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REVIEW ARTICLE

Gabapentin: pharmacology and its use in pain management

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Summary

Although its exact mode of action is not known, gabapentin appears to have a unique effect on voltage-dependent calcium ion channels at the postsynaptic dorsal horns and may, therefore, interrupt the series of events that possibly leads to the experience of a neuropathic pain sensation. Gabapentin is especially effective at relieving allodynia and hyperalgesia in animal models. It has been shown to be efficacious in numerous small clinical studies and case reports in a wide variety of pain syndromes. Gabapentin has been clearly demonstrated to be effective for the treatment of neuropathic pain in diabetic neuropathy and postherpetic neuralgia. This evidence, combined with its favourable side-effect profile in various patient groups (including the elderly) and lack of drug interactions, makes it an attractive agent. Therefore, gabapentin should be considered an important drug in the management of neuropathic pain syndromes.

Keywords *Pharmacology*: gabapentin. *Pain*: neuropathic.

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Gabapentin [1-(aminomethyl)cyclohexane acetic acid] is a novel anti-epileptic agent, originally developed as a gamma-aminobutyric acid (GABA)-mimetic compound to treat spasticity, and has been shown to have potent anticonvulsive effects [1, 2]. Initially approved only for use in partial seizures, it soon showed promise in the treatment of chronic pain syndromes, especially neuropathic pain.

The aims of this article are to review the pharmacology of gabapentin and its use in pain management.

Chemistry

Gabapentin, a structural analogue of GABA, is a water-soluble, bitter-tasting, white crystalline substance with a structure resembling GABA with a cyclohexane ring incorporated (Fig. 1).

Its molecular weight is 171.34, and at physiological pH it is highly charged, existing as a zwitterion with two pK_a values of 3.68 and 10.70 [3]. It is assayed in plasma and urine using gas chromatography [4] and high-performance liquid chromatography [5]. Although it is stable at room temperature, a small amount of lactam formation occurs in aqueous solutions, and this is minimised at a pH of 6.0.

Pharmacokinetics

Gabapentin, available only as oral preparations, is absorbed in the small intestine by a combination of diffusion and facilitated transport. Its transport from the gut following oral administration is facilitated by its binding to an, as yet unidentified, receptor linked to a saturable L-amino acid transport mechanism [6]. As this carrier-dependent transport is saturable, the bioavailability of gabapentin varies inversely with dose. The bioavailability of a 300-mg dose is $\approx$60% [7], whereas that of a 600-mg dose is $\approx$40% [8], and this decreases to $\approx$35% at steady state with doses of 1600 mg three times daily [9]. Peak plasma levels (C_{max}) of gabapentin of 2.7–2.99 mg.l^{-1} are achieved 3–3.2 h after ingestion of a single 300-mg capsule [7, 10]. As a result of the dose-dependent saturable absorption of gabapentin, C_{max}

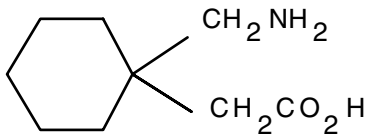

Figure 1 Structure of gabapentin.

increases less than threefold when the dose is tripled from 300 to 900 mg [9].

Its extensive distribution is reflected in a volume of distribution of ≈0.6–0.8 $l.kg^{-1}$ [7, 9]. Cerebrospinal fluid (CSF) concentrations are 20% of plasma concentrations [11] and have been estimated at between 0.09 and 0.14 $\mu g.ml^{-1}$ [12]. Brain tissue concentrations are ≈80% the plasma level [13]. In rats, the pancreatic and renal tissue concentrations were found to be eight and four times, respectively, higher than serum concentrations [11]. Pancreatic accumulation of the drug does not occur in humans as it exists in a highly ionised state at physiological pH and concentrations in adipose tissue are low [11].

Gabapentin is not metabolised in humans and is eliminated unchanged in the urine [9, 11]. It undergoes first-order kinetic elimination and renal impairment will consequently decrease gabapentin elimination in a linear fashion with a good correlation with creatinine clearance [3, 11, 14]. The elimination half-life of gabapentin is between 4.8 and 8.7 h [3, 7, 10, 14–17]. Gabapentin is removed by haemodialysis, so patients in renal failure should receive their maintenance dose of gabapentin after each treatment [18]. Unlike other anticonvulsant drugs, it does not induce or inhibit hepatic microsomal enzymes.

Interactions

Gabapentin is conspicuous among anticonvulsant drugs for its lack of clinically relevant drug interactions, because of the lack of hepatic metabolism and ability to induce or inhibit hepatic microsomal enzymes, and low protein binding. No pharmacokinetic interaction has been demonstrated with other anticonvulsant drugs. Cimetidine, however, decreases the clearance of gabapentin by 12% because cimetidine decreases glomerular filtration rate [9]. Busch *et al.* reported that antacids reduce the bioavailability of gabapentin by ≈20% when given concomitantly with, or up to 2 h post, gabapentin administration [19].

Mechanism of action

Gabapentin has no direct GABAergic action and does not block GABA uptake or metabolism. Gabapentin blocks the tonic phase of nociception induced by formalin and carrageenan, and exerts a potent inhibitory effect in neuropathic pain models of mechanical hyperalgesia and mechanical/thermal allodynia.

Gabapentin binds preferentially to neurons in the outer layer of the rat cortex at sites that are distinct from other anticonvulsants [20]. It is likely that gabapentin acts at an intracellular site as the maximal anticonvulsant effect is achieved 2 h after an intravenous injection of gabapentin in rats. This occurs after the plasma and interstitial fluid concentrations have peaked and reflects the additional time required for intraneural transport [21].

Several theories have been proposed to explain the cellular mechanism of its anticonvulsant effect. The most favoured theory involves an interaction with an as yet undescribed receptor linked with the L-system amino acid transporter protein. Suman Chauhan *et al.* [22] demonstrated that L-amino acids potently inhibited binding of an active enantiomer of gabapentin ([^{3}H]gabapentin). This was further supported by Taylor *et al.* [23] who showed that the potent anticonvulsant, 3-isobutyl GABA (an analogue of gabapentin) potently and stereoselectively bound to the same receptor. These findings renewed interest in the isolation of the receptor protein that may responsible for this anticonvulsant effect.

Other proposed biochemical events in the central nervous system (CNS) that may explain its anti-epileptic effect include the increased extracellular GABA concentrations in some regions of the brain caused by an increase in activity of glutamic acid decarboxylase that produces GABA, and a decreased breakdown by GABA decarboxylase [3, 24]. Although a study [25], using magnetic resonance imaging (MRI) spectroscopy showed a global increase in GABA in the brain after the administration of gabapentin, there is no evidence that gabapentin increases intraneuronal GABA concentrations, binds $GABA_A$ or $GABA_B$ receptors, or exerts any GABA-mimetic action [3, 23].

Other effects of gabapentin have been described but are not considered to play a significant pharmacodynamic role. These include small decreases in the release of monoamine neurotransmitters (dopamine, noradrenaline and serotonin) [26, 27] and the attenuation of sodium-dependent action potentials (suggesting sodium channel blockade) after prolonged exposure to gabapentin [28].

The mode of action of gabapentin in the treatment of neuropathic pain has not been fully elucidated. Although early studies [29] indicated that gabapentin had only a central anti-allodynic effect, gabapentin has been shown to inhibit ectopic discharge activity from injured peripheral nerves [30]. The mechanisms of the anti-allodynic effects of gabapentin proposed include: CNS effects (potentially at spinal cord or brain level) due to either enhanced inhibitory input of GABA-mediated pathways (and thus reducing excitatory input levels);

antagonism of NMDA receptors; and antagonism of calcium channels in the CNS and inhibition of peripheral nerves [29–46]. Of these, antagonism of the NMDA receptor and calcium channel blockade have the most supporting evidence. Field *et al.* [31] discounted an antihyperalgesic action via opioid receptor binding after demonstrating that morphine tolerance does not alter the efficacy of gabapentin and naloxone does not reduce its antihyperalgesic effect.

Research into a peripheral site of action for gabapentin has produced contradictory results [29, 30]. Intrathecal administration of gabapentin blocks thermal and mechanical hyperalgesia without affecting sympathetic outflow or acute nociception, and this suggests a spinal site of action [32–34]. Patel *et al.* [35] demonstrated a presynaptic site of action for gabapentin in the rat spinal cord.

Although gabapentin does not bind to $GABA_A$ or $GABA_B$ receptors, increased synthesis and reduced breakdown of GABA have been described [3, 24]. Potentiation of inhibitory GABA-ergic pathways seems unlikely to be responsible for its anti-allodynic effect because GABA receptor antagonists do not reduce this effect [8, 36].

The NMDA receptor complex is a ligand-gated ion channel that mediates an influx of calcium ions when activated. The NMDA receptor complex has a number of binding sites for various ligands that regulate its activity, including the strychnine-insensitive glycine binding site, phencyclidine binding site, polyamine binding site, redox modulatory site and a proton-sensitive site. Partial depolarisation of the neuron after glutamine activation will release a magnesium plug and allow calcium influx into the neuron. These receptors are known to be found in high concentrations in the hippocampus and have been attributed a key role in the process of central sensitisation of painful stimuli, commonly known as the 'wind-up' phenomenon, leading to hyperalgesia. Evidence linking gabapentin to the NMDA receptor follows research demonstrating the reversal of the antihyperalgesic effect of gabapentin by D-serine, an agonist at the NMDA-glycine binding site [33, 34, 36, 37]. However, receptor binding studies have failed to demonstrate a direct binding site for gabapentin at the NMDA receptor [38–40].

The $\alpha_2\delta$ subunit of the voltage-dependent calcium channel is a binding site for gabapentin and the *S*-isomer of pregabolin (*S*-(+)-3-isobutylgaba) [4, 33, 37, 41]. Because only gabapentin and the *S*-isomer of pregabolin produce antihyperalgesic effects, it is postulated that the antihyperalgesic action for gabapentin is mediated by its binding to this site on the voltage-dependent calcium channel. Fink *et al.* [45] showed that, in the rat neocortex, gabapentin inhibits neuronal calcium influx in a concentration-dependent manner by inhibiting P/Q-type calcium channels. The decreased calcium influx reduces excitatory amino acid (e.g. glutamate) release leading to decreased AMPA receptor activation, and noradrenaline release in the brain. These findings support the hypothesis that calcium channel inhibition mediates the analgesic effects of gabapentin in chronic neuropathic pain. A decrease in potassium ion-evoked glutamate release from rat neocortical and hipppocampal slices by gabapentin has been demonstrated [46].

Adverse effects

Gabapentin is well tolerated with few serious adverse effects. Reviewing data from controlled clinical trials conducted prior to 1995, Ramsay [47] reported that somnolence (20%), dizziness (18%), ataxia (13%) and fatigue (11%) were the most common side-effects. McLean *et al.* [48] in a large open-label multicentre study involving 2216 patients to examine the safety and tolerability of gabapentin as an adjunctive therapy in seizure control, showed that the most common adverse effects were somnolence (15.2%), dizziness (10.9%) and asthenia (6.0%). The most serious adverse effect was convulsions (0.9%).

The relative safety of gabapentin is supported by case reports of massive overdoses of the drug in which serious toxicity was absent. Fisher *et al.* [49] reported a patient who ingested 48.9 g of gabapentin from which a full recovery was achieved after symptoms of lethargy and dizziness. Verma *et al.* [50] reported a case of sustained massive overdose of gabapentin in a patient on haemodialysis three times a week taking 1800 mg of gabapentin per day. A serum assay revealed a level of 85 $\mu g.l^{-1}$ (therapeutic level 2–15 $\mu g.l^{-1}$). The gabapentin was decreased to 600 mg post dialysis and the patient suffered no clinically significant toxicity.

Recent case reports have suggested that gabapentin may cause reversible acute renal allograft dysfunction [51] and Stevens–Johnson syndrome [52]. Following the exacerbation of myasthenia gravis in a patient after a 3-month course of gabapentin 400 $mg.day^{-1}$ that improved with the cessation of gabapentin, Boneva *et al.* [53] treated rats with experimental autoimmune myasthenia gravis with high doses of gabapentin (150 $mg.kg^{-1}$) and observed a transient decrease in amplitude of muscle contraction with repetitive nerve stimulation. The authors suggested that gabapentin can possibly unmask myasthenia gravis, and therefore should be used with caution in patients with this disease.

Recent trials have been conducted to determine the safety and efficacy of gabapentin in the paediatric population. A prospective open label trial reported that gabapentin was safe at doses of 26–78 $mg.kg^{-1}.day^{-1}$ in 52 children and adolescents (mean age 11.1 years) [54].

Teratogenicity and use in pregnancy/lactation

Studies in mice and rats revealed no evidence of teratogenicity. As no well-controlled studies involving pregnant women are available, it is recommended that the drug should only be used in pregnancy if clearly needed. As gabapentin is excreted in human milk, the drug is not recommended for mothers who are breast feeding.

General indications

Seizures

Gabapentin has proved to be efficacious as an adjunct to other anticonvulsants in the treatment of partial seizures and generalised tonic-clonic seizures in patients over 12 years of age. Leiderman [55] conducted a meta-analysis of five placebo-controlled clinical trials and confirmed its effectiveness in partial epilepsy, using doses between 900 and 1800 $mg.day^{-1}$. Three large multi-centre, double-blind, randomised dose, controlled trials involving 649 patients demonstrated the efficacy and safety of gabapentin as a monotherapy in partial seizures [56]. Gabapentin is not effective in absence seizures.

Several studies have shown the psychotropic effects of gabapentin [8, 57]. In a double-blind study of 201 patients with uncontrolled partial seizures who were converted from one to two anti-epileptic drugs to gabapentin monotherapy, improvements in emotional and interpersonal adjustment were observed after administration of gabapentin [57].

Neuropathic pain

Gabapentin has proved to be efficacious in the treatment of neuropathic pain and is now approved for this indication in patients over 18 years of age. Evidence for its efficacy is discussed below.

Dosage and administration

Oral doses of gabapentin are administered three times a day (tds) because of its short half-life. Dosages up to 2400 $mg.day^{-1}$ are recommended for epilepsy in adults and children > 12 years. Rapid titration may be achieved with doses of 300 mg once daily (often at bedtime to minimise sedation) on the first day followed by 300 mg twice daily on the second day and 300 mg tds on the third day. Dosage may be further increased if efficacy is not achieved at this dose.

In children aged 3–12 years, 25–35 $mg.kg^{-1}.day^{-1}$ in three divided doses is recommended. Rapid titration is achieved with daily doses of 10 $mg.kg^{-1}$ on the first day, 20 $mg.kg^{-1}$ on the second and 30 $mg.kg^{-1}$ on the third. Doses of 40–50 $mg.kg^{-1}.day^{-1}$ appear to be well tolerated and up to 60 $mg.kg^{-1}.day^{-1}$ have been administered to a small number of children [59].

The recommended starting dose in the treatment of neuropathic pain is 300 mg three times a day with titration if necessary to a maximum of 3600 $mg.day^{-1}$ but doses up to 4200 mg, have been reported [59].

Uses in pain management

Evidence from both animal and human studies supports the use of gabapentin in neuropathic pain and in a number of specific chronic pain syndromes. Tricyclic antidepressants, opioids and other anticonvulsants have been used in the treatment of chronic pain but are associated with numerous adverse effects. Gabapentin may become an attractive therapeutic option because of its relative lack of interactions and serious adverse effects if its efficacy can be established in neuropathic pain and other types of chronic pain.

Neuropathic pain

The development of neuropathic pain involves several mechanisms including primary and secondary hyperalgesia, peripheral and central sensitisation and wind-up phenomena. Neurotransmitters play a critical role in the process [59, 60]. Glutaminergic subtypes such as AMPA and neurokinin prime the NMDA receptor by triggering the release of intracellular calcium ions that unblock the magnesium ion plug in the NMDA receptor resulting in the influx of calcium ions into the cell. These calcium ions act as secondary messengers that initiate protein kinase C activation, proto-oncogene expression (c-*fos*, c-*jun*) and nitric oxide production. NMDA receptor activation therefore increases the excitability of the nociceptive system. The rationale for the use of anticonvulsant drugs for the treatment of neuropathic pain is based on the similarities in the pathophysiological events observed in epilepsy and neuropathic pain models.

Animal studies

Numerous studies in rats have shown the efficacy of gabapentin on allodynia and hyperalgesia. Intraperitoneal gabapentin attenuated mechanical hyperalgesia induced by thermal injury in rats [43]. Partridge *et al.* demonstrated its efficacy in the treatment of secondary hyperalgesia induced by substance P [33]. Gabapentin was effective against abnormal sensory processing in diabetic rats using the formalin test, and it was suggested that it may be effective in diabetic neuropathy in humans [61]. In a study on facilitated pain in rats following the formalin test, Yoon & Yaksh [62] found that gabapentin and ibuprofen were both independently effective against

the hyperalgesia with an additive interaction when the drugs were administered concurrently.

Gabapentin was superior to morphine and amitriptyline in blocking both static and dynamic components of allodynia in rats when administered orally or intrathecally, but not when injected locally into the site of allodynia [44]. Chen *et al*. [63] found that intrathecal administration of gabapentin to rats produced a dose-dependent increase in the withdrawal threshold to a painful stimulus. In addition, there was a strong synergistic effect when gabapentin was administered intrathecally with 6-cyano-7-nitroquinoxaline-2,3dione (CNQX). This confirmed other rat studies demonstrating the analgesic effects of intrathecal gabapentin [4, 32].

Human studies

Case reports and pilot studies

In a study of 122 chronic pain patients [97 with neuropathic pain (postherpetic neuralgia, diabetic neuropathy, sympathetically maintained pain and phantom pain)] treated with gabapentin for at least 30 days, Rosenberg *et al*. [64] showed a statistically significant ($p < 0.0001$) reduction in pain scores on a median dose of 1200 $mg.day^{-1}$ in patients with neuropathic pain. The mean visual analogue pain score decreased from 7.3 to 5.4.

Attal *et al*. [65], in a pilot study on the effects of gabapentin on central and peripheral neuropathic pain involving 18 patients who had pain from either peripheral or central nerve lesions, showed that gabapentin produced moderate and statistically significant relief of ongoing pain, especially paroxysmal pain. Gabapentin significantly reduced brush-induced and cold allodynia with no effects on detection and pain thresholds to static mechanical and hot stimuli, suggesting a preferential antihyperalgesic and/or anti-allodynic effect of gabapentin.

The efficacy of gabapentin in the treatment of 10 patients with refractory neuropathic pain in the head and neck region was reported by Sist *et al*. [66]. Using doses of gabapentin up to 2400 $mg.day^{-1}$ as necessary, 8/10 patients had no neuropathic pain, whereas the other two had only partial relief at 5–10 months follow-up. Ness *et al*. [67] reported the efficacy of gabapentin in 350 patients with chronic pain of varying aetiologies. After a 14% dropout rate, due to initial side-effects, 73% of the remaining patients experienced a reduction in pain scores, with 54% reporting a reduction of at least 3 points on a pain scale of 1–10. Other case reports have also shown the efficacy of gabapentin in the treatment of neuropathic pain with gabapentin [9, 68].

Hays & Woodroffe [70] concluded that gabapentin could be an effective agent for many neuropathic pain states after a review of 20 citations between 1995 and 1998. Similarly, Laird & Gidal [60] reviewed the clinical literature between 1990 and 1999 and concluded that gabapentin was effective in the treatment of neuropathic pain disorders.

Randomised controlled studies

Randomised controlled clinical trials have been conducted to determine the efficacy of gabapentin in the treatment of diabetic neuropathy and postherpetic neuralgia [8, 71].

Diabetic neuropathy. A double-blind, placebo-controlled, parallel group multicentre study of 165 diabetic patients with a 1–5-year history of painful peripheral diabetic neuropathy reported a beneficial effect with gabapentin [71]. Eighty-four patients were allocated to the gabapentin group and 81 to the placebo group. Gabapentin was titrated to a maximum of 3600 mg daily. Gabapentin was generally well tolerated and 67% of the gabapentin group reached 3600 $mg.day^{-1}$. A statistically significant ($p < 0.0001$) reduction in mean daily pain score (using an 11-point Likert scale) in the gabapentin group (baseline 6.4, endpoint 3.9), compared with placebo (baseline 6.5, endpoint 5.1), was achieved. The number-needed-to-treat (NNT, defined as the number of patients needed to be treated for one patient to receive at least 50% pain relief) for the analgesic effects in neuropathic pain with gabapentin in this study was 3.8 [72]. This compares with a NNT of 2.3 for carbemazepine and 2.1 for phenytoin in other randomised controlled trials [72]. Another double-blind, placebo-controlled trial of gabapentin in 32 diabetic patients with neuropathic pain showed a statistically significant analgesic effect during the first month of treatment [73].

Morello *et al*. [74] conducted a randomised, double-blind cross-over study comparing the efficacy of gabapentin with that of amitriptyline in diabetic peripheral neuropathy and found both drugs provided equal pain relief.

In an open-label pilot study over 12 weeks involving 25 randomised patients (13 received gabapentin, 12 received amitriptyline), gabapentin significantly reduced pain scores ($p = 0.026$) and paraesthesia ($p = 0.004$) compared with amitriptyline [75]. Adverse effects were also less frequent in the gabapentin group ($p = 0.003$). Further trials are required to confirm these preliminary results indicating that gabapentin is more efficacious than amitriptyline in diabetic peripheral neuropathy.

Postherpetic neuralgia. Gabapentin is reported to be efficacious in the treatment of neuropathic pain associated with postherpetic neuralgia. In a multicentre, randomised, double-blind, placebo-controlled, parallel design, 8-week

study involving 229 subjects with postherpetic neuralgia, Rowbotham *et al.* [76] demonstrated the efficacy of gabapentin in the treatment of postherpetic neuralgia. Patients were received gabapentin to a maximum of 3600 mg.day^{-1} of gabapentin or matching placebo. The study showed a statistically significant ($p < 0.001$) decrease in pain scores (using an 11-point Likert scale) from 6.3 to 4.2 for the gabapentin group, compared with 6.5–6.0 in the placebo group. Secondary measures of pain, as well as sleep interference, were improved with gabapentin ($p < 0.001$). The NNT for gabapentin was 3.2, compared with a combined analysis of three randomised controlled trials on carbemazepine in postherpetic neuralgia in which the NNT was 2.5 [72].

Other types of neuropathic pain

Neuropathic pain in malignancy

Caraceni *et al.* [77] reported that gabapentin was effective in treating pain in 22 cancer patients when used as an adjunctive medication. One to two weeks after gabapentin was added to their regimen, global pain scores as well as burning pain, shooting pain episodes and allodynia were all significantly reduced.

Trigeminal neuralgia

Trigeminal neuralgia is a painful condition for which traditional anticonvulsants (carbemazepine, phenytoin and lamotrigine) are used as the first-line treatment. These are sometimes discontinued because of side-effects. An open-label trial [78] and case reports [79, 80] have shown the efficacy of gabapentin for trigeminal neuralgia. In an open-label trial investigating the efficacy of gabapentin on 13 patients with idiopathic trigeminal neuralgia, 6 patients had not been treated with carbemazepine, and 7 were already established on carbemazepine 400–800 mg daily without adequate analgesia achieved. The mean daily dose of gabapentin was 1107.7 mg (range 600–2000 mg.day^{-1}). Overall, 5/6 patients not on carbemazepine and 4/7 patients on carbemazepine experienced significant pain relief with gabapentin over a mean follow-up period of 6 months.

Multiple sclerosis

Patients with multiple sclerosis (MS) suffer a variety of types of acute and chronic pain such as facial neuralgic pain (e.g. trigeminal neuralgia), retro-orbital pain from optic neuritis, shock-like paroxysmal limb pain, dyaesthetic extremity pain, low back pain and painful tonic spasms of the extremities [81]. Various pain syndromes are present in 53–57% of patients at some time during their disease. Pain in MS is commonly a difficult problem to treat and it is often treated with antidepressants or traditional anticonvulsants. Khan [79] and Solaro *et al.* [80] reported the beneficial effects of gabapentin in 7 and 11 patients, respectively, suffering from trigeminal neuralgia associated with MS that was refractory to previous therapies, or whose treatment was interrupted by side-effects. Further randomised, controlled trials comparing the use of gabapentin, carbemazepine, phenytoin and lamotrigine in trigeminal neuralgia are required to establish the value of gabapentin for this condition.

Cutter *et al.* [82] conducted a prospective double-blind, placebo-controlled, crossover study on 21 patients using a 6-day dose titration up to 900 mg of gabapentin tid or placebo, with a 14-day washout period. A reduction in spasticity compared with placebo, without adverse effects, was shown. This reinforced the earlier findings by Mueller *et al.* [83], who showed statistically significant improvements in spasticity and disability in MS patients on gabapentin doses of only 400 mg tds.

In an open-label study, Houtchens *et al.* [84] evaluated the effectiveness of gabapentin in 25 MS patients who had pain that was resistant to conventional therapies, using a range of doses of 300−2400 mg.day^{-1}. It was found that 31.8% of patients experienced excellent pain relief, and another 36.3% reported moderate relief from throbbing pains, pins and needles and cramping pains, dull aching pains were the least responsive. In another open label trial of gabapentin in MS patients, 14/18 patients who completed the trial experienced complete resolution of symptoms, whereas the other 4 experienced partial improvement [85].

In an open label trial Solaro *et al.* [86] successfully treated nocturnal spasms in 20/22 MS patients with low dose (up to 600 mg per day) gabapentin. A larger, double-blinded, placebo-controlled trial is required to study the value of gabapentin in MS.

Complex regional pain syndrome

Complex regional pain syndromes (CRPS) follow injury to bone, soft tissue and nerve tissue, characterised by severe burning pain, hyperpathia, allodynia, vasomotor and sudomotor changes, oedema, stiffness and discoloration, and may progress to fixed trophic changes if untreated [87, 88]. Further, the burning pain that may follow within minutes or hours of the injury is often out of proportion to the original injury, and many other symptoms can develop to involve areas beyond the area of original injury – sometimes even to the opposite extremity.

Mellick & Mellick [89] reported the use of gabapentin in nine patients with refractory CRPS who had previously undergone a variety of procedures (including stellate ganglion and lumbar sympathetic blocks) as well as other drug therapy. Patients (who received 900–2400 mg.day^{-1}

of gabapentin over 2–6 months) reported good to excellent pain relief. Further evaluation with a blinded, randomised, controlled study is required. Wheeler *et al.* [90] reported the successful use of gabapentin for the treatment of CRPS in the paediatric population.

Headache syndromes

Di Trapani *et al.* [91] conducted a double-blind, randomised, placebo-controlled study on the prophylactic effect of gabapentin in migraine involving 63 patients over 3 months. Thirty-five patients received gabapentin, 28 received placebo, with no significant difference in gender distribution or frequency or intensity of attacks. The study demonstrated a statistically significant reduction in the frequency of attacks (5.08–3.13 in patients without aura, 5.14–2.47 in patients with aura) and intensity of migraine (2.33–1.59 in patients with aura, 2.38–1.16 without aura) in patients receiving gabapentin.

The efficacy of gabapentin in reducing left ocular, temple and facial pain associated with tearing and conjunctival injection, which occurred 25 times daily in a syndrome of severe unilateral neuralgiform headache with conjunctival injection and tearing, rhinorrhea and subclinical sweating (SUNCT syndrome) has been shown in a case report [92]. The successful use of gabapentin in chronic cluster headache has also been reported [93].

Spinal injury

Following partial or complete spinal cord lesion, pain is commonly present. Central dysaesthetic pain following spinal cord injury is often refractory to conventional pharmacological therapy [94]. Gabapentin has been reported to reduce central pain [7, 95] and spasms associated with spinal cord injury [9, 98].

HIV neuropathy

Following the efficacy of gabapentin in treating other types of painful neuropathy, Gatti *et al.* [100] reported significant reduction in pain in eight patients with confirmed diagnoses of distal symmetric axonopathy treated with gabapentin (2000 and 2400 $mg.day^{-1}$). Newshan [101] reported the efficacy of gabapentin in three patients with HIV suffering from distal sensory polyneuropathy. More investigation is required in this area.

Erythromelalgia

This is a rare disorder characterised by episodic burning pain, erythema and elevated temperature of the feet, hands, or both [102]. The pain is episodic, and attacks may last from minutes to days. McGraw & Kosek [103] described two cases of erythromelalgia in which the pain resolved after the introduction of gabapentin 900 and 1200 $mg.day^{-1}$, respectively.

Postpoliomyelitis pain

Gabapentin has been reported to be efficacious in treating pain following poliomyelitis that results from a combination of neuropathic and mechanical origin [104].

Other painful conditions

Case reports and/or open-label trials have described the efficacy of gabapentin in interstitial cystitis [105], muscle cramps [106], taxane-induced myalgias [107], hemifacial spasm [108], vulvodynia [109], anaesthesia dolorosa [110] and dysaesthetic pain after reconstructive surgery [111].

Non pain-related uses

Gabapentin is also used in a diverse group of other conditions. Gabapentin may be beneficial in the treatment of alcohol withdrawal [112, 113]. Gabapentin has been used successfully for a number of psychiatric conditions such as bipolar disorder [9, 114], schizoaffective disorder [115] and posttraumatic stress disorder [120]. Gabapentin can reduce agitation and behavioural disturbances associated with dementia [3, 121], Lesch–Nyhan syndrome [124], essential tremor [125], 'restless legs syndrome' [126], brachioradial pruritis [127] and hemichorea/hemiballismus [128].

The role of gabapentin in pain management

Opioids, non-steroidal anti-inflammatory drugs (NSAIDs), antidepressants, and anticonvulsants are used as pharmacological agents to treat pain. However, no single class of drugs has been found to be effective in all types of pain, presumably because pain syndromes involve different mechanisms. In addition, each of the currently available drugs is associated with adverse effects, some of which are potentially serious or life-threatening such as idiosyncratic or toxic reactions.

Traditionally, the treatment of neuropathic pain has involved anticonvulsants, such as carbemazepine, valproic acid and phenytoin, and tricyclic antidepressants, such as amitriptyline and nortriptyline and doxepin. The main disadvantages of the anticonvulsants are their potential for drug interactions via the induction of hepatic enzymes, or resulting from inhibition of hepatic enzymes by other drugs. Minor side-effects such as sedation, ataxia, vertigo and diplopia are associated with carbemazepine and phenytoin, whereas, anorexia, nausea, vomiting and tremor are associated with valproic acid. Chronic phenytoin use may cause peripheral neuropathy (30%) and gingival hyperplasia (20%), and fetal hydantoin syndrome if administered during pregnancy. Carbemazepine can cause chronic diarrhoea or the syndrome of inappropriate ADH

secretion, and rarely aplastic anaemia, thrombocytopaenia, hepatocellular jaundice and cardiac arrhythmias.

Tricyclic antidepressants also cause side-effects that can be troublesome or potentially dangerous, such as anticholinergic effects (dry mouth, blurred vision, urinary retention, ileus), sedation, orthostatic hypotension, tachycardia and atrio-ventricular conduction disturbances. Such adverse effects are likely to reduce the tolerance of this group of drugs in elderly or unwell patients. Some subgroups of patients with painful neuropathy such as diabetes may also have autonomic neuropathy and may not tolerate the orthostatic hypotension associated with tricyclic antidepressants.

With increasing evidence of the efficacy of gabapentin in a wide variety of pain syndromes, especially neuropathic pain, gabapentin may be potentially useful because of its relative freedom from serious adverse effects, its lack of interactions with other drugs and its lack of potential for causing drug dependence.

A comparison of the evidence available of efficacy and toxicity for anticonvulsants (gabapentin, phenytoin and carbemazepine) and antidepressants (tricyclic antidepressants and SSRIs) in patients with diabetic neuropathy and postherpetic neuralgia has recently been made by Collins *et al*. [129] These two neuropathic pain conditions were chosen according to strict diagnostic criteria. Although two previous systematic reviews of anticonvulsants and antidepressants in diabetic neuropathy showed no significant difference in efficacy or adverse effects between the two drug classes [130, 131], Collins *et al*. found that when data from randomised controlled trials for both diabetic neuropathy and postherpetic neuralgia were pooled, the NNT for at least 50% pain relief was identical for both classes of drugs. When gabapentin was compared with other anticonvulsants, there was no significant difference in efficacy. The NNT for gabapentin was 3.4 compared with 2.2 for phenytoin/carbemazepine. The number needed to harm (NNH, defined as the number needed to harm one patient from the therapy) for minor adverse effects was 2.7 for both antidepressants and anticonvulsants. Collins *et al*. used two trials to provide data on minor adverse effects for gabapentin and two trials for phenytoin. The NNH (minor adverse effects) was 2.6 similar to that of gabapentin and 3.2 for phenytoin. The NNH (major adverse effects) for the tricyclic antidepressants was 17, and no significant difference in the incidence of major adverse effects was found between anticonvulsants and placebo. Collins *et al*. suggested that the difference in the incidence of major adverse effects can be compared by using the ratio between treatment specific benefit and treatment specific harm (defined as the number of patients needed to experience at least 50% benefit for one to experience a major adverse effect that warranted discontinuation of treatment). The ratio for gabapentin was 6 compared with an average of 8 for all anticonvulsants, and 6 for all antidepressants. As adverse data were pooled from both diabetic and postherpetic neuralgia studies, methodological factors and heterogenicity in these data may limit the validity and robustness of these ratios. The spectrum of the pain and short study duration tend to underestimate the treatment effect, whereas the small sample size of the studies overestimate the treatment effect.

The above evidence suggests that gabapentin is as efficacious at treating neuropathic pain with no significant difference in minor adverse effects and a low propensity for serious adverse effects compared with other anticonvulsants and antidepressants. Therefore, gabapentin is a useful agent in the multimodal approach in the management of neuropathic pain.

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