

Van Seventer R, Bach FW, et al. Pregabalin in the treatment of post-traumatic peripheral neuropathic pain: a randomized double-blind trial. Eur J. Neurol 2010;17:1082-1089.

Design: Randomized clinical trial

Population/sample size/setting:

- 254 patients (129 women, 125 men, mean age 51) treated for post-traumatic pain at multiple centers in Europe and Canada
- Eligibility criteria were diagnosis by a pain specialist of post-traumatic (surgical, unspecified trauma, amputation) neuropathic pain at least 3 months after the inciting event, with a pain score of at least 40 on a 100 mm VAS, and to have completed a daily pain diary in the 2 weeks before treatment
- Exclusion criteria included diabetic or post-herpetic neuropathic pain, radiculopathy, trigeminal neuralgia, carpal tunnel syndrome, and CRPS I or II; taking gabapentin at the time of entry, creatinine clearance <60 ml/min, or positive urine illicit drug screen

Main outcome measures:

- Randomization was preceded by a 2 week placebo run-in period, during which patients were screened for meeting all entry requirements
- Randomized to 8 weeks of pregabalin (n=127) or to identical-appearing placebo (n=127)
- Mean duration of neuropathic pain was 4.4 years (maximum was 29 years in placebo group and 26 years in pregabalin group)
- Pain medications were being taken by 80% of both groups: opioids by 12% of placebo group and 16% of pregabalin group; tramadol by 32% of placebo group and by 33% of pregabalin group; about 1/3 of each group took anticonvulsant drugs other than gabapentin
- Study medication was begun at 150 mg/d and increased to 300 mg/d in the second week; the 300 mg dose could be increased to 600 mg in the third week if needed for efficacy; only one dose reduction was allowed
- Primary outcome was mean pain score during the last 7 entries in the daily pain diary
- Other outcomes were sleep, anxiety/depression scores, and Patient Global Impression of Change (PGIC) on a scale of 1=very much improved to 7=very much worse
- During the 8 week study period, 31 of 127 pregabalin and 29 of 127 placebo patients discontinued the study
- The dropouts in the pregabalin group were mostly due to adverse events (n=25); in the placebo group, lack of efficacy (n=12) and adverse event (n=9) accounted for most of the dropouts
- At the end of the study, the dose distribution of pregabalin was: 38 taking 150 mg, 58 taking 300 mg, and 30 taking 600 mg; the corresponding numbers taking the same "doses" for the placebo group were 13, 18, and 94

- For 30% improvement in pain score (moderate relief), pregabalin (50 of 126, or 39.7%) was better than placebo (32 of 125, or 25.4%)
- For 50% improvement (substantial benefit), pregabalin (30 of 126, or 23.8%) did not differ significantly from placebo (18 of 125, or 14.3%) [this not reported in the article, but supplied by the corresponding author on request]
- For PGIC, “much improved” or “very much improved” was better in the pregabalin group (40/120, or 33%) than in the placebo group (28/125, or 22%) [data presented in Fig. 2 do not give exact numbers; these were supplied by the corresponding author on request]
- Anxiety/depression scores did not change appreciably between baseline and the end of the study; no difference between pregabalin and placebo was recorded
- Sleep problems (100 point scale) improved in the pregabalin group (from 43.4 to 35.9) more than in the placebo group (from 45.9 to 44.6)
- Adverse events were reported in 86% of the pregabalin group and in 58% of the placebo group; dizziness, somnolence, and fatigue were the most common
- One patient on 600 mg pregabalin had dyspnea and tremor; the patient discontinued the study and recovered

Authors' conclusions:

- Pregabalin was significantly effective in treating post-traumatic neuropathic pain and sleep disturbances in an 8 week trial
- The two-week run-in with placebo did not appear to have removed a large number of placebo responders in this study, though it has been suggested to do so elsewhere
- The patient population was highly heterogeneous and had pain for an average of over 4 years; this may put into context the fact that there was not a statistically significant difference between pregabalin and placebo in the reduction of pain by 50% or more, since there is more variability in the data
- Pregabalin was generally well tolerated and provided meaningful patient benefit

Comments:

- The study is said to be randomized, but the method of sequence generation and concealment of allocation are not clearly stated (an “Interactive Voice Recognition System” was used to randomize patients, but this is not explained)
- Blinding is likely to have succeeded due to the identical-appearing placebo; overall, the risk of bias is probably not high
- The response rates are given for the entire pregabalin group together; it is not reported whether there were differences between the response rates of those receiving 150, 300, or 600 mg [first author has been contacted by e-mail for this information]
- As with other studies, a minority of patients treated with pregabalin have large improvements

Assessment: Adequate for evidence that pregabalin is likely to be effective in the treatment of post-traumatic neuropathic pain and the accompanying sleep disturbance, but that the drug may be highly effective in only a minority of patient