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Antiepileptic Drugs in the Treatment of Neuropathic Pain

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Abstract

Antiepileptic drugs are an effective treatment for various forms of neuropathic pain of peripheral origin, although they rarely provide complete pain relief. Multiple multicentre randomised controlled trials have shown clear efficacy of gabapentin and pregabalin for postherpetic neuralgia and painful diabetic neuropathy. Theses drugs can be rapidly titrated and are well tolerated. Topiramate, lamotrigine, carbamazepine and oxcarbazepine are alternatives for the treatment of painful diabetic neuropathy, but should be titrated slowly. Carbamazepine remains the drug of choice for trigeminal neuralgia; however, oxcarbazepine and lamotrigine are potential alternatives.

There is an apparent need for large-scale randomised controlled trials on the efficacy of antiepileptic drugs in neuropathic pain in general, and in cancer-related neuropathic pain and neuropathic pain of central origin in particular. Trials with long-term follow-up are required to establish the long-term efficacy of antiepileptic drugs in neuropathic pain. There is only limited scientific evidence to support the idea that drug combinations are likely to be more efficacious and safer than each drug alone; further studies are warranted in this area.

According to Foley,[1] 2 million individuals in the US experience neuropathic pain. Neuropathic pain is complicated in terms of its diagnosis and management. It has multiple aetiologies, and may be associated with trauma, inflammation, ischaemia, metabolic disorders and other insults to the peripheral or central somatosensory nervous system. Common examples of neuropathic pain include diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia and central post-stroke pain. In addition, neuropathic pain has many different presenting symptoms, including spontaneous burning, aching or shooting pain sensations, abnormal sensitivity to normal, innocuous stimuli (allodynia), or increased sensitivity to noxious stimuli (hyperalgesia).[2] Neuropathic pain, like many other forms of chronic pain, often has a negative impact on quality of life (QOL).

Mainstream pharmacotherapy for neuropathic pain involves the administration of antidepressants, antiepileptic agents and opioids. Clinical trials with the aim of assessing the efficacy and safety of antiepileptic drugs for the treatment neuropathic

pain have been conducted for nearly 4 decades. However, effective analgesia has been shown in fewer than half of the patients with neuropathic pain who have received antiepileptic drugs.[3] Such outcomes may be partially attributable to the large variability in the presentation of each neuropathic pain syndrome and to the lack of a clear understanding of the precise neural mechanisms underlying each clinical symptom. Thus, our current knowledge does not allow us to determine if one drug is more efficacious than another in reducing, for example, the burning pain or allodynia experienced by a patient with postherpetic neuralgia. Another cause for the relatively high proportion of treatment failures with antiepileptics is the high prevalence of toxicity associated with their use. Carbamazepine, for example, one of the oldest drugs in this class, is still being commonly prescribed for various forms of neuropathic pain, even though its use is associated with frequent (and sometimes serious) adverse events.[4,5]

The emergence of newer drugs, such as gabapentin, lamotrigine, topiramate, pregabalin and others, which have been tested in a wider range of neuropathic pain syndromes, in part in large-scale high-quality trials, seems to have opened new avenues of therapy for these disorders.

This article critically reviews the published literature in this area and provides updated information on the efficacy and safety of the currently available antiepileptic drugs for the treatment of neuropathic pain. The main pharmacological properties of the drugs are summarised in table I, whereas a summary of the relevant randomised controlled trials (RCTs) can be found in table II.

1. Carbamazepine

1.1 Pharmacology

When used in the treatment and prevention of seizures, carbamazepine has a 'therapeutic window' of 4–12 μg/mL,[53] but the therapeutic concentration required for pain therapy has not yet been established. Oral tablets have a bioavailability of 70–80%[54] and this is increased by the presence of food in the stomach. Carbamazepine is 76% protein bound.[55] The drug is mainly metabolised in the liver (98%) via the cytochrome P450 (CYP) isoenzyme 3A4. During prolonged treatment, carbamazepine induces its own metabolism. Carbamazepine-10,11-epoxide is an active metabolite of carbamazepine, which is partly responsible for carbamazepine intoxication.[54] Higher concentrations of the epoxide are seen in patients receiving concomitant sodium valproate or lamotrigine therapy.[56] Excretion of the drug is 72% renal and 28% faecal.[54] The half-life of a single dose is 25–65 hours. Carbamazepine can be eliminated by haemodialysis, but concentrations are only minimally affected by peritoneal dialysis.[57]

1.2 Analgesic Mechanisms

Animal studies have shown that carbamazepine blocks voltage-dependent sodium channels. Its analgesic mechanism is therefore believed to be related to a reduction in ectopic nerve discharges and stabilisation of neural membranes.[58]

1.3 Clinical Efficacy

1.3.1 Trigeminal Neuralgia

Trigeminal neuralgia is one of the main disorders treated with carbamazepine. Most studies that have examined the use of carbamazepine in this disorder were conducted in the 1960s–70s in small groups of patients. It was found that 58–80% of the patients had better pain relief with carbamazepine than with placebo.[6-8,59] In a 5-day trial, in which the carbamazepine dosage was titrated up to 1000 mg/day, a complete or very good response was reported by 19 of 27 treated patients.[8] A higher dosage, of up to 2400 mg/day, was used in a 2-week trial that resulted in a good to excellent response in 15 of 20 randomised patients.[6] The largest trial included 77 patients who were treated with carbamazepine 400–800 mg/day for 2 weeks. Maximal pain intensity dropped by 58% during active treatment, compared with a 26% reduction in patients receiving placebo.[7] In another small, short-term (3-week) trial, carbamazepine at a maximal dosage of 900 mg/day was more effective than tizanidine (an α_2-adrenergic agonist) for the reduction of pain intensity measured using a visual analogue scale (VAS).[9] A further study compared carbamazepine 1200 mg/day with pimozide 12 mg/day (a diphenylbutylpiperidine derivative with neuroleptic proper-

Table I. A summary of the main pharmacological characteristics of antiepileptic drugs used for the treatment of neuropathic pain

Characteristics	Carbamazepine	Oxcarbazepine	Topiramate	Gabapentin	Lamotrigine	Pregabalin
Bioavailability (%)	70–80	Oral dose totally absorbed	80	60 (dose dependent)	98	90
Protein binding (%)	76	40–60	9–41	3–13	56	Not protein bound
Inhibits CYP	No	2C19	2C19	No	No	No
Metabolised by CYP	3A4, 2C8, 2C9, 1A2	No	1A2, 2A6	No	No	No studies
Induces CYP	2C9, 3A Family	3A4, 3A5	No	No	No	
Active metabolites	Carbamazepine 10,11-epoxide	10-hydroxy carbazepine	Probably active	No metabolites	Inactive 2N-glucuronide	No metabolites
Elimination half-life (h)	25–65	Parent drug: 1–2.5 Active metabolite: 9	18–24	5–7	13–30	6.3
Dialysis[a]	Haemodialysis	Unknown	Haemodialysis	Haemodialysis	Unknown	Haemodialysis[b]
Effect of food on absorption	Fat increases absorption	No effect	No effect	No effect	No effect	No effect
Use in patients with liver impairment	Contraindicated	No dose modification required	Dose reduction required	Not established	Child-Pugh B, reduce dose by 50%; Child-Pugh C, reduce dose by 75%	Not established
Use in patients with renal impairment	No dose modification required	Loading dose reduction by half required	Dose reduction by at least half required	Renal clearance decreases (may require dose reduction)	Dose reduction required	Dose reduction according to CL_{CR} required[c]
Main drug interactions	Azithromycin, clarithromycin, ciclosporin, anti-HIV drugs, warfarin, valproic acid (valproate sodium), tramadol, tiagabine, topiramate, antidepressants, chemotherapy, oxcarbazepine, phenytoin, hypericum (St John's Wort)	Carbamazepine, ethinyl estradiol, evening primrose oil, *Ginkgo biloba*	Carbamazepine, estrogens, *Ginkgo biloba*, evening primrose oil, phenytoin	Antacids (aluminium, magnesium), cimetidine, felbamate, phenytoin	Oxcarbazepine, estrogens, *Ginkgo biloba*, evening primrose oil, carbamazepine, valproic acid, ritonavir, phenytoin	Not yet established

a Eliminated by dialysis.

b Supplemental doses must be added after 4 hours of dialysis.

c If ≥60 mL/min: full dose; 30–60 mL/min: half-dose; 15–30 mL/min: one-quarter of the planned dose; <15 mL/min: one-sixth of the planned dose.

CL_{CR} = creatinine clearance; **CYP** = cytochrome P450.

Table II. A summary of the randomised controlled trials of antiepileptic drugs in the treatment of neuropathic pain (table refers only to full-length published articles)

Study	Diagnosis	Design	No. of pts treated with active drug	Maximal dosage (mg/day)	Treatment duration (wk)	Results
Carbamazepine						
Nicol[6]	Trigeminal neuralgia	co	20	2400	2	Carbamazepine > placebo
Campbell et al.[7]	Trigeminal neuralgia	co	77	800	2	Carbamazepine > placebo
Killan and Fromm[8]	Trigeminal neuralgia	co	27	1000	5 days	Carbamazepine > placebo
Vilming et al.[9]	Trigeminal neuralgia	pg	6	900	3	Carbamazepine > tizanidine
Lechin et al.[10]	Trigeminal neuralgia	co	48	1200	8	Carbamazepine < pimozide
Lindstrom and Lindblom[11]	Trigeminal neuralgia	co	12	Maximal tolerated	2	Carbamazepine = tocainide
Rull et al.[12]	Diabetic polyneuropathy	co	30	400	2	Carbamazepine > placebo
Wilton[13]	Diabetic polyneuropathy	co	40	400	2	Carbamazepine > placebo
Gomez-Perez et al.[14]	Diabetic polyneuropathy	co	16	200	4	Carbamazepine = nortriptyline
Harke et al.[15]	Mixed types	pg	43	600	8 days	Carbamazepine > placebo
Oxcarbazepine						
Dogra et al.[16]	Diabetic polyneuropathy	pg	69	1800	16	Oxcarbazepine > placebo
Groskopf et al.[17]	Diabetic polyneuropathy	pg	71	1200	16	Oxcarbazepine = placebo
Topiramate						
Thienel et al.[18]	Diabetic polyneuropathy	pg	878	400	18–22	Topiramate = placebo[a]
Raskin et al.[19]	Diabetic polyneuropathy	pg	214	400	12	Topiramate > placebo
Khoromi et al.[20]	Lumber radiculopathy	co	42	200	8	Topiramate = diphenhydramine; topiramate > diphenhydramine[b]
Gabapentin						
Hahn et al.[21]	HIV-related neuropathy	pg	15	2400	4	Gabapentin > placebo
Rice and Maton[22]	Postherpetic neuralgia	pg	223	2400	7	Gabapentin > placebo
Rowbotham et al.[23]	Postherpetic neuralgia	pg	113	3600	8	Gabapentin > placebo
Pandey et al.[24]	Guillian-Barre syndrome	co	18	15 mg/kg/day	1	Gabapentin > placebo; gabapentin > carbamazepine
Pandey et al.[25]	Guillian-Barre syndrome	pg	12	900	1	Gabapentin > placebo
Caraceni et al.[26]	Neuropathic cancer pain	pg	79	1800	10 days	Gabapentin > placebo
Backonja et al.[27]	Diabetic polyneuropathy	pg	84	3600	8	Gabapentin > placebo
Morello et al.[28]	Diabetic polyneuropathy	co	26	1800	6	Gabapentin = amitriptyline

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Table II. Contd

Study	Diagnosis	Design	No. of pts treated with active drug	Maximal dosage (mg/day)	Treatment duration (wk)	Results
Gilron et al.[29]	Diabetic polyneuropathy + postherpetic neuralgia	co	57	3200	5	Gabapentin > lorazepam; gabapentin < morphine; gabapentin < gabapentin + morphine[c]
van de Vusse et al.[30]	Complex regional pain syndrome I	co	58	1800	3	Gabapentin > placebo
Bone et al.[31]	Phantom limb	co	19	2400	6	Gabapentin > placebo
Levendoglu et al.[32]	Spinal cord injury	co	20	3600	8	Gabapentin > placebo
Tai et al.[33]	Spinal cord injury	co	7	1800	4	Gabapentin > placebo[d]
Serpell et al.[34]	Mixed types	pg	153	2400	8	Gabapentin > placebo
Lamotrigine						
Eisenberg et al.[35]	Diabetic polyneuropathy	pg	29	400	8	Lamotrigine > placebo
Simpson et al.[36]	HIV-related neuropathy	pg	20	300	14	Lamotrigine > placebo
Simpson et al.[37]	HIV-related neuropathy	pg	150	600	11	Lamotrigine = placebo; lamotrigine > placebo[e]
Vinik et al.[38]	Diabetic polyneuropathy	pg	360	400	19	Lamotrigine > placebo[f]
Finnerup et al.[39]	Spinal cord injury	co	22	400	8	Lamotrigine = placebo; lamotrigine > placebo[g]
Vestergaard et al.[40]	Central post-stroke pain	co	30	200	8	Lamotrigine > placebo
Zakrzewska et al.[41]	Trigeminal neuralgia	co	14	400	2	Lamotrigine > placebo
McCleane[42]	Mixed types	pg	50	200	8	Lamotrigine = placebo
Pregabalin						
Richter et al.[43]	Diabetic polyneuropathy	pg	161	600	6	Pregabalin > placebo
Lesser et al.[44]	Diabetic polyneuropathy	pg	240	600	5	Pregabalin > placebo
Rosenstock et al.[45]	Diabetic polyneuropathy	pg	76	300	8	Pregabalin > placebo
Freynhagen et al.[46]	Diabetic polyneuropathy + postherpetic neuralgia	pg	273	600	12	Pregabalin > placebo
Sabatowski et al.[47]	Postherpetic neuralgia	pg	157	300	8	Pregabalin > placebo
Dworkin et al.[48]	Postherpetic neuralgia	pg	89	600	8	Pregabalin > placebo
van Seventer et al.[49]	Postherpetic neuralgia	pg	273	600	13	Pregabalin > placebo
Zonisamide						
Atli and Dogra[50]	Diabetic polyneuropathy	pg	13	600	12	Zonisamide = placebo

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Table II. Contd

Study	Diagnosis	Design	No. of pts treated with active drug	Maximal dosage (mg/day)	Treatment duration (wk)	Results
Valproic acid						
Otto et al.[51]	Mixed types	co	31	1500	4	Valproic acid = placebo
Divalproex sodium (valproate semisodium)						
Kochar et al.[52]	Postherpetic neuralgia	pg	48	1000	9	Divalproex sodium = placebo

a Findings from three double-blind placebo-controlled trials.

b No significant difference between topiramate and placebo in pain score (primary outcome measure), but significant difference in global pain relief score.

c In this four-arm study, gabapentin was superior to placebo, but less effective than morphine and the combination of gabapentin plus morphine.

d A significant decrease of 'unpleasant feeling' and a trend toward a decrease in both the 'pain intensity' and burning sensation.

e Lamotrigine was superior to placebo in patients who received neurotoxic antiretroviral therapy, but not in patients who did not receive such therapy.

f Pooled data from two trials; only lamotrigine 400 mg/day, but not 200 mg/day or 300 mg/day, was superior to placebo.

g Lamotrigine was superior to placebo in patients with incomplete spinal cord injury and evoked pain, but equal to placebo in patients with complete spinal cord injury without evoked pain.

co = crossover; **pg** = parallel group; **pts** = patients; **>** indicates that antiepileptic drug was superior to the comparator in terms of pain reduction; **<** indicates that antiepileptic drug was inferior to the comparator in terms of pain reduction; **=** indicates that antiepileptic drug was equal to the comparator in terms of pain reduction.

ties) for 8 weeks.[10] Each of the 48 enrolled patients was switched to the other therapy for an additional 8 weeks (crossover design), following a 4-week washout interval. A greater reduction in pain was noted with pimozide than with carbamazepine treatment. Intravenous tocainide (an antiarrhythmic drug) was as effective as the maximal tolerated oral dose of carbamazepine in another crossover study with 2-week treatment periods in 12 patients with trigeminal neuralgia.[11]

1.3.2 Diabetic Neuropathy

Carbamazepine was also one of the first antiepileptic drugs used in the treatment of painful diabetic neuropathy. In a 2-week, placebo-controlled, crossover study, pain relief was reported in 28 of the 30 participants.[12] In another 2-week, crossover study in 40 patients with painful diabetic neuropathy, a significantly greater reduction in pain was recorded with the active drug compared with placebo on days 10 and 14.[13] A small number of clinical trials of carbamazepine in patients with painful diabetic neuropathy have been conducted more recently.[14,15] Carbamazepine was compared with the tricyclic antidepressant nortriptyline for the treatment of painful diabetic neuropathy in a 30-day crossover trial, and no difference in pain reduction was observed between the two treatments.[14] Notably, both treatments resulted in significant reductions (≥50%) from baseline in pain and paraesthesia.

1.3.3 Other Forms of Neuropathic Pain

An interesting study was conducted in 43 patients with neuropathic pain of peripheral origin that was responsive to spinal cord stimulation (SCS).[15] Patients were converted to a painful state by inactivation of SCS and were randomised to receive either carbamazepine (600 mg/day) or placebo for 8 days. In cases of intolerable pain, patients were authorised to reactivate their SCS. A significant delay in the increase of pain was observed in patients who received carbamazepine compared with those who received placebo. Notably, only 2 of 22 carbamazepine-treated patients experienced complete pain relief and preferred to continue the medication rather than switching back to SCS.

The numbers needed to treat (NNT) in order to achieve a 50% reduction in pain with carbamazepine in patients with trigeminal neuralgia and painful

diabetic neuropathy found in a systematic review were 2.6 (range 2.2–3.3) and 3.3 (range 2–9.4), respectively.[60,61] However, these figures were based primarily on old trials (performed in the 1960s and 70s), most of which were conducted in small patient groups and for relatively short treatment periods. Nonetheless, the quality of studies of carbamazepine in trigeminal neuralgia is still rated as level 1 (good quality, patient-oriented evidence); however, the quality of studies of carbamazepine in painful diabetic neuropathy and other forms of neuropathic pain is rated level 3 (not good evidence).[60,61]

1.4 Safety

According to one study,[13] more than half of the patients treated with carbamazepine experienced adverse effects from the treatment. In another study, more prominent adverse effects were noted with pimozide-treatment than with carbamazepine.[10] Common adverse effects include dizziness, nausea, drowsiness, blurred vision and ataxia. Rare, but serious adverse effects include leukopenia, impairment of liver function and reduction of plasma sodium levels, which is generally attributed to the syndrome of inappropriate antidiuretic hormone, although this mechanism is not well established.[4,5]

2. Oxcarbazepine

2.1 Pharmacology

Oxcarbazepine is keto-analogue of carbamazepine. The therapeutic windows for the treatment of seizures and for pain therapy with this drug have yet not been established.[62] Oral absorption is rapid, with no food effect, and the time to peak concentration is 4.5 hours (range 3–13 hours).[63] The drug is 40–60% albumin-bound.[64] The liver is the main organ involved in the metabolism of the drug, but mild to moderate hepatic impairment does not significantly affect the pharmacokinetic profile of oxcarbazepine.[65] The active metabolite, 10-hydroxy-carbazepine, is primarily excreted in the urine as the glucuoronide conjugate.[66] The parent drug has a half-life of 1–2.5 hours, which is prolonged to 19 hours in patients with renal impairment (creatinine clearance <30 mL/min).[67] It is generally accepted that the rapid conversion of oxcarbazepine to the monohydroxy derivative provides its antinociceptive effect.[68]

2.2 Analgesic Mechanisms

The analgesic mechanism of oxcarbazepine has not been established yet, but is likely to be related to its antiepileptic mechanism of action, which is similar to that of carbamazepine. Oxcarbazepine and its active 10-hydroxy metabolite inhibit voltage-dependent sodium channels and also, to a lesser extent, potassium channels.[68] In models of neuropathic pain in cats, oxcarbazepine has been shown to dose-dependently inhibit evoked potentials in damaged nerves.

2.3 Clinical Efficacy

2.3.1 Trigeminal Neuralgia

The efficacy of oxcarbazepine in relieving trigeminal neuralgia has been tested in three RCTs.[69-71] It should be noted that these studies have only been presented in abstract form thus far. In one crossover trial in 15 patients, oxcarbazepine, at dosages of 900–1200 mg/day administered for 3 weeks, had an analgesic effect comparable to that of carbamazepine 400–1200 mg/day.[69] This was confirmed in two other studies, one in patients with new-onset trigeminal neuralgia[70] and one in patients with trigeminal neuralgia that was refractory to previous treatments.[71] Oxcarbazepine was as effective as carbamazepine in reducing the number of weekly pain attacks (91% reduction with oxcarbazepine and 88% with carbamazepine), decreasing evoked pain, and as reflected by the global assessment of efficacy and safety. In the majority of patients, the effective dosage ranged from 600 to 1200 mg/day, although patients with intractable trigeminal neuralgia may need dosages as high as 2400 mg/day.

2.3.2 Diabetic Neuropathy

The effectiveness of oxcarbazepine in the treatment of painful diabetic neuropathy was studied in a multicentre, double-blind, placebo-controlled, 16-week trial.[16] Oxcarbazepine was initiated at a dosage of 300 mg/day and titrated over 4 weeks to a maximal dosage of 1800 mg/day and then continued at a maintenance dose (mean 1445 ± SD 389 mg/

day). Sixty-nine patients were treated with oxcarbazepine and 77 received placebo. A significant decrease in average pain score (VAS) from baseline was observed in the active drug-treated group ($p = 0.01$). Also, a greater proportion of patients in the oxcarbazepine-treated group reported a ≥50% pain reduction from baseline (active drug 35.2%; placebo 18.4%; $p = 0.02$). The NNT was determined to be 6.0. Secondary parameters such as the patients' global assessment of therapeutic effect, sleep disturbances and QOL also showed significant improvement in the oxcarbazepine treatment group compared with the placebo group. A second RCT evaluated the efficacy and safety of oxcarbazepine 1200 mg/day in patients with diabetic polyneuropathy.[17] In this multicentre, 16-week trial, 71 patients were randomised to receive oxcarbazepine and 70 were randomised to receive placebo. The primary efficacy variable was the change in mean pain score from baseline. The results failed to show a statistically significant difference in therapeutic effect between the two treatments.

2.3.3 Other Forms of Neuropathic Pain

A total of 136 patients were enrolled in seven studies on oxcarbazepine for the treatment of a mixture of types of neuropathic pain (i.e. radiculopathy, painful diabetic neuropathy, trigeminal neuralgia and others).[72] All were open-label, monotherapy trials of 9 weeks' duration and consisted of a 1-week prospective screening phase that was followed by an 8-week treatment phase. The treatment phase was divided into a 4-week titration period (initiated at 150–300 mg/day and increased by 150mg increments every 3–5 days until efficacy was achieved or to the maximum tolerated dose or 1800 mg/day), and was followed by a 4-week fixed-dose maintenance period. The mean pain VAS score decreased from 77 at baseline to 38 following oxcarbazepine treatment (a mean reduction of 50.2%). The proportion of patients who responded to treatment (had a mean pain VAS score reduction ≥50%) was 49.2%.

The efficacy and tolerability of oxcarbazepine in postherpetic neuralgia has also been evaluated in open-label trial.[73] Twenty-four patients who were unresponsive to treatment with other antiepileptic drugs (carbamazepine and gabapentin) and local anaesthetic blocks were treated with oxcarbazepine (maintenance dose of 900 mg/day) for 8 weeks. A significant decrease in the mean pain VAS score from baseline, a clinically significant reduction in allodynia and improvements in patients' functioning and QOL were noted.

In summary, oxcarbazepine seems to have similar efficacy to carbamazepine in the treatment of trigeminal neuralgia; however, overall, there are only limited data regarding the efficacy and safety of this drug in the treatment of other neuropathic pain syndromes.

2.4 Safety

Data from a trial in patients with painful diabetic neuropathy[16] showed that the most common adverse effects associated with oxcarbazepine use were dizziness, somnolence and gastrointestinal complaints such as diarrhoea and nausea/vomiting. Dermatological complications such as erythema multiforme are rare. In this trial, 27.5% of the patients receiving oxcarbazepine discontinued drug therapy because of adverse effects (vs 7.8% in the placebo group), mostly during the titration period. In the trial that involved patients with a mixture of types of neuropathy,[72] adverse events occurred in 56% of the patients, but none of the patients withdrew from the trial because of adverse events. Hyponatraemia was not reported in any of these trials.

3. Topiramate

3.1 Pharmacology

The therapeutic drug concentration of topiramate required for epilepsy or pain control therapy has not yet been established.[74] After an oral dose, the time to maximum concentration is 1.5–4 hours.[75] Peak plasma concentrations of 1.7, 3.7 and 8 μg/mL, respectively, have been found following oral administration of topiramate 100, 200 and 400mg; with multiple doses, accumulation is observed (approximately 2-fold).[75] The relative bioavailability of topiramate in tablet form compared with solution is 80% and topiramate can be given with food without any significant effect on bioavailability.[76,77] Topiramate is 9–41% bound to human plasma proteins over blood concentrations ranging from 0.5 to 250

μg/mL.[75,78] The drug exhibits significant binding to erythrocytes.[79] The metabolism of topiramate consists of hydroxylation and hydrolysis. Six metabolites, most of which are probably inactive, have been identified in humans, none of which constitutes >5% of an administered dose.[79] Topiramate has a renal clearance of 13.9 mL/min, which is expected to be reduced in elderly patients (65–85 years of age) who have reduced renal function.[75] The half-life of the drug is 18–24 hours[75,77] and haemodialysis is an effective way of removing topiramate from the bloodstream.[80]

3.2 Analgesic Mechanisms

Topiramate is a weak carbonic anhydrase inhibitor with multiple mechanisms of action that are possibly relevant to neuropathic pain; these include prolongation of voltage sensitive sodium channel inactivation, $GABA_A$ agonism and non-*N*-methyl-D aspartate glutamate receptor antagonism.[81]

3.3 Clinical Efficacy

3.3.1 Trigeminal Neuralgia

A pilot study in three patients with trigeminal neuralgia using a randomised, double-blind, placebo-controlled, two-period crossover design showed preliminary efficacy in the main study, with reductions in pain by topiramate of 31%, 42% and 64% in each of the three patients ($p = 0.04$).[82] However, in a second confirmatory phase, topiramate showed no effect.[82]

3.3.2 Diabetic Neuropathy

Three similar double-blind trials to evaluate the efficacy and tolerability of topiramate in patients with painful diabetic polyneuropathy have been conducted.[18] 1259 patients with moderate to extreme pain (pain scores ≥2 using a 0–4 categorical scale [where zero represents no pain and four represents the worst imaginable pain]) were randomised to placebo or topiramate (100, 200 or 400 mg/day) treatment. After 18–22 weeks of double-blind treatment, reductions in pain were numerically greater with topiramate in two studies, but differences in pain VAS scores and in the secondary endpoints did not reach statistical significance. The design of the studies may have precluded positive results, since the inclusion of patients was based on pain scored using a 0–4 scale and questions with regard to pain ratings did not specify the time and location of the pain.

Raskin et al.[19] performed a 12-week, multicentre, randomised, double-blind trial in 323 subjects with painful diabetic polyneuropathy. Patients were included if their pain VAS score was at least 40mm on a scale from 0 to 100mm. In the topiramate group (n = 214), the dosage was titrated to 400 mg/day or the daily maximum tolerated dose. Twelve weeks of topiramate treatment reduced the mean pain VAS score from 68 to 46.2 compared with a reduction from 69.1 to 54 in the placebo group ($p = 0.038$). Fifty percent of topiramate-treated patients and 34% of placebo-treated patients experienced a reduction of at least 30% in their pain VAS score in response to treatment. A 50% reduction in pain VAS score was observed in >30% of patients in the topiramate treatment group. Topiramate significantly reduced the worst pain intensity and the severity of sleep disturbance. Of the patients in the topiramate treatment group, 24.3% discontinued treatment due to adverse effects such as diarrhoea, loss of appetite, somnolence and nausea. Patients in the topiramate group lost, on average, 2.6kg of bodyweight. Another small placebo-controlled pilot trial of topiramate therapy in patients with painful diabetic neuropathy provided positive results.[83] In this 13-week, double-blind, pilot study in 27 subjects with painful diabetic neuropathy, topiramate treatment resulted in greater analgesia than placebo (41% decrease vs 9% increase in pain measured using a VAS scale, respectively; $p = 0.007$).

3.3.3 Other Forms of Neuropathic Pain

Topiramate has been shown to be effective in types of neuropathic pain other than trigeminal neuralgia and painful diabetic neuropathy. Khoromi et al.[20] conducted a double-blind, randomised, 2-period crossover trial in patients with chronic lumbar radicular pain. They assessed the efficacy of topiramate (50–200 mg/day) versus diphenhydramine (6.25–50 mg/day) as an active control. In 29 of the 42 patients who completed the study, topiramate reduced leg pain by a mean of 19% ($p = 0.065$). Global pain relief scores were significantly better in patients who received topiramate ($p < 0.005$).

3.4 Safety

Frequent adverse effects and withdrawals were noted with the use of up to 200 mg/day of topiramate in patients with painful radiculopathy.[20] Common adverse effects included somnolence, dizziness, fatigue, paraesthesias, nausea, problems with concentration and weight loss.

4. Gabapentin

4.1 Pharmacology

Optimal plasma gabapentin concentrations for antiepileptic therapy have not been established.[84] The peak plasma concentration occurs 1.5–4 hours after administration of an oral dose.[85,86] The bioavailability of gabapentin is dose dependent and is 60% for an oral dosage of 900 mg/day, 47% for 1200 mg/day, 33% for 3600 mg/day and 27% for 4800 mg/day, if administered in three divided daily doses as recommended.[87] Opening gabapentin capsules and mixing the contents with food did not significantly impair absorption.[85] The drug is not metabolised and the majority is excreted unchanged in the urine, but some excretion (10–23%) occurs via the faeces.[85,87] The renal clearance of gabapentin decreases in patients with impaired renal function.[88] The elimination half-life of the parent compound is 5–7 hours[85] and the drug is dialysable by haemodialysis.

4.2 Analgesic Mechanisms

Gabapentin is a GABA receptor agonist. The ability of the drug to block L-type voltage-dependent Ca^{2+} channels is the probable reason for its antiepileptic and analgesic properties.[89]

4.3 Analgesic Efficacy

Since its introduction in the mid-1990s, gabapentin has become a central pillar in the treatment of neuropathic pain. It has been shown to be efficacious in different neuropathic pain syndromes and to possess a good safety profile.[23,24,27] In addition, gabapentin is effective in the suppression of various qualities of neuropathic pain.[89] The trials with the best presentation of methodology, results and adverse effects are reviewed.

4.3.1 Neuropathic Pain in Patients with HIV

Hahn et al.[21] performed a placebo-controlled trial of gabapentin for the treatment of painful HIV-associated sensory neuropathies. Patients were followed throughout 1-week screening, 4-week double-blind treatment and 2-week open treatment phases. The dosage of gabapentin was 1200–2400 mg/day. The primary outcome measure was an improvement in median pain score, as measured using a VAS, from the screening week to the fourth week of treatment. Fifteen patients received gabapentin and 11 patients received placebo. Gabapentin-treated patients had a 44.1% decrease in pain and a 48.9% decrease in sleep interference, as measured by VAS. The placebo-treated patients had no significant improvement in pain or sleep scores.

4.3.2 Postherpetic Neuralgia

A 7-week multicentre, randomised, double-blind, placebo-controlled study evaluated the efficacy and safety of gabapentin 1800 or 2400 mg/day in the treatment of 334 patients with postherpetic neuralgia.[22] The primary outcome measure was the change in the daily pain score between the baseline and final weeks of treatment. Secondary outcomes included the mean weekly sleep interference score, the Short-Form McGill Pain Questionnaire (SF-MPQ), Short-Form 36 (SF-36) Health Survey and others. Pain scores showed a significantly greater improvement with gabapentin than placebo. The decreases from baseline at the final week were 34.5% for the 1800 mg/day dosage, 34.4% for the 2400 mg/day dosage and 15.7% for placebo. The difference was significant ($p < 0.01$) between placebo and each of the gabapentin dosages. There were significant differences in favour of gabapentin for a number of patients reporting a >50% reduction in their pain intensity, changes in scores on the SF-MPQ, and in changes in scores for the vitality, bodily pain and mental health domains of the SF-36 Health Survey.

Rowbotham et al.[23] conducted an RCT in 229 patients with postherpetic neuralgia. This was a parallel-design, 8-week trial in which gabapentin was titrated to a dosage of 3600 mg/day over 4 weeks. The average daily pain score was evaluated based upon daily pain diaries utilising a 0–10 Likert scale. Recruited patients had to have a minimum average pain score of ≥4. A total of 113 patients

received gabapentin, 89 (78.8%) of whom completed the trial, whereas 116 patients received placebo, of whom 95 (81.9%) completed the study. A statistically significant reduction in pain was observed at week 2 while patients were receiving gabapentin 1800 mg/day. In an intention-to-treat analysis, patients receiving gabapentin had a significant reduction in daily pain score from 6.3 to 4.2 points, compared with a change from 6.5 to 6 points in subjects randomised to receive placebo ($p < 0.001$). Of the gabapentin-treated patients, 60.6% reported some degree of improvement at week 8 compared with 19.9% of placebo-treated patients. Secondary measures of pain, as well as changes in pain intensity and sleep interference, showed improvement with gabapentin ($p < 0.001$). Measures of mood, depression, anger-hostility, fatigue and QOL were also significantly improved.

4.3.3 Pain in Guillain-Barre Syndrome

A randomised, double-blind, crossover trial was conducted in 18 patients with Guillain-Barre syndrome who were admitted to the intensive unit for ventilatory support.[24] Patients were assigned to receive either gabapentin (15 mg/kg/day) or placebo for 7 days. Fentanyl 2 μg/kg was used as a rescue analgesic. The 0–10 numeric pain score (NPS), sedation score, consumption of fentanyl and adverse effects were noted. The NPS decreased from 7.22 ± 0.83 to 2.33 ± 1.67 on the second day following initiation of gabapentin treatment and remained low during the period of gabapentin treatment. There was a significant decrease in the consumption of fentanyl during the 7-day period of gabapentin treatment (211.11 ± 21.39 to 65.53 ± 16/17 μg/day) compared with placebo (319.44 ± 25.08 to 316.67 ± 24.25μg) [$p < 0.001$]. This study showed that gabapentin had a sparing effect with regard to opioid use in the management of pain in Guillain-Barre syndrome.

Pandey et al.[25] performed a second trial in 36 patients with Guillain-Barre syndrome; in this study, patients were randomly assigned to receive gabapentin 900 mg/day, carbamazepine 300 mg/day or matching placebo. Fentanyl 2 μg/kg was used as a supplementary analgesic on patient demand. The NPS, 1–6 Ramsay sedation score and daily fentanyl consumption were recorded. The gabapentin group had a lower median pain score compared with the placebo and carbamazepine groups ($p < 0.05$). From day 2 of treatment onwards, the gabapentin group had the lowest fentanyl consumption ($p < 0.05$). The authors' conclusion was that gabapentin is more effective than carbamazepine for decreasing pain and fentanyl consumption. This trial shows the rapid analgesic effect of gabapentin; however, the small number of patients, the relatively small dose of carbamazepine, and the short duration of treatment are obvious limitations of this trial.

4.3.4 Cancer-Related Neuropathic Pain

Patients with neuropathic pain due to cancer (n = 121) participated in a randomised, double-blind, placebo-controlled, parallel-design, 10-day trial that aimed to determine the analgesic effect of the addition of gabapentin to treatment for relief of their pain.[26] Gabapentin was titrated from 600 to 1800 mg/day in addition to stable opioid doses. Rescue opioids were available on an as-needed basis. The average daily NPS was the primary outcome measure. Fifty-eight patients completed the trial in the gabapentin group, compared with 31 patients who received placebo and completed the study. An intention-to-treat analysis of covariance showed a significant difference in average pain intensity between gabapentin and placebo recipients (NPS of 4.6 vs 5.4, respectively; $p = 0.025$). Among the secondary outcome measures, dysesthesia scores showed a statistically significant difference between gabapentin and placebo recipients ($p = 0.008$).

4.3.5 Painful Diabetic Neuropathy

The first well designed trial that unequivocally showed that gabapentin is indeed an effective analgesic in patients with neuropathic pain was a randomised, double-blind, placebo-controlled, 8-week trial in 165 patients who had a 1- to 5-year history of pain attributed to diabetic neuropathy.[27] Patients who were recruited had to have a minimal pain score of 40 on a 100mm VAS scale. Gabapentin was titrated from 900 to 3600 mg/day. Eighty-four patients received gabapentin and 70 completed the study. Eighty-one patients received placebo and 65 completed the study. In an intention-to-treat analysis, the pain scores of gabapentin-treated patients decreased from a baseline value of 6.4, measured on a 0–10 Likert scale, to 3.9 at study end, whereas in

the placebo-treated patients, pain scores decreased from 6.5 to 5.1. The difference between the endpoint scores for the two groups was significant ($p < 0.001$). Additional statistically significant differences favouring gabapentin treatment were observed in measures of QOL and profiles of mood states. Sleep interference, an issue of major chronobiological importance given the that neuropathic pain in patients with diabetic neuropathy and postherpetic neuralgia tends to increase during the evening and night,[90] was also reduced by gabapentin. Morello et al.[28] performed a double-blind, randomised trial comparing gabapentin with amitriptyline in 26 veterans with painful diabetic neuropathy. Patients were treated for 6 weeks with gabapentin 900–1800 mg/day or amitriptyline 25–75 mg/day, followed by a 1-week washout period, after which they were crossed over to the other treatment. There was a statistically significant reduction in pain scores following treatment with both gabapentin ($p < 0.001$) and amitriptyline ($p < 0.001$), according to a 2-tailed, paired Student t-test. Nevertheless, analysis of mean diary scores showed that differences in pain relief with gabapentin and amitriptyline were not statistically significant. The conclusion was that both drugs are equally effective for painful diabetic neuropathy. However, this conclusion should be regarded with caution because of the small number of patients recruited, the limitation of the dose of gabapentin to 1800 mg/day and the lack of a placebo-treated group in the trial.

In an interesting study, Gilron et al.[29] utilised an original methodology. They compared the efficacy of a combination of gabapentin and morphine with that of each as a single agent in patients with painful diabetic neuropathy or postherpetic neuralgia. In this randomised, double-blind, four-period crossover trial, patients received an active control (lorazepam), sustained-release morphine, gabapentin, and a combination of gabapentin and morphine, each given orally for 5 weeks. The primary outcome measure was the mean daily pain intensity in patients receiving a maximal tolerated dosage of any of the medications. Secondary outcomes included pain (rated according to the SF-MPQ), adverse effects, maximal tolerated dose, mood and QOL. Of the 57 patients who underwent randomisation (35 with diabetic neuropathy and 22 with postherpetic neuralgia), 41 completed the trial. The mean daily pain score, using a scale of 1–10, was 5.72 at baseline and 4.49 following lorazepam treatment, 4.15 following gabapentin treatment, 3.70 following morphine treatment, and 3.06 following treatment with the gabapentin-morphine combination ($p < 0.05$ for the combination vs placebo, gabapentin and morphine). Total scores on the SF-MPQ (on a scale from 0 to 45) were 14.4 with lorazepam, 10.7 with gabapentin, 10.7 with morphine and 7.5 with the gabapentin-morphine combination ($p < 0.05$ for the combination vs placebo, gabapentin, and morphine). The maximal tolerated doses of morphine and gabapentin were lower ($p < 0.05$) with the combination than for each drug given as a single agent. At the maximal tolerated dose, the gabapentin-morphine combination resulted in a higher frequency of constipation than gabapentin alone ($p < 0.05$) and a higher frequency of dry mouth than morphine alone ($p < 0.05$). The authors concluded that gabapentin and morphine in combination achieved better analgesia at lower doses of each drug than either as a single agent. This is an important trial since it shows that the combination of gabapentin and morphine has an additive analgesic effect with respect to neuropathic pain. The increased adverse effects with the combination should not deter physicians from judicious utilisation of this option.

4.3.6 Complex Regional Pain Syndrome

van de Vusse et al.[30] conducted a randomised, controlled crossover trial of gabapentin in patients with complex regional pain syndrome type I (CRPS-I). There were two 3-week treatment periods, during which patients received either gabapentin (600–1800 mg/day) or matching placebo. The patients were re-evaluated at 3, 5 and 8 weeks after randomisation. During the trial, the patients noted their pain score of the past 24 hours (VAS) and the use of additional analgesics. During each visit, the global perceived effect of treatment on pain, the NPS, sensibility to Von Frey monofilament skin application, static pressure with the finger tip and impairment and disability scales were assessed and the mechanical allodynia test with brush strokes and qualitative evaluation of autonomic abnormalities were performed. Fifty-eight patients were recruited. Comparing gabapentin and placebo users in terms of pain relief, there was significant pain relief in favour

of gabapentin in the first period. The effect of treatment in the second period was smaller and no significant effect was seen when the results of both periods were combined. The analysis of global perceived effect showed a significantly larger effect with gabapentin compared with placebo (with 43% pain relief vs 17%, respectively; p = 0.002). Sensory deficits were significantly reversed by gabapentin compared with placebo (p = 0.027). No effect of gabapentin was found on allodynia. In terms of reported functional improvement, ten patients improved with gabapentin versus seven with placebo. The difference was not significant. Also, no difference was found in the rates of oedema and discolouration or the range of motion of the affected limb between placebo and gabapentin. The authors concluded that gabapentin had a mild effect on pain in patients with CRPS-I, as a result of significantly reducing the sensory abnormalities in the affected limb.

4.3.7 Phantom Limb Pain

Bone et al.[31] conducted a small, 6-week, double-blind, placebo-controlled cross-over trial in 19 patients with post-amputation phantom limb pain. The dose of gabapentin was titrated up to 2400 mg/day. Pain scores, as measured on a VAS, were compared at the end of each treatment period. Secondary measures were indices of sleep interference, the Hospital Anxiety and Depression scale, and activities of daily living. Fourteen of 19 patients completed both arms of the study. Both placebo and gabapentin treatments resulted in reduced VAS scores compared with baseline. The pain intensity difference associated with gabapentin treatment was significantly greater than that for placebo therapy at the end of the treatment (3.2 ± 2.1 vs 1.6 ± 0.7; p = 0.03). There were no significant differences between placebo and gabapentin therapy in terms of the number of tablets of rescue medication required or effects on sleep interference, the Hamilton Anxiety and Depression scale, and activities of daily living. The medication was well tolerated with few reports of adverse effects. The authors concluded that, after 6 weeks of therapy, gabapentin is better than placebo for the treatment of phantom limb pain. The fact that the effects of these treatments on sleep interference and activities of daily living were not significantly different could be ascribed to the small number of patients (such that a type II statistical error cannot be excluded).

4.3.8 Other Forms of Neuropathic Pain

Small randomised, placebo-controlled trials have shown the efficacy of gabapentin for the treatment of neuropathic pain in patients with spinal cord injury.[32,33] Serpell et al. conducted a large, a double-blind, placebo-controlled trial in patients with diverse neuropathic pain syndromes.[34] This trial compared 153 patients treated with gabapentin with 152 patients treated with placebo. Gabapentin was titrated to a maximum dosage of 2400 mg/day. The primary outcome measure was the change in average daily pain diary score (baseline vs final week) measured using a 11-point Likert scale. Over the 8-week study, this score decreased (i.e. improved) by 1.5 (21%) in gabapentin-treated patients and by 1.0 (14%) in placebo-treated patients (p = 0.048). Significant differences in favour of gabapentin ($p < 0.05$) were seen in the Clinician and Patient Global Impression of Change score, scores for some domains of the SF-MPQ and in patient-reported assessments of QOL measured by several domains of the SF-36 Health Survey. Gabapentin was well tolerated and the majority of gabapentin recipients completed the study (79% vs 73% for placebo). This study showed that gabapentin reduces pain and improves some QOL measures in patients with a wide range of neuropathic pain syndromes.

In summary, the majority of well controlled trials of gabapentin in patients with various neuropathic pain syndromes demonstrate that this drug is efficacious for the treatment of neuropathic pain. It reduces pain and may reduce sleep interference, and improves, to a certain degree, the QOL. In addition, it is a well tolerated drug with very few adverse effects secondary to its CNS effects. The recommended dosage is 900–3600 mg/day. Gabapentin could be combined with opioids for additive effects in patients with mixed pain and neuropathic pain.

4.4 Safety

The most commonly reported adverse effects of gabapentin were dizziness and somnolence, both appearing in >20% of treated patients.[22,27,34] Additional adverse effects include confusion and peripheral oedema.[22,27] Gabapentin is generally well tol-

erated by most patients, even if dosages are rapidly up-titrated. The dosage should be reduced in patients with renal failure.

5. Lamotrigine

5.1 Pharmacology

Lamotrigine is absorbed rapidly and completely from the gastrointestinal tract, with no effects of food on drug absorption.[91] The bioavailability of orally administered lamotrigine has been established as being 98%.[91] The reported therapeutic drug concentration for neuropathic pain appears to be 3–7 μg/mL, according to two open-labeled trials.[91] Lamotrigine is approximately 56% bound to plasma proteins. The kidneys are responsible for 94% of the excretion of the drug, although this mode of excretion is reduced in patients with renal failure. The elimination half-life of lamotrigine is 13–30 hours.[91-94] The pharmacokinetic profile appears to be linear, and kinetic parameters after multiple-dose administration are similar to those observed after a single dose.[95]

5.2 Analgesic Mechanisms

Lamotrigine has at least two properties with potential antinociceptive activity that should make it conducive to reducing neuropathic pain. First, it stabilises neural membranes by blocking the activation of voltage-sensitive sodium channels.[96,97] Second, it inhibits the pre-synaptic release of glutamate.[96,97]

5.3 Analgesic Efficacy

5.3.1 Diabetic Neuropathy

The efficacy of lamotrigine in relieving painful diabetic neuropathy was tested in a single-centre, parallel-designed RCT.[35] Fifty-nine patients with painful peripheral neuropathy received either lamotrigine (titrated from 25 to 400 mg/day) or a placebo over a period of 8 weeks. The entire course of treatment was completed by 83% of the patients receiving lamotrigine and 73% of the patients receiving placebo. Self-recording of pain intensity twice daily with a 0–10 NPS revealed that pain was reduced from 6.4 ± 0.1 to 4.2 ± 0.1 in the lamotrigine-treated group and from 6.5 ± 0.1 to 5.3 ± 0.1 in the placebo group. The differences in pain intensity between the two groups were statistically significant for lamotrigine dosages of 200, 300 and 400 mg/day. The NNT to obtain at least 50% pain relief in one additional patient with painful diabetic neuropathy compared with placebo that was calculated from this study was 4.0 (95% CI 2.1, 42). Secondary efficacy measures, including the daily consumption of rescue analgesics, the McGill Pain Questionnaire (MPQ), the Beck Depression Inventory and the Pain Disability Index, remained unchanged in both groups. The global assessment of efficacy favoured lamotrigine treatment over placebo. Thus, the authors concluded that lamotrigine is effective and safely used as a means of decreasing the intensity of pain associated with diabetic neuropathy.

Two additional large-scale multicentre RCTs examined the efficacy of lamotrigine in diabetic neuropathy.[38] Each study randomised 360 patients to receive either lamotrigine 200, 300 or 400 mg/day, or placebo, and consisted of a 7-week dose-escalation phase and a 12-week maintenance phase. The primary outcome measure, the change in mean pain intensity from baseline during the last week of the maintenance phase, was significantly different compared with placebo for the 400 mg/day dosage in one study (−2.7 points on an 11-point scale) but not in the other. Pooled data from both studies showed 2.5- and 2.7-point improvements in mean pain intensity from baseline for the 300 mg/day and 400 mg/day dosages, respectively, but only the 400 mg/day dosage was significantly superior to placebo. One additional open-label trial also suggested that lamotrigine may reduce pain intensity in patients with painful diabetic neuropathy.[98]

5.3.2 HIV-Associated Polyneuropathy

Two RCTs have tested the efficacy of lamotrigine in HIV-associated polyneuropathy. In one multicentre, parallel study,[36] 42 subjects were enrolled in a 14-week course of treatment and received either lamotrigine or placebo. The lamotrigine therapy was initiated at 25 mg/day and slowly titrated over a 7-week period to 300 mg/day. Only 29 patients completed the 14-week study, with 20 patients receiving placebo and nine receiving lamotrigine. The reduction in average pain from baseline to week

14, as measured on the modified Gracely scale, was significantly greater in the lamotrigine group (−0.55) than in the placebo group (−0.18), after adjusting for baseline levels of pain. The very different numbers of patients available for assessment at study end in the lamotrigine and placebo treatment groups suggest that the results of this study should be interpreted with caution.

The second study in patients with HIV-related neuropathic pain yielded contradictory results.[37] The study population consisted of two different groups of patients. One group was comprised of 92 patients who were receiving neurotoxic active antiretroviral treatment. Sixty-two of these patients were randomised to receive lamotrigine and 30 were randomised to receive placebo. The second group consisted of 135 patients who were not receiving antiretroviral therapy, with 88 receiving lamotrigine and 47 receiving placebo. Lamotrigine was titrated up to a daily dosage of 600 mg/day over a period of 7 weeks and maintained at a stable dose for an additional 4 weeks. Significantly greater improvements in the slope of the change in the Gracely Pain Scale, the change from baseline for VAS scores of pain intensity and the McGill Pain Assessment Scale, as well as patient and clinician ratings of global impressions of change in pain, were demonstrated with lamotrigine compared with placebo in the antiretroviral-treated group, but not in the group that was not using antiviral therapy. The difference in the responses to lamotrigine between the two groups could not be explained.

5.3.3 Central Pain

Two small RCTs have tested the efficacy of lamotrigine for neuropathic pain of central origin. In the first trial,[39] 30 patients with pain following spinal cord injury were randomised to receive either lamotrigine or a placebo over a period of 8 weeks. The lamotrigine dosage was slowly increased to a maximum of 400 mg/day. Following a 2-week washout period, patients were switched to the second treatment arm. Twenty-two patients completed the trial. No statistically significant effect of lamotrigine was found in the total sample, as measured by the change in median pain score from the baseline week to the last week of treatment. However, in patients with incomplete spinal cord injury, lamotrigine significantly reduced pain at or below the level of the injury. Additionally, all seven patients with evoked allodynia and wind-up-like pain in the area of maximal pain experienced a positive effect from lamotrigine, in contrast to only 1 of 14 patients without such evoked pain. The second trial[40] investigated the effect of lamotrigine versus placebo in 30 patients with post-stroke pain. The study was conducted in two centres and used a crossover design. Each arm consisted of an 8-week treatment period separated by 2 weeks of washout. When administered at the maximal dosage of 200 mg/day, lamotrigine significantly reduced the median pain score as measured on an 11-point Likert scale from 6 (range 4–10) at baseline to 5, compared with a score of 7 associated with placebo. No significant effect was obtained at lower doses of lamotrigine. The authors concluded that lamotrigine 200 mg/day is a moderately effective treatment for central post-stroke pain.

5.3.4 Trigeminal Neuralgia

Lamotrigine was tested as an add-on therapy to a steady dose of carbamazepine or phenytoin in 14 patients with refractory trigeminal neuralgia.[41] Patients received either placebo or lamotrigine 400 mg/day in a crossover design. Each treatment period lasted 14 days, with an intervening 3-day washout period. Of the 13 patients who completed the study, 11 had better outcomes when receiving lamotrigine than placebo, based on the use of escape medication, total pain scores and global evaluations. The NNT to obtain at least 50% pain relief in one patient with trigeminal neuralgia was 2.1 (95% CI 1.3, 6.1). An open-label study has also suggested that lamotrigine is efficacious in relieving trigeminal neuralgia.[92]

5.3.5 Other Types of Neuropathic Pain

One RCT has examined the use of lamotrigine in patients with a mixture of types of painful neuropathy of peripheral origin.[42] Of 100 patients in total, 50 were randomised to receive lamotrigine up to 200 mg/day over an 8-week period and 50 were randomised to placebo. Of the initial 100 subjects, 74 completed the regimen and were available for statistical analysis. No significant changes were recorded in any of the variables measured, including total pain, character of the pain, sensitivity, numbness, paraesthesia, sleep, mobility, mood, QOL or

analgesic consumption. The author concluded that, at the dosage used and with the dose escalation regimen described, lamotrigine had no effect on either pain symptoms or on QOL variables.

The results of several open-label studies in humans indicate that lamotrigine may reduce symptoms of CRPS-I,[99] chronic refractory neuropathic pain of mixed aetiologies [100] and sciatic pain.[35] However, these results should be regarded as 'suggestive' in terms of lamotrigine efficacy because of the open-labelled design and the small number of patients participating in each trial (<20). Two trials provide stronger efficacy data by reporting positive correlations between the clinical response, administered dose and plasma lamotrigine concentrations.[92,93] In both trials, the effective dosage was 400 mg/day.

In summary, the results of these trials seem to provide fairly strong evidence regarding the efficacy of lamotrigine in a variety of neuropathic pain conditions. The only RCT that provided negative results[42] used lamotrigine 200 mg/day as monotherapy, which seems to be a clinically sub-analgesic dose. Two other sub-populations of patients failed to respond to lamotrigine: the first consisted of patients with HIV-related painful polyneuropathy who were not receiving antiretroviral therapy, and the second consisted of patients with complete spinal cord injuries and deafferentation pain. The two subgroups differed considerably from each other in the underlying cause of their pain and the mechanisms leading to their pain may be quite different, thereby making it difficult to explain the lack of effect.

A major shortcoming of these studies that must be noted is the relatively short duration of treatment (14 weeks at most). Therefore, in contrast to the results of trials of lamotrigine in patients with epilepsy, we do not have data on the long-term efficacy of lamotrigine in the treatment of neuropathic pain. This is, however, a common shortcoming of clinical trials related to neuropathic pain in general.

5.4 Safety

In a recent review of post-marketing surveillance for lamotrigine in patients with refractory epilepsy, 12.4% of the patients treated with lamotrigine were shown to have discontinued their therapy for reasons other than treatment failure.[101] Of the newer antiepileptic drugs, lamotrigine is the most frequently associated with skin rash. According to earlier reports, skin rash may occur in up to 7–10% of patients.[102,103] On the basis of a review of 10 894 patients, Acharya et al.[101] recently reported a much lower prevalence of skin rash of 1.8%. However, all available data indicate that lamotrigine should be discontinued at the first appearance of any rash because there is no way to predict which rash will prove to be dangerous or life-threatening. Severe skin rash may be induced by lamotrigine, as part of a hypersensitivity response, with a prevalence of 1 in 300 for adults.[104] The most dangerous reactions, which may lead to hospitalisation or even death, are Stevens-Johnson syndrome or toxic epidermal necrolysis.[105] The risk of Stevens-Johnson syndrome and/or toxic epidermal necrolysis for patients receiving lamotrigine treatment has been estimated at 2.5 per 10 000 new users (or 14 cases from 55 154 users). This number is higher than for carbamazepine (1.4 per 10 000 new users) and sodium valproate (0.5), but lower than for phenytoin (8.3) and phenobarbital (phenobarbitone) [8.1].[106] More than 90% of serious rashes have been found to occur in the first 63 days of antiepileptic drug use. Notably, discontinuation of the drug may not prevent the development of serious and life-threatening complications.

Other common adverse effects include nausea/vomiting, sedation/drowsiness, dizziness, malaise, headaches, visual disturbances and ataxia.[35-37,39-42] The overall adverse effect profile for lamotrigine is dose-related.[38] Very rarely, lamotrigine may cause cardiovascular effects, such as a slight increase in the incidence of clinically non-significant PR interval prolongation, or haematological effects, including agranulocytosis, aplastic anaemia, haemolytic anaemia, red cell aplasia, disseminated intravascular coagulation, neutropenia and pancytopenia.[107] Lamotrigine overdose may cause seizures, respiratory depression and coma.[108]

6. Pregabalin

6.1 Pharmacology

Pregabalin is rapidly absorbed after oral administration, with 90% bioavailability and the achievement of peak plasma concentrations after 1 hour.[109] It is prescribed in regimens of two or three divided doses. The rate, but not the extent, of absorption is reduced by administration with food, but this is not clinically significant. Steady-state drug concentrations are achieved after 1–2 days of treatment. Pregabalin is not bound to plasma proteins and undergoes negligible metabolism. About 98% of a dose is excreted in the urine as unchanged drug. The mean elimination half-life is 6.3 hours. Pregabalin blood concentrations can be reduced by 50% by haemodialysis.[110] In addition to the daily dose, patients receiving haemodialysis should receive a supplementary pregabalin dose of 25–100mg immediately after each 4-hour haemodialysis session.[47] For neuropathic pain, the initial adult dosage is 150 mg/day in 2–3 divided doses. The dosage can be increased after 3–7 days to 300 mg/day and then to 600 mg/day after another 7 days as needed.[45,111,112]

6.2 Analgesic Mechanism

Pregabalin is believed to exert its analgesic effect by binding to the α_2 delta subunit of voltage-gated calcium channels on primary afferent nerves, and reducing the release of neurotransmitters from their central terminals.[113]

6.3 Efficacy

The efficacy of pregabalin has been tested in ten RCTs that included 2750 patients with either diabetic polyneuropathy or postherpetic neuralgia.[43-49] All trials were of intermediate duration, with treatment periods lasting ≤13 weeks. In nine of the trials, pregabalin was administered at fixed dosages of 75–600 mg/day, and in one trial, both flexible and fixed dosage regimens of up to 600 mg/day were used.[114]

6.3.1 Painful Diabetic Neuropathy

Four full-length trials that have evaluated the efficacy of pregabalin in relieving diabetic polyneuropathy have been published.[43-46] In all of them, patients with symmetrical distal polyneuropathy due to type 1 or type 2 diabetes mellitus, with a duration between 1 and 5 years, were enrolled. The effect of the drug on pain intensity, which was recorded daily by the patients on an 11-point pain scale was the primary endpoint in all trials. The minimal pain intensity required for enrolment was 4.

In a 6-week, randomised, double-blind, multicentre study,[43] 246 patients with painful diabetic neuropathy received pregabalin (150 or 600 mg/day) or placebo. Dose titration lasted 2 weeks and was followed by a fixed-dose treatment of 4 weeks. Drugs were administered three times daily. Pregabalin at 600 mg/day (but not 150 mg/day) decreased mean pain scores to a significantly greater extent compared with placebo (4.3 vs 5.6; $p = 0.0002$). The proportion of patients reporting a ≥50% decrease in pain level from baseline was also significantly higher in the pregabalin 600 mg/day group compared with the placebo group (39% vs 15%; $p = 0.002$). Pregabalin 600 mg/day also significantly reduced sleep interference. More patients receiving pregabalin than placebo showed improvement, as rated on the Clinician and Patient Global Impression of Change scale. The effects of the pregabalin 150 mg/day dosage were essentially no different from those of placebo.

In another 5-week double-blind, multicentre trial,[44] the efficacy and tolerability of pregabalin (at dosages of 75, 300, 600 mg/day) was compared with placebo. 338 patients were randomised to receive one of three dosages of pregabalin or placebo in three daily doses. The treatment phase of the trial consisted of a 1-week titration phase and a 4-week fixed dose period. Mean pain scores (calculated from the last seven pain scores while receiving study medication) were significantly lower in the 300 and 600 mg/day groups compared with the placebo group, by 1.26 and 1.45 points, respectively ($p = 0.0001$). The proportion of patients reporting a ≥50% decrease in pain level from baseline was also significantly higher for the pregabalin 300 and 600 mg/day groups compared with the placebo group (48% and 46% vs 18%). Significant improvements compared with placebo were also seen in scores for the SF-MPQ, sleep interference, patient global impression of change, and the clinical global impression of change, as well as for some of the function

domains measured by the SF-36 Health Survey and the Profile of Mood Status (POMS).

The third randomised, double-blind, placebo-controlled, parallel-group, multicentre trial was very similar in its design to the previous trials.[45] In this trial, only one dose of pregabalin (100mg three times daily) was administered for a total of 8 weeks (1-week titration and 7-week fixed dose). Pregabalin was associated with significant improvements in mean pain and sleep interference scores compared with placebo (1.47 and 1.54 point differences, respectively, on an 11-point scale; $p < 0.0001$). Significant improvements relative to placebo were also found for several SF-36 scales, the total SF-MPQ score, and patient and clinical global assessment scales, as well as the Total Mood Disturbance and Tension-Anxiety components of the POMS.

Freynhagen et al.[46] used two separate pregabalin treatment regimens in a 12-week randomised, double-blind, multicentre, placebo-controlled, parallel-group study, in which they evaluated the efficacy and safety of pregabalin in patients with chronic postherpetic neuralgia or painful diabetic polyneuropathy. The first regimen consisted of a flexible schedule of pregabalin 150, 300, 450 and 600 mg/day with weekly dose escalation based on patients' individual responses to and tolerance of treatment. The second regimen was based on a fixed schedule of 300 mg/day for 1 week followed by 600 mg/day for 11 weeks. Drugs were administered twice daily. Although the results for patients with diabetic polyneuropathy and those with postherpetic neuralgia receiving each of the schedules were not presented separately, the authors stated that similar magnitudes of improvement in pain symptoms were achieved in patients with each of these diseases. Pain relief that was superior to that with placebo was experienced by the end of week 2 in the flexible-dose group ($p = 0.002$) and by the end of the first week of treatment in the fixed-dose group ($p < 0.001$). This means that significant analgesia was achieved at a dosage of 300 mg/day in both groups. Both treatment regimens also resulted in a significant improvement in pain-related sleep interference ($p < 0.001$) compared with placebo. A significant shortcoming of this study is that data were not presented on the number of patients receiving each of the four possible maximal daily doses in the flexible-dose group. It should be noted that at least three additional trials on pregabalin for the treatment painful diabetic neuropathy have been published in abstract form[115-117] and were not included in the present review.

6.3.2 Postherpetic Neuralgia

Sabatowski et al.[47] randomised 238 patients with postherpetic neuralgia refractory to treatment with gabapentin ≥1200 mg/day to receive pregabalin 150 mg/day (n = 81), 300 mg/day (n = 76) or placebo (n = 81) in three divided doses for 8 weeks. Both pregabalin 150 mg/day and 300 mg/day provided superior reductions in mean pain scores at study endpoint compared with placebo. Pain relief was observed as early as the first week and was maintained throughout the study. Other secondary outcomes that were significantly different from placebo included the percentages of patients who reported at least 50% pain relief from baseline (26% in the 150 mg/day group, 28% in the 300 mg/day group and 10% in the placebo group), sleep interference scores and several domains of health-related QOL measured by the SF-36 Health Survey.

Another 8-week RCT[48] adjusted the pregabalin dose according to the patients' individual renal function. Patients with a creatinine clearance >60 mL/min received pregabalin 600 mg/day, whereas those with creatinine clearance of 30–60 mL/min received 300 mg/day. Pregabalin treatment for 8 weeks resulted in greater decreases in pain scores than placebo (endpoint mean pain score of 3.60 vs 5.29; $p = 0.0001$). Notably, significant differences in pain intensity were reported as early as after the first full day of treatment. Pregabalin treatment was also associated with significantly greater percentages of patients achieving ≥30% and ≥50% decreases in mean pain scores, significantly less sleep interference, and significantly higher patient and clinician ratings of global improvement.

The most recent study, which was performed in The Netherlands,[49] re-evaluated the efficacy of the fixed doses of pregabalin (150, 300 or 600 mg/day), or placebo administered twice daily for the relief of postherpetic neuralgia over 13 weeks in 370 patients. Pregabalin treatment resulted in significant, dose-related pain relief. The difference from placebo in mean pain score (measured on a 0–10 pain

scale) was −0.88 for the 150 mg/day group, −1.07 for the 300 mg/day group and −1.79 for the 600 mg/day group ($p < 0.001$ for all comparisons). Sleep interference in all pregabalin groups was also significantly improved compared with the placebo group, beginning at week 2. Another trial that evaluated pregabalin treatment in patients with postherpetic neuralgia[46] has already been reviewed in section 6.3.1 of this article.

6.4 Safety

Data on the safety of pregabalin in 1800 patients with diabetic polyneuropathy or postherpetic neuralgia who participated in RCTs in which pregabalin was compared with placebo have been pooled by Pfizer Inc.[114] The most common adverse events that occurred during these controlled clinical trials were dizziness, somnolence, dry mouth and oedema. Additional adverse events included blurred vision, weight gain and abnormalities in thinking (primarily difficulties with concentration/attention). Overall, 14% of patients discontinued pregabalin treatment because of adverse effects compared with 7% of patients receiving placebo, with somnolence being the most frequent reason (4%). Adverse effects were dose-dependent and reversible.

In summary, solid evidence indicates that pregabalin is an effective drug for reducing the intensity of pain associated with diabetic polyneuropathy and postherpetic neuralgia. There is also evidence for improvements in sleep and perhaps also QOL in these patients.

7. Other Agents

Several new antiepileptics have been evaluated for the treatment of neuropathic pain in open label studies or small-scale, double-blind, randomised trials. Levetiracetam was used in patients with postherpetic neuralgia in an open-label study.[118] Three patients who were defined as treatment responders experienced a 67–75% improvement in pain intensity, while three additional patients were considered partial responders and reported 11–50% reduction in pain.

In one trial,[50] zonisamide, a sulfonamide with sodium and calcium channel blocking properties,[119] was administered to patients with painful diabetic neuropathy. Forty-two patients were recruited and 25 were randomised to zonisamide (n = 13) or placebo (n = 12). The study drug was titrated over 6 weeks and continued at a fixed dosage for a 6-week maintenance period. Decreases in pain scores were greater for the zonisamide group, yet the differences between the zonisamide and placebo group did not reach statistical significance.

Tiagabine, a new GABA reuptake inhibitor, was compared with gabapentin in an open-label study.[120] Ninety-one patients were recruited. The study duration was 3 months. Both drugs significantly reduced pain intensity. Improvement in sleep quality was significantly greater in tigabine-treated patients versus gabapentin-treated patients ($p = 0.04$). Lacosamide, another new antiepileptic drug, has shown efficacy in several animal models of neuropathic pain;[121,122] however, no human data are currently available.

Several other antiepileptic drugs are worthwhile mentioning. Valproic acid and divalproex sodium (valproate semisodium) [valproic acid and sodium valproate in molar ratio 1 : 1; 1000mg] have been evaluated in one trial each. Valproic acid at a dosage of 1500 mg/day was not superior to placebo in reducing pain associated with polyneuropathy over 4 weeks of treatment.[51] In contrast, divalproex sodium 1000 mg/day significantly reduced pain intensity (measured by four different scales) compared with placebo over 9 weeks in 48 patients with postherpetic neuralgia.[52] The drug was well tolerated by all patients.[52]

Three RCTs have tested the efficacy of phenytoin for the treatment neuropathic pain; two in patients with diabetic polyneuropathy[123,124] and one in patients with various neuropathies.[125] The two trials in patients with diabetic polyneuropathy yielded conflicting results; the first showed analgesic efficacy[123] and the second found no significant improvement with this drug.[124] The trial in patients with various neuropathies reported that intravenous phenytoin 15 mg/kg administered over 2 hours demonstrated analgesic efficacy, suggesting that it can be useful in acute episodes of neuropathic pain. Although these trials provide some evidence for the efficacy of phenytoin in the treatment of neuropathic pain, this drug is not currently used clinically due to its unfavourable safety profile.

Anecdotal reports suggest that fosphenytoin and clonazepam can be efficacious in the treatment of neuropathic pain,[126,127] but these drugs have not been studied in RCTs.

8. Antiepileptic Drugs: Current Role in the Treatment of Neuropathic Pain

Antiepileptic drugs should be regarded as a 'corner stone' in the treatment of neuropathic pain. Multiple RCTs have shown the efficacy of many of these drugs in a large variety of types of neuropathic pain. Yet complete relief of any form of neuropathic pain is only rarely achieved with the use of antiepileptic drugs. A realistic expectation would therefore be to reduce the pain by 50% in no more than one-half of treated patients. The only exception is trigeminal neuralgia, in which complete pain relief, at least temporarily, is indeed attainable.

Perhaps the most extensively studied agent is pregabalin, which has shown, in a large number of multicentre RCTs, a clear efficacy in reducing pain and improving sleep, functioning and QOL in patients with postherpetic neuralgia and diabetic polyneuropathy. The effective dosage is 300–600 mg/day, administered in two to three divided doses. Pregabalin dosages can be rapidly increased. Improvement can be seen within days. The main limitation of pregabalin is that it has not been studied in types of neuropathic pain other than diabetic polyneuropathy and postherpetic neuralgia; therefore, its efficacy for conditions other than postherpetic neuralgia or diabetic polyneuropathy is primarily hypothetical.

On the basis of multiple RCTs, there is strong evidence for the efficacy of gabapentin at dosages of 900–3600 mg/day in the treatment postherpetic neuralgia and diabetic polyneuropathy. Since the efficacy, putative mechanism of action and the safety profile of pregabalin and gabapentin are comparable, these drugs should be regarded as interchangeable for these conditions. Gabapentin has also shown efficacy in other forms of neuropathic pain, such as HIV-associated painful neuropathy, pain in Guillian-Barre syndrome, phantom limb pain, cancer-related neuropathic pain and CRPS-I, but only on the basis of single or limited numbers of studies. Thus, the evidence for the efficacy of gabapentin for conditions other than postherpetic neuralgia and diabetic polyneuropathy is much weaker. The pharmacokinetics of pregabalin enable twice-daily administration; this also constitutes an advantage over gabapentin, which is typically administered three times daily.

There is also considerable evidence for the efficacy of topiramate, lamotrigine, carbamazepine and oxcarbazepine in the treatment of painful diabetic neuropathy. However, the need for a relatively slow titration and the adverse-effect profile of the last three drugs should be regarded as a disadvantage.

Carbamazepine has been the drug of choice for trigeminal neuralgia for decades. The fact that its efficacy was established only on the basis of small-sized RCTs has not been challenged by large multicentre trials. Oxcarbazepine and lamotrigine have been studied to a limited extent in this context. Although no head-to-head comparisons have been conducted, these agents do not seem to be superior to carbamazepine and can therefore be used as an alternative therapy for trigeminal neuralgia if carbamazepine treatment fails.

There is also limited evidence of efficacy of antiepileptic drugs in other forms of neuropathic pain of peripheral origin, such as phantom limb pain, HIV-related neuropathy and radiculopathy. At the same time, other important conditions, such as pain following traumatic nerve injury, have not been studied at all. Similarly, only two small RCTs have tested the efficacy of lamotrigine for neuropathic pain of central origin and these showed a moderate effect at best. Only one study has tested the effect of antiepileptic drugs in cancer-related pain. Furthermore, studies have been limited to 2–3 months of treatment at most. Thus, clinical trials in these indications and for longer terms are desperately needed.

It should also be noted that the management of any form of chronic pain requires not only a reduction in pain intensity but also improved QOL in dimensions such as sleep, mood, work, and social and recreational capacities. Fortunately, there is a growing use of such measurement tools in more recent trials, which have indeed demonstrated improvements in QOL.

Drug combinations, although commonly used in the clinical practice, have only been tested in one trial, in which gabapentin plus morphine was found to be more efficacious than each drug administered

alone. Given the limited effectiveness and the adverse-effect profile of current treatments for neuropathic pain, polypharmacotherapy could enhance analgesia with fewer adverse effects. Concomitant administration of antiepileptic agents with different mechanisms of action and the combination of antiepileptic drugs with other agents such as opioids or antidepressants are theoretically justified. Future trials with the aim of finding such drug combinations while addressing the issue of drug interactions could be useful. RCTs of antiepileptic drugs should also determine their differential efficacy for the various components of neuropathic pain, such as allodynia, lancinating pain and burning pain.

A reasonable algorithm for the usage of antiepileptic agents in the treatment of neuropathic pain should be based on head-to-head large comparative trials. However, as yet, there are no such trials and the prioritisation of antiepileptic drugs for the treatment neuropathic pain is based on the NNTs, which have been calculated from placebo-controlled trials.[128] Nevertheless, if compared with other drugs, both pregabalin and gabapentin are efficacious and share a good safety profile and should therefore be considered first-line therapy for neuropathic pain. Since the analgesic effect of antiepileptic drugs is dose-dependent, the chosen drug should be up-titrated to the maximal tolerated dose, provided that a reduction of pain is experienced. Clinicians should be aware of the fact that even a 30% pain reduction is clinically important to patients.[129] If pain reduction is not obtained, a switch to a different agent should be considered. If this or another single drug treatment attempt fails, the use of a drug combination should be considered.

9. Conclusions

Pharmacotherapy is currently the mainstay of treatment for neuropathic pain. Antiepileptic drugs are a major constituent of this therapy. More specifically, gabapentin and pregabalin are often regarded as first-line therapy for post-herpetic neuralgia and painful diabetic neuropathy, whereas carbamazepine and perhaps oxcarbzapine, are used as first-line therapy for trigeminal neuralgia. The evidence for efficacy of these agents for the treatment of other forms of neuropathic pain is not as strong. Other antiepileptic drugs are regarded as second- and third-line therapy for neuropathic pain. Ideally, the goal of pain management is total alleviation by a single agent. The reality is that monotherapy frequently only reduces pain to a more tolerable level. Therefore, combination therapy, which consists of two or more agents with different mechanisms of action, might be necessary. As yet, the evidence suggests that the combination of gabapentin and morphine is more efficacious than either drug administered alone. The concept of simultaneous administration of two antiepileptic drugs with potentially synergistic mechanisms of action (i.e. pregabalin plus lamotrigine), as often used in patients with refractory epilepsy, should be investigated in patients with neuropathic pain.

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