Gabapentin

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Introduction
Gabapentin, an analogue of the inhibitory neurotransmitter GABA (γ-aminobutyric acid), is an anticonvulsant medication with recognised efficacy in the treatment of both epilepsy and neuropathic pain. It is frequently used in diabetes for the treatment of painful neuropathy.

Pharmacology
Figure 1 outlines the proposed pharmacological action of gabapentin which was initially synthesised to mimic the chemical structure of the inhibitory neurotransmitter GABA. Its exact mechanism of action is unknown, with no evidence that it binds directly to GABA receptors nor that it has any effect on the uptake or breakdown of GABA.

However, in neuropathic pain the therapeutic effect is thought to be related to its affinity for the α2δ1 subunit on pre-synaptic voltage-gated N-type calcium ion channels in the central nervous system. Gabapentin binds to the α2δ1 subunit, inhibiting calcium influx leading to reduced neurotransmitter release and attenuation of post-synaptic activity. Other effects include activation of GABAB receptors, modulation of pre-synaptic NMDA (N-methyl-D-aspartic acid) receptors and reduced release of glutamate and other excitatory neurotransmitters.

Gabapentin is renally excreted and dose reduction is required in those with a creatinine clearance of <60ml/min.

Trials of safety and efficacy
Gabapentin was first licensed in 1994 as adjunctive therapy for the treatment of partial seizures. Since then, over 8.7 million patients have received gabapentin in clinical trials and everyday practice without any evidence of any serious organ toxicity.

In a double-blind, randomised, placebo-controlled study conducted to evaluate the efficacy and safety of gabapentin in the treatment of neuropathic pain, 305 patients were randomised to receive either gabapentin or placebo over an eight-week period. Patients had a wide range of neuropathic pain syndromes and were recruited based on the presence of two or more of the following symptoms: allodynia, burning pain, shooting pain, or hyperalgesia. Gabapentin was given in three divided doses, initially titrated to 900mg/day over three days, followed by two further increases, to a maximum of 2400mg/day if required.1

In the gabapentin group there was a mean reduction of average daily pain score of 21% compared to a 14% reduction in placebo treated patients (p=0.048). Improvements were also shown in patient-reported outcomes in quality of life. Gabapentin was well tolerated and the majority of patients completed the study (79% vs 73% for placebo). The most common adverse events were mild to moderate dizziness and somnolence, most of which were transient and occurred during the titration phase.

Specific evidence for use in diabetes
Monotherapy
Several studies have examined the analgesic effects of gabapentin in patients with painful diabetic peripheral neuropathy. The largest of these was an eight-week randomised, double-blind, placebo-controlled study conducted in the United States. In all, 165 patients with a one- to five-year history of painful diabetic peripheral neuropathy and a minimum 40mm pain score on the

**Figure 1. The proposed pharmacological action of gabapentin (see ‘Notes’ below the diagram)**

![Diagram of Gabapentin's Action](https://example.com/gabapentin-diagram)

NOTES. Gabapentin is thought to work in neuropathic pain by binding to the α1δ2 subunit of the pre-synaptic voltage-gated calcium channel, inhibiting calcium influx and reducing neurotransmitter release. Other mechanisms may also be involved, including modulation of the N-methyl-D-aspartic acid (NMDA) receptors.
Two studies have looked at combination therapy with opiates.

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Despite proven efficacy as monotherapy, approximately 50% of patients fail to respond to gabapentin therapy and, in the 50% who do respond, a significant proportion of these are left with significant residual pain. Two studies have looked at combination therapy with opiates.

One looked at gabapentin versus or in combination with morphine in a randomised, active placebo-controlled, clinical cross-over study. Fifty-seven patients with neuropathic pain, including 33 with painful diabetic neuropathy, were randomised to receive morphine, gabapentin, a combination of gabapentin and morphine, or active placebo (lorazepam). Combination therapy with gabapentin and morphine resulted in lower daily pain scores than in the groups treated with morphine (p=0.04), gabapentin (p<0.001), and placebo (p=0.001). Combination therapy was also associated with less pain-related interference with mood and with higher scores for vitality and social functioning. Lower doses of both gabapentin and morphine were required in the combination therapy group suggesting a possible additive effect. At the maximum tolerated doses the combination group had a higher frequency of constipation than in the gabapentin group (p<0.05) and a higher frequency of dry mouth than in the morphine alone group (p<0.05), but the combination was otherwise well tolerated. It is difficult to comment on sedation frequency as a sedative placebo was used.

In a larger multi-centre placebo-controlled study, 338 patients with a three-month history of pain due to diabetic neuropathy, on a stable maximum tolerated dose of gabapentin and with moderate to severe residual pain, were randomised to treatment with long acting oxycodone (OxyContin) or placebo. Combination therapy with oxycodone and gabapentin was found to reduce mean daily pain scores by 33% from baseline (p=0.007). Patients in the combination therapy group also required less breakthrough medication (paracetamol) (p=0.03), had fewer nights of disturbed sleep (p<0.05) and had a much lower rate of discontinuation due to lack of therapeutic effect (14% vs 54%) than those treated with gabapentin alone. Opiate-induced adverse events were not exacerbated by the combination therapy.

Discussion

Gabapentin appears to have a role in the treatment of painful diabetic peripheral neuropathy by providing partial pain relief and also appears to have positive effects on sleep disturbance, mood and quality of life. Combination therapy with either morphine or long acting oxycodone appears to provide more effective analgesia than monotherapy alone. This most likely reflects the multiple mechanisms resulting in neuropathic pain.

The most efficacious dose of gabapentin therapy is not entirely clear, with study doses ranging from 600–3600mg per day. Most studies have attempted to mimic clinical practice by allowing the maximum tolerated dose aiming to achieve maximum efficacy while minimising the occurrence of adverse effects. The evidence described above is generally limited by small study numbers, and further research is required into specific doses and over a longer time period.

Conflict of interest statement

Dr MacEwan and Dr McKay have no conflict of interest. Dr Fisher has received lecture fees from and has advised on advisory panels for Pfizer.

References