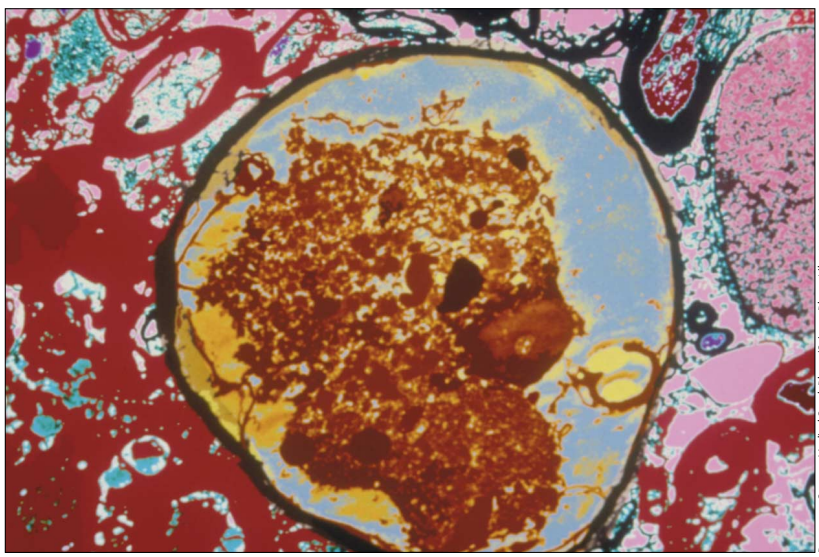
Pregabalin for painful neuropathy

Neuropathic pain can occur in systemic diseases or toxic states causing purely sensory or sensorimotor peripheral neuropathy and after peripheral nerve injury. Precise estimates of the prevalence of neuropathic pain are not available, but in the USA alone there may be more than 3 million people with painful diabetic neuropathy.[1] After nerve injury, estimated incidence of pain is 2·5–5%, and postherpetic neuralgia occurs in 10% of the patients after acute herpes zoster infection. Small-fibre damage and partial axonal injury seem to be prerequisites for the development of neuropathic pain, and the mechanisms involve both peripheral and central sensitisation. Increases in glutamate activity at the NMDA receptor sites and release of other excitatory neurotransmitters (eg, substance P and calcitonin gene-related peptide) are among the best known central changes after nerve injury. Structurally related to gabapentin, pregabalin selectively binds to the α_2-δ subunit of the voltage dependent calcium channel thereby blocking the influx of calcium into presynaptic nerve terminals and reducing the release of excitatory neurotransmitters.[2] Similarly to gabapentin, which is effective in the treatment of neuropathic pain,[1,3] pregabalin specifically targets an important pronociceptive site of the central sensitisation cascade.

Complaints of pain by patients with peripheral neuropathy are easily overlooked because the main concern may lie in the search for the cause of polyneuropathy or surgical treatment possibilities in focal nerve lesions. In addition, treatment of neuropathic pain is commonly thought of as difficult. With recommended pharmacological treatments, clinically significant pain relief (usually defined as at least a 50% decrease in pain intensity on a subjective rating scale) can be achieved in about a half to two-thirds of patients. Scarcity of large, adequately blinded, randomised controlled trials makes it difficult to plan optimum treatment for individual patients.

In a recent multicentre randomised controlled trial[2] in 338 patients, pregabalin was effective in the treatment of painful diabetic distal sensorimotor neuropathy. This is one of the largest studies on the treatment of neuropathic pain ever done. In addition to the primary efficacy measure—reduction of pain intensity on a numerical rating scale (0–10)—it included several secondary measures of quality of life.[2] The number needed to treat (NNT) to obtain one patient with at least 50% reduction in pain rating was, I calculated, 3·6 at a dose of 300 mg/day and 3·3 at 600 mg/day. This is somewhat better than the NNT of 4·1 reported for gabapentin in a meta-analysis.[3] In addition to the significant reduction of pain intensity, pregabalin also substantially improved secondary efficacy measures such as sleep interference scores, social function, and tension-anxiety mood scores.[2] Pregabalin is also effective for postherpetic neuralgia (NNT 3·3).[4]



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Damage to axons in the peripheral nervous system causes neuropathic pain in diabetes

The main weakness of this multicentre trial of pregabalin for painful diabetic neuropathy[2] is common to most clinical trials of treatments for neuropathic pain—the poorly defined diagnosis of neuropathy. Because the researchers did not give details of the diagnostic work-up and criteria, the diagnosis of polyneuropathy was presumably based on history and clinical examination only; hence diagnosis accuracy was likely poor.[5] Diagnostic accuracy necessary for clinical trials on polyneuropathy can only be achieved with a combination of concordant clinical and electrodiagnostic findings.[5] The lack of exact operational definition of polyneuropathy results in inconsistency in the selection of patients. As regards this particular study,[2] one might ask whether all of the non-responders had true neuropathic pain. Furthermore, electrodiagnostic and thermal quantitative sensory testing would allow quantification and detailed profiling of the neurophysiological and psychophysical features of the pain in individual patients. This might elucidate the rationale for differences in efficacy of a given drug. Another question arises from the fact that gabapentin non-responders (at $\geqslant$1200 mg/day) were excluded.[2] This is an unusual exclusion criterion, and may have influenced the results.

Although there are no direct comparison studies, pregabalin seems to offer certain practical advantages compared with gabapentin (eg, linear pharmacokinetics across its therapeutic range with low variability among patients[2] and lower cost). Unlike gabapentin, a long individual titration period is unnecessary with pregabalin: 300 mg /day was started at full dose, and 600 mg/day was

titrated over 1 week, and the compliance was excellent. The reported adverse effects (somnolence, dizziness, and peripheral oedema) were generally mild to moderate, and did not lead to discontinuation from the study.[2]

When choosing drugs to treat neuropathic pain and taking cost-effectiveness into account, the inexpensive tricyclic antidepressants, with NNTs between 1·6 and 3·3,[3,4] should still be considered first line treatment. Nevertheless, as there are no serious adverse effects or known drug interactions, pregabalin presents an effective alternative for neuropathic pain in the elderly, in patients on polypharmacy, or in psychiatric patients at risk of suicide or substance abuse. Pregabalin has not been studied in combination therapy. With its very selective mechanism of action, it should be useful as an add-on to tricyclics, opioids, or dopamine agonists alleviating pain via different central mechanisms.

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I have no conflicts of interest.

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