REVIEW ARTICLE

Drugs 2000 Nov; 60 (5): 1029-1052
0012-6667/00/0011-1029/$25.00/0

Anticonvulsants for Neuropathic Pain Syndromes

Mechanisms of Action and Place in Therapy

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Abstract

Neuropathic pain, a form of chronic pain caused by injury to or disease of the peripheral or central nervous system, is a formidable therapeutic challenge to clinicians because it does not respond well to traditional pain therapies. Our knowledge about the pathogenesis of neuropathic pain has grown significantly over last 2 decades. Basic research with animal and human models of neuropathic pain has shown that a number of pathophysiological and biochemical changes take place in the nervous system as a result of an insult. This property of the nervous system to adapt morphologically and functionally to external stimuli is known as neuroplasticity and plays a crucial role in the onset and maintenance of pain symptoms. Many similarities between the pathophysiological phenomena observed in some epilepsy models and in neuropathic pain models justify the rational for use of anticonvulsant drugs in the symptomatic management of neuropathic pain disorders.

Carbamazepine, the first anticonvulsant studied in clinical trials, probably alleviates pain by decreasing conductance in Na^+ channels and inhibiting ectopic discharges. Results from clinical trials have been positive in the treatment of trigeminal neuralgia, painful diabetic neuropathy and postherpetic neuralgia.

The availability of newer anticonvulsants tested in higher quality clinical trials has marked a new era in the treatment of neuropathic pain. Gabapentin has the most clearly demonstrated analgesic effect for the treatment of neuropathic pain, specifically for treatment of painful diabetic neuropathy and postherpetic neuralgia. Based on the positive results of these studies and its favourable adverse effect profile, gabapentin should be considered the first choice of therapy for neuropathic pain.

Evidence for the efficacy of phenytoin as an antinociceptive agent is, at best, weak to modest. Lamotrigine has good potential to modulate and control neuropathic pain, as shown in 2 controlled clinical trials, although another randomised trial showed no effect. There is potential for phenobarbital, clonazepam, valproic acid, topiramate, pregabalin and tiagabine to have antihyperalgesic and antinociceptive activities based on result in animal models of neuropathic pain, but the efficacy of these drugs in the treatment of human neuropathic pain has not yet been fully determined in clinical trials.

The role of anticonvulsant drugs in the treatment of neuropathic pain is evolving and has been clearly demonstrated with gabapentin and carbamazepine. Further advances in our understanding of the mechanisms underlying neuropathic pain syndromes and well-designed clinical trials should further the opportunities to establish the role of anticonvulsants in the treatment of neuropathic pain.

Neuropathic pain refers to a group of painful disorders characterised by pain due to dysfunction or disease of the nervous system at a peripheral level, a central level or both. In contrast to nociceptive pain, which results from the activation of pain receptors (nociceptors), neuropathic pain is the result of injury to the pain-conducting nervous system. Examples of neuropathic pain syndromes include postherpetic neuralgia (PHN), painful diabetic neuropathy (PDN), the complex regional pain syndrome (CPRS) and the central poststroke pain syndrome. Neuropathic pain is a complex entity with many symptoms and signs that fluctuate, in number and intensity, with time. Neuropathic pain responds poorly to traditional therapeutic approaches and to 'standard' doses of analgesics. All of these factors make most neuropathic pain syndromes a great challenge for clinicians. The heterogeneity of these pain syndromes and the lack of understanding of the underlying pathogenetic mechanisms have made progress in treating neuropathic pain very slow.

Advances reported in clinical trials are slowly overcoming a nihilistic attitude towards the treatment of neuropathic pain. The development of animal models and consequent advances in our understanding of the basic pathophysiology of neuropathic pain have led to increased use of adjuvant analgesics in clinical trials and clinical practice. In particular, anticonvulsant drugs, which act on specific neurotransmitter receptors involved in the genesis and maintenance of hyperexcitability, are an important area of progress in the research and therapy of neuropathic pain.

In this article, we present the current experimental and clinical evidence regarding the use of anticonvulsants for the relief of neuropathic pain. This review concentrates on randomised controlled clinical trials, also taking into account information from nonblind trials and case series. However, the mech-

anisms underlying neuropathic pain that form a basis for understanding why and how anticonvulsants can be effective in the treatment of neuropathic pain syndromes is reviewed first.

1. Neuropathic Pain: Theoretical Background and Scientific Evidence

Pain in association with nerve trauma was well described over a century ago by W.S. Mitchell, but it was not until the reproduction of many symptoms of neuropathic pain in animal models that the mechanisms underlying neuropathic pain could be more directly investigated and better understood.[1,2] The pathophysiological mechanisms of neuropathic pain are presented in this section. Most of the information comes from animal studies since human studies of neuropathic pain mechanisms have not been performed consistently. However, the final proof for any mechanisms of human disorders has to come from controlled clinical trials and well-documented clinical experience.

Many diseases affecting the nervous system, ranging from injuries and metabolic disorders to infections and degenerative disorders, as a rule manifest with many types of pain symptoms and other positive phenomena such as paresthesiae and dysesthesiae. For neuropathic pain to manifest clinically, there is one prerequisite – classical thermonociceptive pathways, such as peripheral sensory small diameter nerves and the spinothalamic tract and its cerebral projections, have to be affected by the nervous system disease.[3] Examples of disorders manifesting with neuropathic pain include: (i) PHN; (ii) diabetic and other painful polyneuropathies; (iii) trauma to major nerve trunks; (iv) some types of pain related to cancer or its treatment; (v) disorders of the spinal cord such as multiple sclerosis and spinal cord injuries; and (vi) brainstem and hemispheric injuries and strokes. Any insult to the nervous system, be it physical injury or any disorder, leads to changes in its structure and function as a result of reparative processes. This state of altered properties of the nervous system is termed neuroplasticity. In patients with neuropathic pain, neuroplasticity takes the form of peripheral and central sensitisation, and the main characteristic is hyperexcitability.

The natural course of neuropathic pain disorders varies depending on their aetiology. However, all of them manifest with a very similar constellation of symptoms. The first type of neuropathic pain is spontaneous constant pain, which fluctuates in intensity and can change in character over time. The second type of pain comprises variable paroxysmal spontaneous attacks or exacerbations of pain, which are frequently very disturbing to the patients. The third type includes varying degrees of hypersensitivity to many external stimuli, such as touch, light bump or pressure, hot or cold temperatures, and even internal stimuli such as anxiety or excitement. Most of the neuropathic pain disorders manifest with any combination of these 3 types of pain. For example, a patient with PHN who has constant ongoing pain is further disabled because of mechanical hyperalgesia from clothing touching the affected skin. In contrast, a patient with central post-stroke pain in addition to ongoing pain and thermal cold hyperalgesia is very anxious about spontaneous paroxysmal attacks of pain that occur without any apparent pattern.

Experimental models of neuropathic pain have been developed in animals and in humans. The first model used in neuropathic pain research was the neuroma model in which post-traumatic neuromas arose as result of nerve transection.[4] This model is associated with many neuroplastic changes but it lacks the behavioural manifestation of hyperalgesia. The partial nerve injury models, such as loose ligature of the sciatic nerve,[2] partial nerve section,[5] injury of spinal nerves,[6] freezing of peripheral nerves[7] and chemical irritation of peripheral nerves,[8] have allowed the discovery of the neurophysiological and biochemical processes leading to neuroplasticity, which also underlie the clinical manifestations of neuropathic pain. The most widely used human laboratory model is neurogenic inflammation, which is induced by the intradermal injection of capsaicin.[9] This model allows the investigation of the psychophysical and pharmacological characteristics of hyperalgesia.[10,11]

Traditionally, treatment for neuropathic pain disorders was primarily based on the aetiology of the particular disorder. With improved understanding of the mechanisms underlying pain phenomena, and regardless of the disorder that initiated the pain, the concept of developing treatment based on these mechanisms is evolving. The best characterised mechanisms are those underlying dynamic mechanical hyperalgesia (DMH) – pain from a light mechanical stimulus moving across the skin, such as when a cotton tip is dragged across the affected area. A clinical example of DMH pain is seen in patients with painful diabetic neuropathy who cry out when their feet are touched by bed sheets, and for whom any movement of the bed sheets prevents them from sleeping. This type of pain results from a complex of neuroplastic processes. However, the most significant event in such patients is the sensitisation of primary Aβ afferents, which demonstrate phenotypic switch,[12] and activation of the N-methyl-D-aspartate (NMDA) receptors with wind-up and central sensitisation.[13-16] Phenotypic switch occurs when nonpain, large myelinated fibres that project primarily to lamina III start to express substance P receptors, which are specific to pain transmission at the dorsal horn. In addition, these large fibres extend their dendrites into lamina II, or the so-called substantia gelatinosa, which is involved in processing pain impulses. Wind-up refers to an increased responsiveness to noxious stimuli of pain-transmitting dorsal horn neurons with each subsequent stimulus, representing a form of hyperexcitability of these neurons. Central sensitisation is a final sum of many of the hyperexcitability physiological phenomena occurring at the dorsal horn level. The theory of DMH was also supported by a few clinical and human experimental studies.[17-19]

Other phenomena have been characterised to a reasonable extent, such as thermal heat hyperalgesia, which is caused by peripheral nociceptor sensitisation as well as central sensitisation.[20-22] Other pain phenomena appear to be more complex, for example thermal cold hyperalgesia in which the interaction of inhibitory processes with central sensitisation plays a significant role.[23] However, the most complex pain phenomenon is ongoing pain, and although many mechanisms have been proposed, such as the ectopic generation of impulses from primary afferents or the loss of central inhibition, there are probably many more mechanisms and processes that result in ongoing pain which are beyond our understanding at this time. The least well understood mechanisms are those underlying spontaneous paroxysms of pain.

Many pathophysiological processes have been observed in neuropathic pain models and if we were to catalogue the processes that have been described and implicated they would range from the cellular to the intranuclear level. At the cellular level, there is the formation of microneuromas and spontaneous ectopic generators, development of ephaptic transmission, and sensitivity to circulating catecholamines. In the neuronal cell membrane, there is the alteration of Na^+ channels, Ca^{2+} channels and neurotransmitter systems including substance P, NMDA, γ-aminobutyric acid (GABA) and opioid systems. At the intracellular level, there is the activation of a number of second messenger cascades [with adenosine, protein kinase (PK) A and PKC being those best documented], and on the nuclear level, there is the activation of immediate early genes. At present, it is far from clear which of the events that characterise peripheral and central sensitisation has the initiating role and which has a primary predominant role in maintaining neuropathic pain in any given patient. It is most likely that more than one mechanism is responsible for the genesis and maintenance of chronic neuropathic pain. Despite the complexity of the processes demonstrated in neuropathic pain, an understanding of how peripheral and central sensitisation evolve would offer an opportunity to develop therapies that are most specific for the genesis and persistence of neuropathic pain. However, as stated at the beginning of this section, to demonstrate the validity of the mechanism-based concept in human clinical neuropathic pain syndromes, clinical trials would have to be conducted in which specific ther-

apies are assessed for specific clinical pain phenomena.

There is a notable similarity between the pathophysiological and biochemical mechanisms observed in epilepsy and neuropathic pain.[24] What is remarkable is the pathophysiological similarity between wind-up, which is documented at the spinal cord dorsal horn neurons in models of neuropathic pain, and kindling of hippocampal neurons in epilepsy. Both wind-up and kindling appear to result from the activation of NMDA receptors, among other mechanisms.[11] The susceptibility of primary afferent and transmission neurons to the effects of sodium channel blockers in neuropathic pain models has been well recognised and is similar to the susceptibility observed in models of epilepsy.[25] Therefore, it should not be surprising that anticonvulsants can relieve and possibly modify the perception of neuropathic pain.

The conceptual and practical development of neuropathic pain models and the demonstration of neuroplasticity with the associated peripheral and central sensitisation mechanisms have so far been the most significant advances in pain research and therapy. There are many clinical implications resulting from these advances. Clinical evaluation can now be directed towards a more specific assessment and diagnosis of all neuropathic pain phenomena, each of which has its distinct underlying mechanisms. As a result of improved assessment and specific diagnosis, therapy specifically oriented towards the treatment of neuropathic pain can be administered based on those mechanisms. Certainly, the best possible treatment targeted towards the aetiology of underlying disease processes and any associated risk factors is necessary. For example, a patient with painful diabetic neuropathy needs their blood glucose level optimally controlled and any associated comorbidity, such as renal disease, optimally treated, while at the same time it should be possible to identify and treat any and all neuropathic pain symptoms. Treatment of pain symptoms is most likely to be successful if it is based on well-defined underlying pain mechanisms.

2. Methods Used in the Preparation of this Manuscript

This is primarily a descriptive review. The primary method of search was done using MEDLINE from 1960 to August 2000. We also searched using Current Contents and the Adis database. Articles published before 1960 were located with cross-reference articles. We also consulted standard neurology, pharmacology and epilepsy textbooks.

Controlled clinical trials were first identified and then tabulated. Attention was paid to the design and reporting of methods, outcomes and adverse effects. A similar procedure was used for the review and reporting of nonblind studies, case series, retrospective trials and reports of abstracts. Mechanisms of anticonvulsant drug action were also obtained from the review of literature and are presented. The main conclusions were made based on the results of controlled clinical trials but we have not neglected the importance of certain nonrandomised studies.

3. Anticonvulsants for Treatment of Neuropathic Pain

Specific anticonvulsant agents are presented here in the order in which they were studied and reported in the literature. Anticonvulsants studied in controlled clinical trials are presented first, followed by a review of the remaining anticonvulsants.

3.1 Studied in Controlled Randomised Clinical Trials

3.1.1 Carbamazepine

Carbamazepine is an iminostilbene derivative chemically related to the tricyclic antidepressants. The effect of carbamazepine on pain suppression is probably mediated via central and peripheral mechanisms. In rabbits with bradykinin-induced trigeminal pain, carbamazepine suppressed neuronal responses in the subnucleus reticularis dorsalis and trigeminal subnucleus caudalis as measured by microelectrode recordings.[26] Carbamazepine also inhibited action potentials in the rat neuroma in spinal nerve ligation models, suggesting that its effective-

ness in neuropathic pain results from decreased sodium and potassium conductance and suppression of peripheral ectopic spontaneous activity.[27,28] The ability of carbamazepine to block ionic conductance appears to be frequency-dependent, which enables the drug to suppress the spontaneously active Aδ and C fibres responsible for pain without affecting normal nerve conduction.[29,30]

Since Blom reported the analgesic properties of carbamazepine on patients with trigeminal neuralgia in 1962,[31,32] investigators have studied carbamazepine in lancinating tabetic pain, PHN, PDN and central pain syndromes. The analgesic efficacy of carbamazepine has been most frequently documented in trigeminal neuralgia and PDN. Analgesic reports in PHN, tabetic pain, and central pain are less well documented.

Eleven randomised clinical trials evaluating efficacy of carbamazepine in neuropathic pain have been published (table I). Three trials of carbamazepine in trigeminal neuralgia[33,36,56] and 1 trial in various neuralgias including trigeminal neuralgia[34] were double-blind, placebo-controlled, crossover trials that reported positive results compared with placebo. Response rates for carbamazepine in these studies ranged from 70 to 89% after 5 to 14 days of treatment. However, these results are overshadowed by many limitations in the study methodology. There were no washout periods to prevent a carry-over effect,[33,56] the use of concurrent interventions continued and there was a lack of reporting of the statistical analysis.[34,36] All of these shortcomings make it difficult to determine whether the data from these trials represent a specific and significant therapeutic effect of carbamazepine. Additionally, adverse effects of the active drug, such as drowsiness, dizziness, ataxia, nausea and vomiting, may have biased these studies.

Three double-blind trials have compared carbamazepine with active controls.[38-40] Carbamazepine was superior to tizanidine, an α_2-adrenergic agonist in a small (n = 12) trial of 3 weeks' duration.[38] Carbamazepine produced similar pain relief compared with tocainide, an antiarrhythmic agent, in a 4-week crossover study with the same number of patients.[39] In a larger study of 59 patients, carbamazepine was significantly less effective than pimozide, an antipsychotic agent, in relieving pain but pimozide had a high frequency (83%) of adverse effects.[40]

Three randomised trials evaluating carbamazepine in PDN used double-blind, crossover techniques; 2 studies had placebo controls[35,37] and 1 study used an active control arm with nortriptyline and fluphenazine.[42] In one of these trials,[35] carbamazepine demonstrated symptomatic relief of pain and paresthesiae in 28 out of 30 patients after 2 weeks of therapy; however, carry-over effects occurred during placebo administration and no statistical analysis was performed. Wilton[37] reported that carbamazepine had a superior analgesic effect versus placebo in one arm of a crossover study, but not in the arm prior to crossover. Unfortunately, analysis of the combined results was not performed. When carbamazepine was compared with the tricyclic-neuroleptic combination,[42] there were significant improvements from baseline with both therapies but no difference between the treatment arms. Although adverse effects more frequent with the nortriptyline-fluphenazine combination, no statistical analysis was performed to detect differences between the two arms.

There is less well documented clinical evidence supporting the effectiveness of carbamazepine in PHN. In an 8-week trial, Gerson et al.[57] compared carbamazepine and clomipramine with transcutaneous electrical nerve stimulation (TENS) in 29 patients. Blinding was not possible because of the nature of the study. In a combined analysis of available data, including patients who crossed over treatments, carbamazepine plus clomipramine provided better pain relief. The clinical weight of this study is questionable given the number of dropouts relative to the sample size (see table II). Since clomipramine is chemically related to tricyclic antidepressants, it may have confounded the real contribution of carbamazepine in this trial.[47,77-80] More recently, in a small trial, carbamazepine was shown to be as effective as gabapentin in carpal tunnel syndrome.[81] These findings may be impor-

Table I. Completed and fully published randomised trials of anticonvulsant drugs in patients with neuropathic pain[a]

Study	Pain disorder	No. of patients	Design	Treatment	Outcomes	Results	Adverse effects
Carbamazepine (CBZ)							
Campbell et al.[33]	Trigeminal neuralgia	77	PC CO	CBZ up to 400 mg/day -> CO; no washout; total duration 8wk	Pain severity, number of paroxysms per day, effect on triggers	CBZ better than placebo to improve pain and lessen number of paroxysms	7/77 withdrew
Killian & Fromm[34]	Various neuralgias (trigeminal, post-herpetic, tabetic, atypical facial)	42	PC CO	CBZ 400-1000 mg/day vs placebo × 5 days then CO × 5 days; open trial for 36 months	Pain relief (complete, very good, fair, no response)	36/42 pts were double-blinded; CBZ better than placebo in trigeminal neuralgia only	4 withdrawals; vertigo (47%) drowsiness (17%)
Rull et al.[35]	Diabetic neuropathy	30	PC CO DB	CBZ or placebo 600 mg/day × 2wk then CO × 2wk; total duration 6wk; no washout	Patient self-report of pain intensity	28/30 had relief; CBZ better than placebo	2 withdrawals (rash); somnolence (50%), dizziness (40%) and gait disturbance (13%) were the most common adverse effects
Nicol[36]	Trigeminal neuralgia	54	PC DB partial CO	CBZ 100-2400 mg/day then CO × 46mo	Post-treatment global rating	CBZ better than placebo	2/37 withdrawals; adverse effects were drowsiness and staggering gait
Wilton[37]	Diabetic neuropathy	40	DB PC CO	CBZ or placebo 600 mg/day × 1wk, 2wk washout then CO × 1wk	Patient self-report, investigator global assessment	CBZ better than placebo after CO ($p < 0.01$)	25 patients reported adverse effects while on CBZ but without interfering with treatment
Vilming et al.[38]	Trigeminal neuralgia	12	DB P	CBZ titrated up to 900 mg/day vs tizanidine 3-6 mg/day × 21 days	Pain intensity, pain relief	4/6 pts with CBZ rated drug as very good against 1/6 with tizanidine)	No withdrawals in CBZ arm
Lindstrom & Lindblom[39]	Trigeminal neuralgia	12	DB CO PC	CBZ at MTD vs tocainide 20 mg/kg/day × 2wk then CO × 2wk	Severity, frequency and duration of attacks	CBZ had same efficacy as tocainide; both were better than placebo	None reported with CBZ
Lechin et al.[40]	Trigeminal neuralgia	59	MC DB PC	CBZ 300-1200 mg/day vs 4-12 mg/day then placebo, washout and CO × 24wk total	Trigeminal neuralgia symptom score	Pimozide better than CBZ	40/48 with pimozide, 21/48 on CBZ; 11 excluded pts (protocol deviation and loss to follow-up)
Leijon & Boivie[41]	Central poststroke pain	15	PC DB CO	CBZ 800 mg/day vs amitriptyline 75 mg/day vs placebo × 4wk; 1wk washout before CO	Pain severity, post-treatment global ratings, comprehensive psychological rating scale	CBZ no better than placebo	1 withdrawal on CBZ; CBZ dose had to be decreased in 4 pts

Table I. Contd

Study	Pain disorder	No. of patients	Design	Treatment	Outcomes	Results	Adverse effects
Gomez-Perez et al.[42]	Diabetic neuropathy	16	DB CO	CBZ 300-600 mg/day vs nortriptyline 30-60 mg/day vs fluphenazine 1.5-3.0 mg/day × 4wk; 2-4wk washout, then CO	Pain and paresthesia intensity (VAS)	Reduction of pain and paresthesias with CBZ, 50% improvement over baseline; no difference between therapies	2 withdrawals
Phenytoin (PHT)							
Saudek et al.[43]	Diabetic neuropathy	30	PC CO	PHT 300 mg/day titrated against plasma concentrations × 23wk; placebo × 23wk	Pain intensity	No difference between treatment and placebo	10% had giddiness
Chadda & Mathur[44]	Diabetic neuropathy	40	PC CO	PHT 300 mg/day × 2wk; placebo × 2wk; PHT 300 mg/day × 2wk	Pain intensity	74% had moderate improvement with PHT vs 26% with placebo	4/38 reported giddiness, 2 drop-outs
Yajnik et al.[45]	Cancer pain	75	DB P	PHT 200 mg/day vs buprenorphine 0.4 mg/day vs PHT 100 mg/day + buprenorphine 0.2 mg/day	Pain intensity	Combined treatment better than PHT or buprenorphine alone; no statistical significance	8% of pts on PHT had headache and giddiness
McCleane[46]	Different types of peripheral neuropathic pain experiencing acute flare-ups	20	DB PC CO	PHT 15 mg/kg iv infusion or placebo then CO after 1wk	Total pain, shooting pain, burning pain, numbness, paresthesias with VAS every 15 min during infusion and od × 1wk	Significant reduction in hyperalgesia, numbness, overall, burning and shooting pain during PHT infusion; analgesic effect was evident up to 5 days after infusion for shooting pain	All had lightheadedness at the end of infusion with PHT; there was also nausea (4 pts) and skin rash (2 pts)
Lorazepam							
Max et al.[47]	Postherpetic neuralgia	58	DB CO	Lorazepam 0.5-6 mg/day vs amitriptyline 12.5-150 mg/day vs placebo	Pain intensity	Lorazepam no better than placebo and significantly less effective than amitriptyline	4 pts had severe depression

Valproic acid (VPA)							
Drewes et al.[48]	Central pain after spinal cord injury	20	PC DB CO	VPA or placebo 600mg po bid × 3wk; 2wk washout, then CO × 3wk	Pain intensity with Danish version of MPQ	No difference between placebo and VPA	4 pts receiving VPA had dizziness
Lamotrigine (LTG)							
Zakrzewska et al.[49]	Refractory trigeminal neuralgia	14	PC CO	LTG escalated from 50 mg/day to 400 mg/day during 14 days placebo × 14 days; all patients were taking PHT, CBZ or both	Pain intensity	LTG better than placebo (p = 0.001)	7/13 reported dizziness, constipation, nausea, somnolence, diplopia
Simpson et al.[50]	HIV-associated painful sensory polyneuropathy	42	DB, PC, P	LTG 25 mg/day titrated up to 300 mg/day × 14wk	Change in mean pain score on a Gracely pain scale	LTG better than placebo (p = 0.03)	5 reported skin rash; high dropout rate (13/42)
McCleane[51]	Intractable neuropathic pain	100	PC DB PC	LTG escalated from 25 to 200 mg/day for a total of 8wk	Pain intensity, change in pain quality, QoL, sleep, mood, number of additional analgesic tablets required	No difference between LTG and placebo in any of the outcome measurements	26 pts did not complete the study; nausea (8 pts), skin rash (2 pts), bad taste of tablets (2 pts), no pain relief (6 pts) and loss to follow-up (8 pts)
Gabapentin (GBP)							
Backonja et al.[52]	Diabetic neuropathy	165	PC P MC	GBP 900 up to 3600 mg/day × 4wk, then MTD × 4wk	Pain severity, sleep interference, post-treatment global ratings, QoL	Less pain and less sleep interference with GBP (p < 0.001); QoL also improved more with GBP	No difference in withdrawal rate between GBP and placebo; dizziness (23.8%) and somnolence (22.6%) most frequent adverse effects
Rowbotham et al.[53]	Postherpetic neuralgia	229	PC P MC	GBP 1200 up to 3600 mg/day × 8wk	Pain severity, sleep interference, post-treatment global ratings, QoL	GBP better than placebo to relieve pain (p < 0.001) and improve sleep (p < 0.001); QoL also better	Slightly higher withdrawal rate in GBP arm (13.3%) than in placebo arm (9.5%); somnolence (27.6%), dizziness (23.9%) and peripheral oedema (9.7%) were the most common adverse effects
Morello et al.[54]	Diabetic peripheral neuropathy	28	DB CO	GBP (900-1800 mg/day) or amitriptyline 25-75 mg/day × 6wk, then 1wk washout, then CO	Pain relief measured by pain scale with verbal descriptors Global Pain Score assessment at the end of trial	No significant difference between GBP and amitriptyline	7 withdrawals (3 from adverse effects)

a The trial by Webb and Kamali[55] is not included in this table as it was in healthy volunteers.

CO = crossover; **DB** = double-blinded study; **MTD** = maximum tolerated dose; **MPQ** = McGill Pain Questionnaire; **mo** = months; **od** = once daily; **P** = parallel; **PC** = placebo-control; **pts** = patients; **QoL** = quality of life; **VAS** = visual analogue scale; **wk** = weeks.

tant in the treatment of entrapment neuropathies, especially in those patients who do not wish to under go surgery or who do not qualify for surgery.

In summary, carbamazepine demonstrated efficacy in neuropathic pain in early studies, and this has since been confirmed in better designed trials. All of the studies in which carbamazepine was compared with placebo showed pain relief, lower pain ratings or both for patients with trigeminal neuralgia.[33,34,36] Carbamazepine also demonstrated efficacy in relieving pain in patients with PDN in 3 out of 3 studies.[35,37,42] In 1 study, central poststroke pain was relieved with carbamazepine in a number of patients but this was not statistically significant,[41] probably because of the small sample size, whereas amitriptyline provided statistically significant pain relief in the same number of patients. Dosages of carbamazepine used in these studies ranged from 300 to 2400mg per day in divided doses. Withdrawal rate due to adverse effects ranged from 0 to 11%, and many patients (up to 50%) experienced tolerable adverse effects such as somnolence, dizziness and gait disturbance. In earlier studies, haematopoietic issues were addressed but no patients were excluded because of those effects of carbamazepine. Dizziness and somnolence were the most frequent tolerable adverse effects.

3.1.2 Phenytoin

Phenytoin became the first anticonvulsant to be used to treat neuropathic pain after Bergouignan[82] reported success with phenytoin in patients with trigeminal neuralgia.[82,83] Current data indicate that the analgesic effect of phenytoin is achieved through the blockage of Na^+ channels, inhibition of presynaptic glutamate release and suppression of spontaneous neuronal ectopic discharges.[84] Like phenobarbital, phenytoin reduces autotomy in rats with dorsal rhizotomy.[85] Nevertheless, intraperitoneal phenytoin was ineffective in suppressing cold and tactile allodynia in two neuropathic pain animal models.[86]

To date, only 5 randomised clinical trials of phenytoin have been published: 2 trials on PDN,[43,44] 1 on cancer pain,[45] 1 in healthy volunteers with cold-induced pain[55] and 1 trial in patients with flare-ups of neuropathic pain.[46] The 2 studies conducted on PDN yielded opposite results. This difference in results could be due to the differences in study design, including sample size, length of follow-up and, most importantly, lack of statistical power to detect differences between placebo and phenytoin (table I). McQuay et al.[87] estimated that the number of patients needed to treat, that is, the number of patients with that pain condition needed to treat to obtain clinical benefit from phenytoin, was within the range similar to other anticonvulsants.[87] This number is very likely to be higher since the data from the negative trial were not available to estimate a global number of patients needed to treat. Case series and reports on the use of phenytoin to treat different neuropathic pain conditions abound (table III).

Phenytoin showed weak to moderate analgesic action in a randomised controlled trial comparing phenytoin alone with buprenorphine and with phenytoin plus buprenorphine in cancer pain.[45] Although the authors did not specify whether pain in these patients was of neuropathic origin, it has been documented a large proportion of patients with cancer pain have a neuropathic pain component through different direct or indirect pathogenetic mechanisms.[120] This trial had its limitations but it points to the need for additional trials using anticonvulsants as adjuvants in treating cancer pain.

Recent data have appeared supporting the hypothesis that phenytoin has antinociceptive properties in humans. A randomised trial using a laboratory model of cold pain comparing lamotrigine, phenytoin and dihydrocodeine in healthy volunteers showed that a single dose of phenytoin 300mg was significantly more effective than placebo in alleviating pain induced by cold.[55] Maximum pain relief for phenytoin was 4.25 hours after administration and this analgesic effect correlated well with plasma concentrations. In a randomised, placebo-controlled trial in 20 patients with different types of peripheral neuropathic pain, an intravenous dose of phenytoin 15 mg/kg given was significantly more effective than phenobarbital in reducing acute exacerbations of neuropathic pain.[46]

Table II. Selected nonblind trials and case series with anticonvulsants for neuropathic pain[a]

Study	Pain condition	No. of patients	Treatment	Outcome measures	Results	Adverse effects/withdrawals
Carbamazepine (CBZ)						
Spillane[58]	Trigeminal neuralgia	57	CBZ 600 mg/day × 2wk	Paroxysms of pain	50% had 'good' response, 31% had 'fair' response, 1% had ongoing paroxysms, 1% no benefit	5 pts excluded at beginning of study (no pain); 25% had giddiness, nausea, emesis or anorexia
Raskin et al.[59]	Post-sympathectomy neuralgia	9	CBZ 600 mg/day × 24h	Pain report	7/9 had 'dramatic reduction in pain' within 24h 1/9 had no relief; 2/9 also had intravenous PHT 250mg	NA
Chakrabarti & Sawantaray[60]	Diabetic Neuropathy	62	CBZ 300-800 mg/day × 1y	Self-reported pain relief, NCV	49/54 had relief of symptoms, 5/54 had no change; NCV studies unchanged	8 pts omitted from analysis: 2 drop-outs (rash and postural hypotension), 6 drop-outs (noncompliance with follow-up); drowsiness (33%), dizziness (22%), nausea (7%), vomiting (4%), ataxia (4%)
Gerson et al.[b] [57]	Postherpetic neuralgia	29	CBZ 150-1000 mg/day plus clomipramine 10-75 mg/day vs TENS × 8wk	Pain, physical activity, mental outlook with VAS	CBZ plus imipramine gave superior pain relief compared with TENS ($p < 0.05$); no difference in physical activity or mental outlook	5 pts lost to follow-up (3 drug, 2 TENS); 4 pts crossed over to TENS from CBZ because of ineffective treatment: 2 with success; 8 pts crossed over to drug, 3 with success; 1 withdrawal due to adverse effect (not revealed)
Tomson et al.[c] [61]	Trigeminal neuralgia	7	CBZ 200-1400 mg/day × 6 days	Pain scores, plasma concentration of CBZ and epoxide metabolite	Best outcome with serum range 5.7-10.1 μg/ml; no plasma concentration-effect in 6 pts	Adverse effects occurred with serum concentrations >7.9 μg/ml; only assessed degree of 'dizziness'
Taylor et al.[62]	Trigeminal neuralgia	143	CBZ 300-1600 mg/day × unknown initial time; 5-16y long term; PHT, amitriptyline, diazepam and simple analgesics permitted	NA	CBZ was 'effective, initially' in 69%; 19 pts relapsed (average 4y) after starting treatment, 8 pts intolerant to drug, 36 pts no benefit	8 pts with adverse effects: 6 rash, 1 nausea/vomiting 1 water intoxication
Valproic acid (VPA)						
Peiris et al.[63]	Trigeminal neuralgia	20	VPA 600 mg/day up to 1200 mg/day	Number of attacks	9/20 had no attacks for at least 6mo or had 50% reduction in attack rates	1/20 pts had persistent nausea
Swerdlow & Cundill[64]	Various chronic pain conditions	51	VPA unknown dose and duration	Pain intensity	20/51 (39%) reported pain relief	NA

Table II. Contd

Study	Pain condition	No. of patients	Treatment	Outcome measures	Results	Adverse effects/withdrawals
Clonazepam						
Caccia[65]	Facial neuralgia	10	Clonazepam 8 mg/day gradually decreasing to 4 mg/day	Pain relief	Complete pain relief in 5/10 (all with trigeminal neuralgia), partial relief in 4 pts	Marked drowsiness in 8/10 pts
Court & Kase[66]	Trigeminal neuralgia	25	Clonazepam 1mg bid to tid with titration to 6-8 mg/day × 10 days	Number of paroxysms, impression on pain severity	40% complete pain relief, 23% partial relief	Somnolence in 22/25 pts, unsteady gait in 20/25 pts
Smirne & Scarlato[67]	Trigeminal neuralgia, glossopharyngeal neuralgia, Sluder's syndrome	21	Clonazepam 1.5-6 mg/day × 11-195 days	Pain, no measurement scales mentioned	Effective in preventing pain attacks in 64% of pts	12/21 pts had drowsiness or fatigue
Swerdlow & Cundill[64]	Various chronic pain conditions	35	Clonazepam 0.5-1.0 mg/day slowly titrated	Pain intensity	23/35 (66%) reported good pain relief	NA
Bouckhoms & Litman[68]	Deafferentiation neuralgias	21	Clonazepam 1-4 mg/day; duration NA	Pain by patient report and clinical assessment, no measurement scales mentioned	Complete or nearly complete pain relief in 6/21; all of these pts had allodynia	Drowsiness (number of pts not reported)
Gabapentin (GBP)						
Rosenberg et al.[d] [69]	Neuropathic pain, low back myofascial pain	Low back myofascial pain = 122 Neuropathic pain = 97	GBP 600-2400 mg/day	Pain severity, opiate use	Decreased pain from baseline ($p < 0.0001$); 53% reduction in pain severity in PHN ($p = 0.004$); opiate use unchanged	Sedation (12.8%), dizziness (8.0%) and gastrointestinal complaints (8%) were most common
Attal et al.[70]	Refractory mixed neuropathic pain syndromes	23	GBP 600-2400 mg/day × 6wk	Severity/frequency of pain attacks, thresholds to nociceptive stimuli	38% reduction in pain severity from baseline ($p < 0.01$); reduction in frequency of pain attacks ($p < 0.001$); no change in nociceptive thresholds	3 pts withdrew due to adverse effects; choreoathetotic movements (1), intense sedation, hypotonia and fatigue (2)
Solaro et al.[71]	Paroxysmal symptoms in multiple sclerosis	21	GBP 300-1200 mg/day × 3mo	Primary outcome: amelioration of symptoms	18/21 achieved main outcome; no dose-concentration correlation observed	3 pts withdrew: poor compliance (2) and severe nausea (1)
Lamotrigine (LTG)						
Canavero & Bonicalzi[72]	Trigeminal neuralgia	21	LTG 50 mg/day to effect; duration NA	Pain relief	With a median dose of 400 mg/day, 80% had complete pain relief	Skin rash (21%), sedation (9%), confusion or vertigo
Lunardi et al.[73]	Trigeminal neuralgia	20	LTG 25-400 mg/day	Pain intensity	16/20 had complete relief, continuing up to 8mo after end of study	1/20 had skin rash; no other adverse effects reported

Landscape table II to be placed here.

The antinociceptive effects of phenytoin were observed during the infusion of the drug and were still significant for the relief of shooting pain 4 days after the infusion. These findings raise the issue of whether patients should receive a loading dose of phenytoin, and similarly with other anticonvulsants, to derive maximum analgesic effects.

In summary, phenytoin is an anticonvulsant that was studied in early clinical trials for pain control, but the first randomised study in 1977 demonstrated that phenytoin was no more effective than placebo.[43] Another study, one year later, showed that phenytoin was more effective than placebo.[44] The dosage used in both studies was 300mg per day and the rate of adverse effects was around 10% in both trials. A common adverse effect was giddiness. Additional information has been published supporting the use of phenytoin as an analgesic or co-analgesic drug.[45,46,55]

3.1.3 Benzodiazepines

Lorazepam, clonazepam and nitrazepam have been used to control neuropathic pain. Benzodiazepines are GABA agonists that have analgesic properties in the spinal cord and brainstem of animal models.[121] In rats with chronic constriction injury to the sciatic nerve, clonazepam significantly normalised the nociceptive threshold in the injured paw.[122] A nonblind clinical study initially suggested that intravenous lorazepam relieved intractable chronic neuralgia[123] but these results were not reproduced in a randomised, double-blind trial in which lorazepam was significantly less effective than amitriptyline in PHN.[47] In addition, 4 patients in the latter study developed severe depression while receiving lorazepam.[47] Swerdlow[83] used nitrazepam in 11 patients with chronic pain, with satisfactory relief in 6 of them.[83] There have been no more reports on nitrazepam to support these preliminary results.

The use of clonazepam in trigeminal neuralgia began as early as the mid-1970s, when 7 out of 10 patients receiving a high dose (10 mg/day) reported complete or adequate pain relief.[65] This initial report was followed by another in which clonazepam 6 to 8 mg/day for 10 days provided

Eisenberg et al.[74]	Diabetic neuropathy	15	LTG 25 mg/day, doubled weekly up to 400 mg/day × 6wk; then washout × 2wk	Pain intensity with VAS, MPQ, NPS and QTT	Significant drop in pain intensity with VAS, MPQ, NPS, but not QTT	2/15 withdrew because of adverse effects
Cianchetti et al.[75]	Different painful phenomena in multiple sclerosis	21	LTG 25 mg/day with 25-50mg weekly increments up to a total dosage of 400 mg/day	Pain intensity and degree of improvement	Mild to total improvement in 13/21 pts; sustained relief > 1y in 11 pts	No adverse effects reported
Topiramate						
Potter et al.[76]e	Neuropathic pain syndromes excluding diabetic neuropathy	14	Topiramate titrated weekly in 25-50mg increments until pain relief or highest tolerated dose achieved × 1-6mo; mean dosage used 271 mg/day	Pain intensity on a VAS	Significant improvement of pain scores vs baseline ($p < 0.0001$)	Not mentioned

a For studies with phenytoin see table III.
b Randomised.
c Single-blind.
d Retrospective chart review.
e Presented as an abstract.

MPQ = McGill Pain Questionnaire; **NA** = data not available; **NCV** = nerve conduction velocity; **NPS** = numeric pain scale; **PHN** = postherpetic neuralgia; **QTT** = quantitative thermal testing; **TENS** = transcutaneous electrical nerve stimulation.

Table III. Summary of the most relevant trials and reports in the literature using anticonvulsants for different pain situations

Disease	Randomised controlled trials with positive results	Non-blind	Case series/reports
Diabetic neuropathy	Carbamazepine[35,37,42] Phenytoin[44] Gabapentin[52]	Carbamazepine[60] Phenytoin[88] Gabapentin[89] Lamotrigine[74]	
Trigeminal neuralgia	Carbamazepine[33,34,36] Lamotrigine[49]	Carbamazepine[31,32,56,58,62,90-95] Phenytoin[31,32,96-98] Gabapentin[100] Lamotrigine[73] Clonazepam[67,90] Valproic acid[90,63]	Clonazepam[65,66] Felbamate[99]
Postherpetic neuralgia, postsympathectomy neuralgia, deafferentation neuralgias	Carbamazepine[34] Gabapentin[53]	Carbamazepine[57,59] Phenytoin[59] Clonazepam[68]	
HIV polyneuropathy	Lamotrigine[50]	Gabapentin[101,102]	
Experimental neuropathic pain	Phenytoin[55] Lamotrigine[55]		
Phantom-limb pain			Carbamazepine[103] Lamotrigine[104] Clonazepam[105]
Paroxysmal pain in multiple sclerosis[a]		Gabapentin[71]	Carbamazepine[106,107] Gabapentin[108] Lamotrigine[109]
Neuropathic pain syndromes (including cancer pain and reflex sympathetic dystrophy)	Phenytoin[45]	Carbamazepine[64,92] Phenytoin[64] Gabapentin[70,115] Valproic acid[64] Clonazepam[64] Topiramate[76]	Phenytoin[110] Gabapentin[69,111-114]
Central poststroke pain		Carbamazepine[92]	Carbamazepine[116] Phenytoin[117-119]

a Including patients with trigeminal neuralgia.

complete or adequate relief to 63% of 25 patients with trigeminal neuralgia, of whom 16 had previously failed carbamazepine.[66] Subsequent trials used lower dosages ranging from 1 to 6 mg/day with similar or better success.[64,67,90] In a series of 21 patients with deafferentation neuralgia, only 6 responded to clonazepam 1 to 4mg at bedtime. All responders had allodynia as a common feature and the investigators suggested that allodynia was a good predictor of response to clonazepam.[68] Despite these data, there have been no randomised controlled trials of clonazepam in neuropathic pain.

In summary, lorazepam, the only benzodiazepine submitted to controlled clinical trials, failed to demonstrate analgesic properties.

3.1.4 Valproic Acid

Valproic acid inhibits sustained neuronal firing in murine cortical and spinal neurons. This effect is mediated by prolonging repolarisation of voltage-activated Na^+ channels. Moreover, valproic acid increases the amount of GABA in the brain, enhancing the activity of glutamic acid decarboxylase and inhibiting GABA degradation enzymes.[25] In the rat hippocampus, valproic acid increases the GABA inhibitory postsynaptic potential (IPSP) slope by more than 50%.[124] Several other investigators have shown that valproic acid has an antinociceptive effect in the mouse hot-plate assay and in the acetic acid writhing test.[125-127] Valproic acid binds $GABA_A$ receptors and decreases the ex-

pression of c-fos after the irritation of meningeal and trigeminal afferent fibres, suggesting that its nociceptive action is mediated partly by $GABA_A$ binding.[128,129] Despite all of this evidence, there is no clear agreement on the analgesic or antinociceptive properties of valproic acid. In one study, valproic acid enhanced the antinociceptive effect of morphine but, alone, it did not have any effect on heat-induced pain in mice.[130]

The first reports about the use of valproic acid in neuropathic pain appeared in the early 1980s. In these studies, valproic acid relieved pain in 50 to 80% of patients with trigeminal neuralgia.[63,90] Many patients in the case series studied by Peiris et al.[63] had already been treated with carbamazepine, phenytoin and clonazepam alone or in combination. Swerdlow[64] gave valproic acid to 79 patients with lancinating pain due to different causes, obtaining satisfactory pain relief in 37% of them. Satisfaction was gauged using self-reporting and daily pain charts. Finally, patients with PHN and tabes dorsalis reported pain relief with valproic acid.[131,132] Taken together, these data show promise for valproic acid in the treatment of neuropathic pain. Unfortunately, the only double-blind, placebo-controlled trial of valproic acid published so far for treatment of neuropathic pain due to spinal cord injury showed no difference between valproic acid and placebo (see table I).[48] This study was well designed but its negative result can be explained partly by the small number of patients, a fact acknowledged by the authors of the study. At present, the precise role of valproic acid in the treatment of neuropathic pain has not been determined and additional randomised trials are still necessary to document the possible effect of valproic acid for neuropathic pain due to peripheral disorders such as diabetic painful neuropathy.

3.1.5 Lamotrigine

Lamotrigine is a phenyltriazine derivative and one of the newer antiepileptic agents initially approved in the US as add-on therapy for partial complex seizures. Lamotrigine blocks voltage-dependent Na^+ channels with the inhibition of glutamate release.[133] Oral lamotrigine induced dose-dependent analgesia in rat experimental models of acute and chronic pain without observable adverse effects.[134,135] Using different chronic pain models in the rat, Hunter et al.[86] showed that lamotrigine could reverse cold allodynia for over 5 hours, although it could not reverse tactile allodynia. Klamt[136] used similar experimental pain models to those used by Nakamura[134,135] and Hunter[86] but he administered intrathecal lamotrigine at 12.5, 25 and 100μg, finding that intrathecal lamotrigine produced a spinal, dose-dependent and lasting antihyperalgesic effect in these models. The administration of lamotrigine immediately after transection of the sciatic nerve in rats drastically moderated the development of neuropathic pain and also markedly decreased the number of autotomies, suggesting a potential prophylactic role in preventing or modulating the onset and course of pain.[137]

At the same time these data were derived from translational research, lamotrigine began to be used empirically for chronic and refractory pain conditions. In a case report, lamotrigine given at doses between 50 and 150mg orally twice daily controlled phantom limb pain in 3 patients.[104] A single dose of lamotrigine 300mg given orally to 12 healthy volunteers with cold-induced allodynia was significantly better at relieving pain than placebo, with maximum pain relief at 1.25 hours after administration.[55] Other nonblind studies in patients with trigeminal neuralgia, PDN and pain related to multiple sclerosis reported good results with lamotrigine.[72-75]

A clinical trial comparing lamotrigine with placebo in patients with trigeminal neuralgia found that lamotrigine was clearly better than placebo (see table I).[49] Another clinical trial with 42 HIV1-positive patients with PDN showed that lamotrigine 25 to 300 mg/day was more effective than placebo in reducing pain intensity, although the high withdrawal rate limited the usefulness of this trial.[50] Not all trials have yielded positive results; lamotrigine given at dosages up to 200 mg/day for 8 weeks was no better than placebo in a randomised,

double-blind, placebo-controlled study of 100 patients with neuropathic pain.[51]

In summary, lamotrigine 50 to 400 mg/day has demonstrated efficacy in relieving pain in patients with trigeminal neuralgia refractory to other treatments, such as carbamazepine, phenytoin or both, which were continued for the duration of the study.[49] Seven out of 13 patients experienced tolerable adverse effects: dizziness, constipation, nausea, somnolence and diplopia. Good experimental and clinical evidence warrants the use of lamotrigine in the other painful conditions, but recent negative results from a clinical trial indicated that more well-designed trials are needed to better define the role of lamotrigine as an analgesic drug.

3.1.6 Gabapentin

Of the new generation of antiepileptic drugs used for treatment of neuropathic pain, gabapentin is perhaps the best agent studied so far. It was developed as a structural GABA analogue but it has no direct GABAergic action and it does not affect GABA uptake or metabolism.[25] Gabapentin blocks the tonic phase of nociception induced by formalin and carrageenan, and it exerts a potent inhibitory effect in several neuropathic pain models of mechanical hyperalgesia, mechanical allodynia, thermal hyperalgesia and thermo-allodynia.[138,139] Preliminary evidence points to the possible effect of gabapentin on the α-2-δ type of Ca^{2+} channels[138] Whereas some investigators have shown that gabapentin appears to have a central and not a peripheral anti-allodynic effect,[140] others have found that gabapentin inhibited the ectopic discharge activity from injured nerves[138,141] and reversed the allodynia induced by anti-GD2 antibodies.[142] Although gabapentin does not have direct effects on GABA or its receptors, a magnetic resonance imaging spectroscopy study documented a global increase in GABA after the administration of gabapentin.[143]

There have been positive results in several open-label studies investigating the effect of gabapentin on different pain conditions, including trigeminal neuralgia and painful tonic spasms associated with multiple sclerosis,[71,108,144] reflex sympathetic dystrophy,[111] painful HIV-related peripheral neuropathy,[101] and neuropathic cancer pain (tables II and III).[115]

Two large randomised clinical trials have established the efficacy of gabapentin for relief from neuropathic pain in patients with PDN and PHN[52,53,145] (table I). Both studies used a placebo-controlled parallel design with a large number of patients, and an intent-to-treat method of analysis was used. In the study of 165 patients with PDN,[52] most (80%) were able to escalate the dosage over 2 weeks, from 900 to 3600 mg/day in 3 divided doses. Pain relief was observed during the second week after the dosage reached 1800 mg/day. Pain relief was maintained after a further dose increase and for the duration of the 8-week study. In the study of 229 patients with PHN,[53] almost identical results were documented. The comprehensive design of these studies allowed for associated symptoms to be assessed; not only was pain relieved but patients had improvements in sleep and mood as well as some measures of quality of life.[52,53,145] The design of these 2 studies has set new standards for clinical trials in neuropathic pain.

In a rare comparative study, the analgesic efficacy of gabapentin was compared with amitriptyline for PDN pain (see table I).[54] In this double-blind, randomised, crossover trial, 21 out of 25 enrolled patients completed 13 weeks of treatment with a week washout period between two 6-week treatments. There was no significant difference in analgesic efficacy between gabapentin and amitriptyline and the adverse effects for both drugs were similar except that more patients receiving amitriptyline (6 versus 0 receiving gabapentin) had bodyweight gain. An extension of this trial has been recently published in full with identical results and conclusions.[54]

At least 1 clinical trial has failed to show any significant difference between gabapentin and placebo in patients with PDN.[146] A possible explanation for this lies in the use of a relatively low dosage of gabapentin (900 mg/day without titration). In this regard, another clinical trial of gabapentin versus placebo in only 25 patients with

Table IV. Randomised trials of newer anticonvulsant drugs in neuropathic pain published as abstracts

Authors	Pain condition	No. of patients	Design	Treatment	Outcome measures	Results	Adverse effects/ withdrawals
Gorson et al.[146]	Diabetic neuropathy	40	DB, PC, CO	GBP 900 mg/day vs PB × 6wk, 1wk washout, then CO × 6wk	Pain intensity, post-treatment global ratings	No difference between GBP and PB	NA
Morello et al.[147]	Diabetic neuropathy	25	DB, PC, CO	GBP 900-1800 mg/day vs amitriptyline 25-75 mg/day	Pain intensity, post-treatment global rating	19 pts completed the study; 68% on amitriptyline and 53% on GBP had moderate or greater pain relief ($p > 0.1$)	NA
Facchetti et al.[81]	Carpal tunnel syndrome	10	DB, P	GBP at 300-1600 mg/day maximum dose vs CBZ 100-600 mg/day × 6wk	VAS, MPQ, Clinical Global Impression of Change	All outcomes statistically significant from baseline for both drugs; no difference between CBZ and GBP	1 withdrawal with CBZ (intolerance) and 1 withdrawal with GBP (skin rash)
Edwards et al.[148]	Diabetic polyneuropathy	27	DB, PC, P	TOP 200mg po bid or MTD *vs* PB × 4wks	Pain scores with VAS SF-MPQ, SFMQ. Assessment of PGIC	TOP better than PB ($p = 0.07$); trend favouring TOP on PGIC	28% withdrawal rate in TOP arm *vs* 11% in PB arm; bodyweight loss, asthenia and confusion most common adverse effect
Iacobellis et al.[149]	Diabetic polyneuropathy	337	DB, PC, P	PGB at 75, 300 or 600 mg/day *vs* PB × 5wks	Pain scores with 0-10mm VAS, PGIC, SFMQ	PGB at 300 and 600 mg/day better than PB (45.7 and 48% *vs* 17.5% respectively); significant improvement on PGIC and SFMQ of TOP over PB	Withdrawal rate: 3.7% (PGB 300); 12% (PGB 600); and 3.1% (PB); dizziness and somnolence were most frequent adverse effects

CO = crossover; **DB** = double-blind; **GBP** = gabapentin; **HIV** = human immunodeficiency virus; **LTG** = lamotrigine; **MC** = multicentre; **MPQ** = McGill Pain Questionnaire; **MTD** = maximum tolerated dose; **P** = parallel; **PB** = placebo; **PC** = placebo-control; **PGB** = pregabalin; **PGIC** = Patient Global Impression of Change; **pts** = patients; **NA** = data not available; **SFMQ** = Short Form McGill Questionnaire; **TOP** = topiramate; **VAS** = Visual Analog Scale; **VAS SF-MPQ** = Visual Analogue Scale of the Short Form McGill Pain Questionnaire; **wk** = weeks.

PDN yielded positive results; the dosage was between 900 and 1800 mg/day, suggesting that higher dosages are more effective for pain control (table IV).[147]

Finally, gabapentin was effective in relieving pain in patients with carpal tunnel syndrome.[81]

In summary, gabapentin has clearly demonstrated its efficacy in relieving pain and associated symptoms in patients with PDN[52] and PHN.[53] The dosages used in these studies ranged from 900 to 3600 mg/day given in 3 divided doses. Gabapentin was well tolerated with no significant difference in adverse events with gabapentin compared with placebo in patients with PDN while patients with PHN had a slightly higher rate of withdrawal than those receiving placebo (13.3 *vs* 9.5%, respectively). Dizziness and somnolence were the most frequent tolerable adverse effects. Gabapentin should be tested in other painful conditions such as facial neuralgias (including trigeminal and glossopharyngeal neuralgias), central pain syndromes secondary to cerebrovascular disease, spinal cord injury and phantom limb pain.

Taken together, the increasing evidence from experimental and clinical studies shows that gabapentin is an effective agent for treating neuropathic pain, particularly that due to PDN and PHN. Additional clinical trials are necessary to evaluate the efficacy of gabapentin in CPRS, phantom limb pain,

central poststroke pain syndrome, trigeminal neuralgia and other facial neuralgias.

3.1.7 Topiramate

Unlike gabapentin, lamotrigine and tiagabin, topiramate resembles phenytoin and carbamazepine in that empirical use as an antinociceptive drug in humans came before systematic, planned research on animal models of pain. Topiramate is a sulfamate-substituted derivative of *d*-fructose with the ability to block Na^+ channels, enhance GABA activity by interacting with a non-benzodiazepine site on $GABA_A$ receptors, and selectively block AMPA/kainate glutamate receptors.[150] Clinical experience with topiramate is limited; a nonblind trial in patients with several neuropathic pain conditions (excluding diabetic neuropathy) found that patients had significantly better pain scores compared with pretreatment values.[76] A case report described one patient with post-thoracotomy pain syndrome unresponsive to other anticonvulsants, antidepressants and opiates who had 80% pain relief with topiramate without intolerable adverse effects for over 6 months.[151] In a randomised, double-blind, placebo-controlled trial using oral topiramate 200mg twice a day for 4 weeks, Edwards et al.[148] reported a statistically significant reduction in average pain scores as measured by the visual analog scale of the Short Form McGill Pain Questionnaire. Although not significant in statistical estimations, there was a trend to improvement in the patients' global assessment of change. These results are encouraging and should prompt active research on the antinociceptive effects of topiramate on animal models and in clinical trials.

3.1.8 Pregabalin

Like gabapentin, pregabalin [S-(+)-3-isobutyl-γ-aminobutyric acid] is a GABA analog without proven agonistic effect on GABA receptors. Pregabalin does not appear to interact directly with Na^+ channels, Ca^{2+} channels or neurotransmitter responses (GABA, glutamate). Pregabalin has been effective in experimental models of neuropathic pain and we have now evidence to suggest that it also works in humans. A randomised, controlled trial comparing 3 different doses of pregabalin (75, 300 and 600 mg/day orally) with placebo in 337 patients with diabetic polyneuropathy reported significant improvement in pain, sleep, and clinical and global impression of change scores for those who took 300mg or more daily.[149] In addition, the withdrawal rate was lower than that seen for other anticonvulsants (12.3% with 600 mg/day). Dizziness, somnolence and peripheral oedema were the most frequent adverse effects reported in this trial. If other clinical trials and clinical experience consistently show similar results, pregabalin will supersede many other anticonvulsants in the treatment of neuropathic pain, at least in diabetic peripheral polyneuropathy.

3.2 Not Yet Studied in Controlled Randomised Clinical Trials

3.2.1 Phenobarbital

Phenobarbital, the first organic antiepileptic drug, has been used in clinical practice since 1912. It was found to enhance synaptic inhibition by interacting with the $GABA_A$ receptor and inhibiting voltage-activated Ca^{2+} channels.[25] Phenobarbital facilitated the GABA IPSP slope by 77% in the rat hippocampus.[124] In addition, phenobarbital significantly suppressed autotomy in the sciatic nerve ligation and dorsal rhizotomy pain models.[152] The suppressive effect on deafferentation behaviour was more potent in the dorsal rhizotomy model, suggesting that phenobarbital is more active in the CNS. Such reduction in the self-mutilating behaviour could not be attributed to a sedative effect. Moreover, intrathecal phenobarbital in rats with acute experimental pain caused a weak antinociceptive effect only after a total dose of 500μg. The effect of phenobarbital on these experimental models of pain appears to be related to its anticonvulsant properties rather than any analgesic effect.

There are no known published reports or clinical trials using phenobarbital in patients with neuropathic pain, so it is unclear at this point whether phenobarbital has any role in the management of this condition.

3.2.2 Felbamate

Felbamate is a dicarbamate that inhibits NMDA-evoked potentials and enhances GABA-evoked responses in hippocampal neurons.[153] Imamura and Bennett[154] tested the effect of felbamate on rats with established heat-hyperalgesia, mechano-hyperalgesia, mechano-allodynia and signs of spontaneous pain.[154] No effect on these endpoints was noted with felbamate 150 mg/kg but significant reductions in all measures of abnormal pain were observed with doses between 300 and 600 mg/kg. The antinociceptive effect of felbamate in these experiments lasted between 2 and 12 hours. Felbamate significantly reduced cold allodynia but not tactile allodynia in rats.[86]

Clinical experience with felbamate in neuropathic pain is limited to a case report in which 3 patients with refractory trigeminal neuralgia received felbamate 400 to 800mg orally 3 times daily.[99] All 3 patients reported complete or near complete analgesia. However, in the same article, Cheshire[99] briefly reports the use of felbamate in 5 other patients with dysesthetic PHN, without success. He reasoned that tonic, dysesthetic pain was less likely to respond to anticonvulsants. The precise mechanisms underlying these differences in analgesic response to anticonvulsant drugs are still not well understood. Given its potential for fatal toxicity of the bone marrow and the liver, the use of felbamate is restricted to some patients with refractory epilepsy. Its use in treatment of pain conditions is not warranted given the existence of many other alternatives.

3.2.3 Vigabatrin, Zonisamide and Tiagabine

Vigabatrin is an anticonvulsant that induces selective and irreversible inhibition of γ-aminobutyric acid aminotransferase (GABA-T), the enzyme that catabolises GABA. Vigabatrin was not approved in the US by the Federal Drug Administration (FDA) because of retinal toxicity but it is widely used in other countries for the treatment of infantile spasms and other difficult to treat epilepsies. A group of Brazilian researchers have described an antinociceptive effect of vigabatrin in an animal model of neuropathic pain.[155] The results showed a possible dose-dependent analgesic effect of vigabatrin (γ-vinyl-GABA) on experimental neuropathic pain, as shown by the significant ($p < 0.05$) decreasing effect of vigabatrin on scratching and by its significant ($p < 0.05$) increasing effect on the latency of the right hindpaw withdrawal of the animals to noxious thermal stimuli. At the time of this writing there are no published data about the antinociceptive properties of zonisamide in animal models of neuropathic pain.

Tiagabine is a nipecotic acid derivative that enhances GABA-mediated inhibitory neurotransmission. This antiepileptic drug inhibits presynaptic neuronal and glial GABA uptake by binding reversibly and saturably with the GABA uptake carriers GAT-1 and GAT-3.[156] Tiagabine induces dose-dependent and long-lasting antinociception in the hot-plate, paw pressure, tight nerve ligation, acetic acid-induced stretching and abdominal constriction tests but not in the tail-flick model.[157,158] This antinociceptive effect appears to be mediated by $GABA_B$ receptors since it can be completely antagonised by pretreatment with a selective $GABA_B$ receptor antagonist.[157] No case reports or trials using tiagabine have been published but these experimental data suggest that the use of tiagabine in patients with neuropathic pain is the next step.

Evidence from nonblind studies (table II) frequently provides positive results, which then sets the stage for randomised clinical trials. It is the results from clinical trials that ultimately provide the evidence for therapeutic efficacy (table III).

4. Future Directions

Research into the mechanisms of neuropathic pain has provided an unprecedented opportunity to glimpse the complexity that underlies neuropathic pain, and from this we have identified several possible targets for therapy. Early developments in this direction have yielded positive results. It is now clear that the mechanisms underlying chronic neuropathic pain not only include inadequacies of the opioid system but a whole cascade of biological changes that occur in the peripheral and central nervous systems, which is termed neuroplasticity.

Thus, any new approach has to take into account these mechanisms.

Research into the mechanisms of neuropathic pain, and in particular its biochemical and molecular mechanisms, should yield results that lead to the development of specific therapeutic recommendations. With many specific nervous system effects related to those mechanisms, anticonvulsants will continue to offer an alternative approach in the treatment of neuropathic pain.

Randomised clinical trials have demonstrated the efficacy of anticonvulsants in relieving neuropathic pain in PDN, PHN and trigeminal neuralgia, with a new standard being set by studies into gabapentin. Future studies in this field will have to be comprehensive. Consequently, they should include not only the primary outcome of pain relief but also the effects on associated symptoms such as sleep and quality of life. The next step would be to design studies based on pain mechanisms so that, in addition to demonstrating pain relief, they answer the question as to which pain mechanism is most responsible for the maintenance of a particular neuropathic pain syndrome, regardless of its aetiology. Helpful tools, such as quantitative sensory testing[159,160] and the neuropathic pain questionnaire,[161] already exist and can be used in clinical trials, although further advances in these tools need to be made before they can be easily implemented in clinical practice and clinical research trials.

For practical as well as for mechanisms-based analysis, it is important to design studies in which pharmacological agents, including anticonvulsants with different mechanisms of action, are compared with each other. Similarly, randomised trials of drugs used in combination will be the next important step in the development of more effective regimens to treat neuropathic pain.

5. Conclusion and Recommendations

From the information presented in this article, it appears that anticonvulsants are and will be increasingly important in the management of neuropathic pain syndromes.

On the strength of current evidence, the most effective anticonvulsant agent for the treatment of neuropathic pain is gabapentin. In two large multicentre studies and a study in which gabapentin was compared with amitriptyline, gabapentin has clearly demonstrated efficacy in relieving PDN and PHN pain. It appears that the therapeutic dosage for neuropathic pain is 1800 mg/day or higher given in 3 divided doses. The evidence that gabapentin can relieve two types of neuropathic pain is a strong argument for considering gabapentin early in the treatment of neuropathic pain in general. Gabapentin has relatively well-tolerated adverse effects, a lack of organ toxicity and no evidence of a significant interaction with other medications, making this agent very attractive as a first choice in the treatment of neuropathic pain. This is particularly the case in the elderly who are sensitive to medications and who frequently take many other medications. The financial cost of gabapentin compared with other drugs is an issue, but cost-effectiveness analyses should take into account the improvement of quality of life, the provision of adequate pain relief and the potential reintegration of patients to a more active life with less disability.

It is clear that, with a reasonable degree of confidence, we can continue to recommend carbamazepine as the treatment of choice for trigeminal neuralgia. Carbamazepine is also to be considered as one of the first-line drugs – along with tricyclic antidepressants and gabapentin — for the treatment of PDN, although comparative studies should help to delineate specific roles for each. The evidence that carbamazepine can relieve 2 types of neuropathic pain would be a sufficient argument to suggest that carbamazepine should be considered early in the treatment of neuropathic pain in general. It appears that to achieve therapeutic effects the dose should be titrated to the target effect or to standard doses leading to a serum concentration of 6 to 10 μg/L.

With mounting data from ongoing and future clinical trials, the role of both the older and newer anticonvulsants in the management of neuropathic pain will be better established.

We are well aware that rapid developments in the pharmaceutical industry and an increasing number of clinical trials will lead to an upsurge of information, which may render this review outdated within a few years. However, in addition to the literature review, we have also attempted to provide a framework or a reference point for future reviews of a similar kind.

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