who were having moderate to severe back pain

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)*	High	This bias arises from having been an open label study, which was probably due to the bedtime dosing of amitriptyline versus the twice daily dosing of pregabalin; the patients were informed of the potential benefits of both medication, and the comparisons were probably not greatly compromised by the open label design
Blinding of outcome assessment *(detection bias)*	High	Similar to above; the high risk of bias is due to the open label design, but the actual degree of compromise in the response comparisons is probably not severe
Incomplete outcome data *(attrition bias)*	Low	Loss to followup due to unknown reasons was equal between groups (15 in each group), and discontinuation due to side effects was equal (11 for amitriptyline and 12 for pregabalin)
Selective outcome reporting? *(reporting bias)*	Low	The study was registered at the Indian Council of Medical Research
Other bias		

Sponsorship if reported		
Study funding sources if reported	None	
Possible conflicts of interest for study authors	None declared	
Notes:		

Comments by DOWC staff

- As noted above, the open label design was probably due to the dosing schedules of the two drugs, and patients were informed that there were benefits to both drugs
- Therefore, the actual degree of compromise of the conclusions would depend on whether patients expected greater benefit from amitriptyline than from pregabalin, and this is far from being clear
- Part of the response rate could be attributable to the bedtime administration of amitriptyline versus the twice daily dosing of pregabalin; convenience of dosing is part of the source of bias but also part of the clinical usefulness of amitriptyline
- The exact equality of the mean VAS and Oswestry at baseline is somewhat curious, but the standard deviations were different
- In table 1, a larger proportion of patients had MRI signs of nerve root compression (68.4%) than disc protrusion (52.6%) or clinical radiculopathy (40.5%); this is an unusual pattern of findings, since asymptomatic disc protrusion is very common and since most nerve root compression is expected to be associated with a radiculopathic pattern of symptoms

Assessment by DOWC staff	
Overall assessment as suitability of evidence for the guideline ☐ High quality ☒ Adequate ☐ Inadequate	Rated as adequate rather than as high quality due only to the open label design of the study, but the comparison was probably not significantly compromised. The study is adequate for some evidence that in the setting of chronic low back pain with or without radiculopathy, amitriptyline is more effective than pregabalin at reducing pain and disability after 14 weeks of treatment

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

Additional references if relevant
-