Critique author	**Ed Whitney**

Bibliographic Data	
Authors	Boyle J, Eriksson ME, et al
Title	Randomized, placebo-controlled comparison of amitriptyline, duloxetine, and pregabalin in patients with chronic diabetic peripheral neuropathic pain: impact on pain, polysomnographic sleep, daytime functioning, and quality of life.
PMID	22991449
Citation	Pain Med. 2012;14(4):526-32
Other information if relevant	

Methods	
Aim of study	To compare amitriptyline, duloxetine, and pregabalin in the setting of painful diabetic neuropathy with respect to pain relief, sleep physiology, and cognitive function
Design	Randomized clinical trial

Participants	
Population from which participants are drawn	Patients 18 and older with type 1 or type 2 diabetes experiencing neuropathic pain of diabetic origin
Setting (location and type of facility)	Surrey Clinical Research Centre in the UK
Age	Mean age 65
Sex	57 men, 26 women
Total number of participants for whom outcome data were reported	83

Inclusion criteria	Diabetes mellitus for at least one year, with diabetic neuropathic pain with at least one of the following: dysesthesia, burning pain, cold or heat allodynia, shooting or lancinating pain, lower extremity hyperalgesia below mid-thigh level, with a score of >12 on the Leeds Assessment of Neuropathic Symptoms and Signs
Exclusion criteria	Evidence of cognitive impairment with a score of <25 on the Mini Mental State Exam, end-stage disease of a major system, evidence of severe hypoglycemic episodes in the past three years, recent cardiac or cerebral ischemic event, alcohol/recreational drug abuse, pregnancy, lactation
Other information if relevant	All participants had an 8 day placebo run-in period during which they completed pain diaries. Three in-clinic visits, each lasting 48 hours, were scheduled for all patients. At the first visit, done at the end of the placebo run-in, a baseline set of cognitive tests was done, and these tests were repeated at the second and third visits. In addition, at each in-clinic visit, patients underwent sleep studies with polysomnography (PSG) which recorded standard measurements such as total sleep time, sleep efficiency, sleep architecture, apnea/hypopnea index, oxygen desaturation, and nocturnal glucose. These sleep studies were done twice at each visit, once in order to acclimate the patient to the sleep lab, and once for assessment of PSG data

Intervention Groups

Group 1	
Group name	Pregabalin
Number in group	27
Description of intervention	Pregabalin titrated for 14 days at a dose of 150 mg bid, followed by 14 days of 300 mg bid
Duration of treatment period	Including the 8 day placebo run-in and the two 14 day drug titration periods, a total of 36 days
Co-interventions if reported	All patients were permitted to continue taking opioids and NSAIDS and were allowed to take up to 4 g acetaminophen per day
Additional information if relevant	

Group 2	
Group name	Duloxetine
Number in group	28

Description of intervention	Duloxetine titrated at a dose of 60 mg every morning for 14 days, followed by 60 mg bid for 14 days
Duration of treatment period	Including the 8 day placebo run-in and the two 14 day drug titration periods, a total of 36 days
Co-interventions if reported	All patients were permitted to continue taking opioids and NSAIDS and were allowed to take up to 4 g acetaminophen per day
Additional information if relevant	
Group 3	
Group name	Amitriptyline
Number in group	28
Description of intervention	Amitriptyline titrated at a dose of 25 mg bid for 14 days, followed by 25 mg in the morning and 50 mg at night
Duration of treatment period	Including the 8 day placebo run-in and the two 14 day drug titration periods, a total of 36 days
Co-interventions if reported	All patients were permitted to continue taking opioids and NSAIDS and were allowed to take up to 4 g acetaminophen per day
Additional information if relevant	

Primary outcome	
Outcome name and criteria for definition	Subjective pain as assessed by the Brief Pain Inventory (BPI)
Time points measured and/or reported	At the end of the 8 day placebo run-in, once at the clinic visit after the first dose titration period, and once at the clinic visit following the second dose titration period
Differences between groups	BPI measures of pain severity, pain interference, and VAS were all improved at the low dose and at the high dose at the end of the titration periods, with no difference in analgesic effectiveness between the three drugs

Additional information if relevant	BPI includes a pain diagram, four items on a scale of 0-10 relating to pain (worst pain in past week, least pain in past week, average pain, and current pain), one item on pain relief from medications, and seven items relating to how much the pain interferes with general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life. It does not include a VAS. The scale on which VAS was measured was adapted from the McGill pain questionnaire.

Secondary outcomes	
Outcome name and criteria for definition	- Numerous secondary outcomes were measured at each of the 48 hour clinic visits, and these did distinguish between the three test drugs - These secondary outcomes consisted of three domains: sleep, cognitive function, and glucose control - Each clinic visit did two full sleep studies on consecutive nights, and the cognitive tests were conducted on the day between the two sleep studies - A battery of neuropsychological tests was administered on these days to test daytime function - These tests included memory tasks (immediate and delayed word recall), reaction time tests, information processing tasks, digit symbol substitution tests, and other tests
Time points measured	At the end of the 8 day placebo run-in, at the end of the 14 day low dose drug titration, and at the end of the 14 day higher dose drug titration

Differences between groups	- There were differences between duloxetine and pregabalin on several of the dimensions of the polysomnogram, and these differences were not all in the same direction - The subjective sleep assessments were essentially equal between the three treatment groups - However, duloxetine was worse than pregabalin and amitriptyline for sleep continuity; duloxetine worsened sleep efficiency and reduced total sleep time compared to placebo, and also increased wake time after sleep onset compared to placebo - Pregabalin significantly increased sleep efficiency and total sleep time, also reducing wake after sleep onset compared to placebo - Amitriptyline had little effect on sleep efficiency and total sleep time - There were no differences between drugs in non-REM sleep - However, REM duration, percent REM, and number of REM cycles was reduced with duloxetine, but not with pregabalin or with amitriptyline - Pregabalin reduced periodic limb movements per hour of sleep compared with placebo; duloxetine and amitriptyline had no effect on these movements - By way of contrast, apneas and hypopneas were significantly increased with pregabalin; duloxetine and amitriptyline had no effect on these variables - Pregabalin also increased the number of oxygen desaturations per hour, but did not affect mean nocturnal oxygen saturation - During the daytime testing, the three groups did not differ on memory tasks - Daytime function appeared to be better on many other tests with duloxetine and with amitriptyline than with pregabalin: psychomotor reaction times were improved with duloxetine and amitriptyline but were prolonged with pregabalin - Tracking error was impaired with pregabalin but not with duloxetine or amitriptyline
Additional information if relevant	- There were small increases in nocturnal blood glucose with pregabalin, small decreases with duloxetine, and no changes with amitriptyline - 10 patients withdrew from the study due to adverse events: 6 from the pregabalin group, 3 from the duloxetine group, and 1 from the amitriptyline group - The withdrawals from the pregabalin group were due to fatigue, dizziness, and somnolence

Conclusions	
Key conclusions of study authors	- Duloxetine, pregabalin, and amitriptyline all reduce pain equally in patients with diabetic peripheral neuropathic pain - Daytime function on cognitive tasks was not impaired by any of the tested drugs - There was increased tracking error on some of the reaction time tests with pregabalin compared to the other two drugs - The sleep examinations gave support to a CNS-activating effect of duloxetine, which reduced total sleep time and disrupted REM sleep - Pregabalin, on the other hand, promoted sleep continuity and reduced periodic limb movements, but had an apparent increase in oxygen desaturations during sleep - Quality of life, as measured by serial administration of the SF-36, did not appear to improve during the 28 days of drug treatment

Risk of bias assessment		
Domain	Risk of bias Low High Unclear	Comments
Random sequence generation *(selection bias)*	Low	Randomization was stratified by age and gender to ensure balance between groups
Allocation concealment *(selection bias)*	Low	Randomization was done by an independent statistician who did the stratification; this probably ensured allocation concealment
Blinding of participants and personnel *(performance bias)*	Unclear	Study is stated to be double blinded, but the method of blinding is not described (i.e., no mention of identical appearing tablets dispensed through a central masked pharmacy)

Blinding of outcome assessment *(detection bias)*	Low	Although pain is by self-report, the sleep studies recorded objective parameters of sleep
Incomplete outcome data *(attrition bias)*	Unclear	Patients were all accounted for, but there were greater withdrawals from the pregabalin group due to CNS adverse events such as fatigue and somnolence
Selective outcome reporting? *(reporting bias)*	Low	The primary outcome was pain relief, but most of the reported results were of the numerous secondary measures, for which great efforts were expended in terms of repeated polysomnograms
Other bias		

Sponsorship if reported		
Study funding sources if reported	Pfizer	
Possible conflicts of interest for study authors	One of the authors received research grants from Pfizer. Other authors have received consultancy fees from Eli Lilly, Novo Nordisk, Abbot Diabetes Care, and Roche	
Notes:		

Comments by DOWC staff

- The study presents scant data on its primary outcome, but is worth reviewing primarily because it is unique in conducting precise measurements of sleep architecture and of daytime function with extensive neuropsychologic testing; since sleep is generally thought to be an important factor in chronic pain, these findings are of considerable interest
- The reporting of the pain outcome was not clear; the scale on which the VAS scores were reported makes no sense, with measurements which are all greater than 10 points, but are too low (on the order of 13 to 29 points) to represent any kind of clinically significant pain on the 100 point scale which is the other scale on which VAS is commonly reported
- The McGill pain, as referenced by the authors (Melzack 1987) has an unmarked horizontal line for the VAS, with no numbers on either side of the line; this is an unsatisfactory method of assessing VAS
- However, the sleep studies did show what are probably clinically important differences between drugs for average total sleep time on the higher doses (410 min for pregabalin vs 338 for duloxetine and 393 min for amitriptyline), duration of REM sleep (62 min for pregabalin vs 29.9 min for duloxetine and 50.2 for amitriptyline)
- By way of contrast, pregabalin had an average of desaturations of >4% per hour of sleep (10.2 versus 1.9 for duloxetine and 2.3 for amitriptyline) as well as the apnea-hypopnea index (11.9 for pregabalin vs. 2.3 for duloxetine and 2.9 for amitriptyline)
- The neuropsychological tests appeared to favor duloxetine over pregabalin, which seemed to increase tracking errors on specialized testing; however, the relevance of these tracking tests to real world function is not clear
- The number of dropouts due to dizziness and fatigue with pregabalin is of clinical importance, and may limit its usefulness in this population

Assessment by DOWC staff	
Overall assessment as suitability of evidence for the guideline ☐ High quality ☒ Adequate ☐ Inadequate	Duloxetine, pregabalin, and amitriptyline are approximately of equal benefit with respect to pain relief in the setting of diabetic peripheral neuropathy. There is some evidence that they exert different effects with respect to sleep variables. Total sleep time and REM sleep duration are likely to be greater with pregabalin than with duloxetine or amitriptyline. However, pregabalin is likely to lead to dizziness and fatigue more frequently than the other drugs, and oxygen desaturation during sleep also appears to be greater with pregabalin.
If inadequate, main reasons for recommending that the article not be cited as evidence	

Additional references if relevant
- Melzack R. The short-form McGill Pain Questionnaire. Pain 1987;30:191–197