Gabapentin and pregabalin for the treatment of neuropathic pain: A review of laboratory and clinical evidence

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I Gilron, SJL Flatters. Gabapentin and pregabalin for the treatment of neuropathic pain: A review of laboratory and clinical evidence. Pain Res Manage 2006;11(Suppl A):16A-29A.

Gabapentin (Neurontin, Pfizer Canada Inc) and pregabalin (Lyrica, Pfizer Canada Inc) were initially developed as antiepileptic drugs and were later discovered to be effective in the treatment of neuropathic pain, creating a relatively novel class of analgesic drugs. The present article reviews the laboratory data on the antinociceptive effects of these drugs in animal models of neuropathic pain, and the clinical trial data on their effects in patients with various neuropathic pain syndromes. Laboratory evidence suggests that both gabapentin and pregabalin can inhibit hyperalgesia and allodynia evoked by a variety of neural insults, including peripheral trauma, diabetes and chemotherapy. Current opinion suggests these antinociceptive effects occur because of drug interaction with the $\alpha_2\delta$ subunit of voltage-gated calcium channels. The majority of clinical evidence supports analgesic efficacy in diabetic neuropathy and postherpetic neuralgia, and limited evidence suggests that this efficacy extends to other, but not necessarily all, neuropathic pain syndromes. Early comparative trials and pooled estimates from meta-analyses suggest that analgesic efficacy of gabapentin and pregabalin is perhaps slightly lower than that of tricyclic antidepressants or opioids. However, the most attractive aspects of these two drugs include their tolerability, lack of serious toxicity and ease of use. Future research efforts are warranted to fully understand the mechanism of action of these drugs, to clearly characterize the safety and efficacy of gabapentin and pregabalin in all clinical neuropathic pain syndromes, and to further explore the role of these drugs in the rational polypharmacy of neuropathic pain.

Key Words: *Animal pain models; Diabetic neuropathy; Gabapentin; Neuropathic pain; Pain measurement; Postherpetic neuralgia; Pregabalin; Randomized controlled trials*

La place de la gabapentine et de la prégabaline dans le traitement de la douleur neuropathique : revue de données cliniques et de données expérimentales

La gabapentine (Neurontin, Pfizer Canada) et la prégabaline (Lyrica, Pfizer Canada) étaient au départ des antiépileptiques, et ce n'est que plus tard qu'on a découvert leur efficacité dans le traitement de la douleur neuropathique, jusqu'à créer une classe relativement nouvelle d'analgésiques. Le présent article passe en revue des données expérimentales sur les effets antinociceptifs de ces médicaments dans des modèles animaux de la douleur neuropathique ainsi que des données cliniques sur les effets de ces médicaments chez des patients souffrant de différents syndromes douloureux neuropathiques. D'après les données expérimentales, la gabapentine et la prégabaline neutraliseraient l'hyperalgie et l'allodynie provoquées par diverses agressions neuronales, notamment les traumatismes périphériques, le diabète et la chimiothérapie. On croit aujourd'hui que ces effets antinociceptifs résulteraient de l'interaction de ces médicaments avec la sous-unité $\alpha_2\delta$ des canaux calciques dépendants des potentiels d'action. Les données cliniques, de leur côté, étayent en grande partie l'efficacité analgésique de ces médicaments dans les cas de neuropathie diabétique ou de névralgie post-zostérienne, mais seul un nombre limité d'entre elles étendraient cette efficacité à d'autres syndromes douloureux neuropathiques, mais encore pas nécessairement à tous. D'après les résultats des premiers essais comparatifs et des estimations groupées de méta-analyses, la gabapentine et la prégabaline auraient une efficacité analgésique légèrement plus faible que les antidépresseurs tricycliques et les opioïdes, mais elles ont comme grands avantages la tolérabilité, une faible toxicité et une utilisation facile. De nouvelles recherches s'imposent donc pour nous permettre de bien comprendre le mécanisme d'action de ces médicaments, de caractériser clairement l'innocuité et l'efficacité de la gabapentine et de la prégabaline dans tous les syndromes douloureux neuropathiques cliniques et d'examiner davantage la place de ces deux médicaments dans une polypharmacie rationnelle de la douleur neuropathique.

Gabapentin, 1-(aminomethyl)cyclohexaneacetic acid, (Neurontin, Pfizer Canada Inc) is a synthetic analogue of gamma-aminobutyric acid (GABA) synthesized in 1977 (1) and was first developed clinically as an anticonvulsant in the late 1980s (2). The laboratory evaluation of gabapentin as an analgesic was driven by the initial clinical case reports of analgesic effects in neuropathic pain (3-5). This resulted in both laboratory (6,7) and clinical (8,9) assessment of the analgesic efficacy of gabapentin occurring in parallel. Pregabalin, (S)-(+)-3-(aminomethyl)-5-methylhexanoic acid, (Lyrica, Pfizer Canada Inc) is another alkylated GABA analogue, synthesized approximately one decade after gabapentin (10), and has similar pharmacological actions and analgesic effects as gabapentin (1). The purpose of the current review is to present laboratory and clinical evidence supporting the use of gabapentin and pregabalin for the treatment of neuropathic pain. In February 2006, a PubMed search of articles written in English containing the words 'gabapentin' and 'pain' generated 582 citations. Thus, it is not possible to review every published article that has used these agents in this area of research. For this reason, we will state our emphasis in the sections below.

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LABORATORY EVIDENCE OF ANALGESIC EFFICACY IN MODELS OF NEUROPATHIC PAIN

Neuropathic pain in humans and animals produces a variety of symptoms, or behavioural signs, such as mechanical allodynia, mechanical hyperalgesia, heat hyperalgesia, cold allodynia and spontaneous pain (11,12). In the present section, we summarize the studies that have evaluated the analgesic efficacy of gabapentin and pregabalin on such behavioural signs in different animal models of neuropathic pain. We reviewed gabapentin and pregabalin studies that used animal models that are most relevant to the clinical setting, ie, models of traumatic nerve injury (chronic constriction injury [CCI], spinal nerve ligation [SNL], partial sciatic ligation [PSL] and spared nerve injury), trigeminal neuralgia, spinal cord injury (SCI), acute herpetic pain, postherpetic neuralgia (PHN), diabetic and chemotherapy-induced neuropathies. We have not included studies that examined the effect of these drugs on acute nociception, formalin-induced pain or in models of inflammatory pain. Gabapentin is now so widely accepted as a treatment for neuropathic pain that it is often used as a comparison or even a positive control in the appraisal of potential novel analgesic therapies in laboratory studies. Consequently, this has markedly enhanced the literature in this area and thus, for the purposes of the present review, we have excluded many of the studies that have used gabapentin as a comparative analgesic standard.

Table 1 summarizes the efficacy of gabapentin in animal models of neuropathic pain and aims to address three questions. First, does gabapentin have differential effects on the different pain behaviours of neuropathic pain? Additionally, how does the dosage of gabapentin or the route of administration influence the antinociceptive effect elicited? This first question was examined by the first study of gabapentin in an animal model (CCI) of neuropathic pain (6). Both intraperitoneal (IP) and intrathecal administration of gabapentin produced the same effects on pain behaviour in CCI rats. Gabapentin partially suppressed mechanical allodynia and completely reversed heat hyperalgesia, but had no effect on mechanical hyperalgesia or spontaneous pain (6). To compare the effect of gabapentin on the assorted pain behaviours of neuropathic pain from multiple studies, we have chosen to examine the studies that employed models of peripheral traumatic nerve injury (ie, CCI, SNL, PSL and spared nerve injury). This group was chosen because it is somewhat homogenous (all involving a peripheral nerve trauma) and the effect of gabapentin has been tested on most of the neuropathic pain pain behaviours (ie, mechanical hyperalgesia, mechanical allodynia, heat hyperalgesia and cold allodynia). To simplify the comparison, only studies that used a single dose, systemic (intravenous, subcutaneous, peroral [PO] or IP) administration of gabapentin in rats were compared. Two studies (13,14) reported gabapentin to be ineffective at inhibiting mechanical hyperalgesia, and in another (15), a partial reversal was seen. Only one of four studies reported a substantial (75%) reversal of mechanical hyperalgesia following systemic gabapentin (16). In comparison, all eight studies that measured mechanical allodynia found an inhibition of this pain behaviour following systemic gabapentin, although the magnitude of reversal was variable. One-half of these studies reported a partial (50% or less) reversal (6,17-19), whereas the other one-half reported a 80% to 100% reversal of mechanical allodynia by gabapentin (13,14,20,21). Two studies have examined systemic gabapentin on nerve injury-evoked heat hyperalgesia (6,19), one reporting a partial (31%) reversal (19) and the other a complete reversal of this pain behaviour (6). The effects of systemic gabapentin on cold allodynia are similarly contrasting, with two reports of dose-related inhibition (16,17) and another of inefficacy (14). It should be noted that all of these differential effects of systemic gabapentin on neuropathic pain behaviours cannot be explained by differences in dosage administered, because very similar dose ranges were employed in these studies (Table 1). Therefore, it can be concluded that gabapentin can inhibit all neuropathic pain behaviours induced by peripheral nerve injury. However, given the lack of efficacy demonstrated in several studies by different laboratories, gabapentin's ability to inhibit neuropathic pain cannot be assumed and a complete reversal of these pain behaviours is also not guaranteed. Thus, it is questionable as to whether it is appropriate to use gabapentin as an 'analgesic standard' in laboratory studies of neuropathic pain models.

The dosage of gabapentin does influence the antinociceptive effect evoked, as demonstrated by the many studies showing dose-related effects of gabapentin on all neuropathic pain behaviours (Table 1). However a particular dose of gabapentin given by the same route, in the same model, will not necessarily produce the same effect on pain behaviours across all studies. In the SNL model, for example, IP 100 mg/kg gabapentin elicited a 51% reversal of the mechanical withdrawal threshold (17), whereas others found a complete reversal of the mechanical withdrawal threshold to the preinjury baseline responses following IP 100 mg/kg gabapentin (21). Similarly, in the CCI model, IP 50 mg/kg gabapentin produced a 31% reversal of the injury-evoked heat hyperalgesia (19), whereas IP 25 mg/kg gabapentin was also found to elicit a complete reversal of this pain behaviour (6). It is also noteworthy that although a single dose of gabapentin may have no effect on the pain behaviour in question, repeated administration at the same or lower dose can prove to be effective. This has been demonstrated in the PSL model with 100 mg/kg PO (13), in chemotherapy-induced neuropathy models with 100 mg/kg IP (22) and in an SCI model at repeated lower doses of 30 mg/kg IP (23). The route of administration is also important in terms of the effect of gabapentin on nociceptive behaviours. Both systemic (intravenous, PO, IP and subcutaneous) and spinal (intrathecal) administration of gabapentin appear to yield similar effects on pain behaviours in models of traumatic nerve injury (6), diabetic neuropathy (24) and PHN (25). In contrast, intraplantar, intracerebroventricular and intracisternal administration of gabapentin have been shown to be ineffective in reducing neuropathic pain behaviours induced by streptozocin (24) and herpes zoster (26).

In marked contrast to the gabapentin literature, we know of only five studies that have assessed the behavioural effects of pregabalin in animal models of neuropathic pain. Oral pregabalin (30 mg/kg) produced a complete reversal of both static and dynamic mechanical allodynia induced by CCI (27), SNL (27) and streptozocin (24). Systemic pregabalin produced a significant inhibition of mechanical allodynia and heat hyperalgesia caused by sciatic nerve injury (28,29). Pregabalin also evoked a substantial (70%) reversal of vincristine-induced mechanical hyperalgesia (30).

MECHANISM OF ACTION

The analgesic efficacy of gabapentin was established in the mid-1990s, yet more than one decade later there is still debate as to the exact mechanism of action of this drug's analgesic

TABLE 1
An overview of the effects of gabapentin on the neuropathic pain behaviours in animal models

Model	Dose	Route	Pain behaviour	Maximal effect observed	Reference
CCI	75 mg/kg	IP	Spontaneous pain	No effect	6
CCI	50 mg/kg and 100 mg/kg	IP	Mechanical AD	35% reversal	19
CCI	10 mg/kg to 75 mg/kg	IP	Mechanical AD	Partial reversal	6
CCI	150 µg/kg	IT	Mechanical AD	Partial reversal	6
CCI	100 mg/kg	IP	Mechanical HA	75% reversal	16
CCI	150 µg/kg	IT	Mechanical HA (pinprick)	No effect	6
CCI	50 mg/kg and 100 mg/kg	IP	Heat HA	31% reversal	19
CCI	10 mg/kg to 75 mg/kg	IP	Heat HA	Dose-related reversal, complete reversal at top dose	6
CCI	15 µg/kg to 75 µg/kg	IT	Heat HA	Dose-related reversal, complete reversal at top dose	6
CCI	150 µg/kg	IT	Heat HA	80% reversal	6
CCI	100 mg/kg and 300 mg/kg	IP	Cold AD	Dose-related increase in PWL	17
CCI	3 mg/kg to 30 mg/kg	IP	Cold AD	Dose-related reversal	16
SNL (L5+L6)	100 mg/kg and 300 mg/kg	IP	Mechanical AD	51% reversal	17
SNL (L5+L6)	50 mg/kg	IP	Mechanical AD	45% reversal	18
SNL (L5+L6)	10 mg/kg to 1000 mg/kg	IT	Mechanical AD	Dose-related reversal	7
SNL (L5+L6)	10 mg/kg to 100 mg/kg	IP	Mechanical AD	Dose-related reversal, complete reversal at top dose	21
SNL (L5)	30 mg/kg and 90 mg/kg	SC	Mechanical HA	30% to 50% reversal	15
SNL (L5+L6)	100 µg/kg and 300 µg/kg	IT	Mechanical HA	79% reversal	119
SNL (L5+L6)	100 µg/kg and 300 µg/kg	IT	Heat HA	74% reversal	119
PSL	30 mg/kg to 90 mg/kg	IV	Mechanical AD	Dose-related reversal, complete reversal at top dose	20
PSL	100 mg/kg	PO	Mechanical AD	80% reversal	13
PSL	100 µg/kg and 300 µg/kg	IT	Mechanical HA	30% reversal	35
PSL	Rep 100 mg/kg and 250 mg/kg	SC	Mechanical HA	50% reversal	35
PSL	10 mg/kg to 100 mg/kg	PO	Mechanical HA	No effect	13
PSL (G-P)	3 mg/kg to 100 mg/kg	PO	Mechanical HA	No effect	13
PSL (G-P)	Rep 30 mg/kg and 100 mg/kg	PO	Mechanical HA	90% reversal	13
SNI	100 mg/kg	IP	Mechanical AD	Complete reversal	14
SNI	30 mg/kg and 100 mg/kg	IP	Mechanical HA/cold AD	No effect	14
CCI-ION/TN	Rep 30 mg/kg and 50 mg/kg	IP	Mechanical AD	Partial reversal	120
Tibial nerve injury	50 mg/kg and 100 mg/kg	IP	Mechanical AD	No effect	121
Brachial plexus avulsion	70 mg/kg	PO	Mechanical HA/cold AD	80% reversal	122
Superior caudal trunk transection	30 mg/kg to 300 mg/kg	IP	Mechanical/warm/cold AD	Dose-related reversal, complete reversal at top dose	123
SCI	10 mg/kg and 30 mg/kg	IP	Mechanical AD	Partial reversal	124
SCI	100 mg/kg	IP	Mechanical AD	Complete reversal	23
SCI	Rep 30 mg/kg	IP	Mechanical AD	Complete reversal by third injection	23
SCI	10 mg/kg and 30 mg/kg	IP	Heat HA	Complete reversal	124
SCI	100 mg/kg	IP	Cold AD	50% reversal	23
Diabetic	10 mg/kg to 100 mg/kg	PO	Mechanical AD	Dose-related reversal, complete reversal at top dose	24
Diabetic	1 µg/kg to 100 µg/kg	IT	Mechanical AD	Dose-related reversal, complete reversal at top dose	24
Diabetic	30 mg/kg and 100 mg/kg	PO	Mechanical HA	Complete reversal after 21 days	125
Diabetic	10 mg/kg to 100 mg/kg	PO	Dynamic AD	Dose-related reversal, near complete reversal at top dose	24
Diabetic	1 µg/kg to 100 µg/kg	IT	Dynamic AD	Dose-related reversal, near complete reversal at top dose	24
Diabetic	1 µg/kg to 100 µg/kg	IPL	Static and dynamic AD	No effect	24
Acute herpetic pain (mouse)	10 mg/kg to 100 mg/kg	PO	Mechanical AD and HA	Dose-related reversal, near complete reversal at top dose	26
Acute herpetic pain (mouse)	10 µg/kg to 100 µg/kg	IT	Mechanical AD and HA	Dose-related reversal, near complete reversal at top dose	26
Acute herpetic pain (mouse)	10 µg/kg to 100 µg/kg	IPL/ICV/IC	Mechanical AD and HA	No effect	26
PHN (mouse)	30 mg/kg and 100 mg/kg	PO	Mechanical AD and HA	Complete reversal	126
PHN	10 mg/kg to 60 mg/kg	IP	Mechanical AD	Dose-related reversal, complete reversal at top dose	25
PHN	10 µg/kg to 30 µg/kg	IT	Mechanical AD	Dose-related reversal, complete reversal at top dose	25
CIN (vincristine)	100 µmol/kg to 400 µmol/kg	PO	Mechanical AD	75% reversal	127
CIN (paclitaxel)	Rep 100 mg/kg	IP	Mechanical AD	50% reversal by third injection	22
CIN (vincristine)	Rep 100 mg/kg	IP	Mechanical AD	75% reversal by fourth injection	22

Studies have employed a variety of animal models of neuropathic pain induced by peripheral nerve trauma, diabetes (streptozocin), herpes zoster or chemotherapy. Unless otherwise stated, studies listed are single-dose behavioural studies performed in rats. For the majority of the studies, mechanical allodynia (AD) was assessed by von Frey stimulation, mechanical hyperalgesia (HA) by paw pressure (Randall-Selitto) test and heat HA by the plantar (Ugo Basile) test (cold AD was assessed by various methods). Mechanical AD refers to static mechanical AD unless otherwise stated. When possible, to aid study-to-study comparisons, the maximal effect observed has been described as a percentage reversal compared with normal (preinjury) baseline responses. CCI Chronic constriction injury to sciatic nerve; CCI-ION Chronic constriction injury to infraorbital nerve; CIN Chemotherapy-induced neuropathy; G-P Guinea pig; IC Intracisternal; ICV Intracerebroventricular; IP Intraperitoneal; IPL Intraplantar; IT Intrathecal; IV Intravenous; PHN Postherpetic neuralgia; PO Peroral; PSL Partial sciatic ligation; PWL Paw withdrawal latency; Rep Repeated dosing; SC Subcutaneous; SCI Spinal cord injury; SNI Spared nerve injury; SNL Spinal nerve ligation; TN Trigeminal neuralgia

properties. Gabapentin was originally designed as an analogue of the inhibitory neurotransmitter GABA to easily cross the blood brain barrier and mimic the effects of GABA. However, gabapentin does not bind to either $GABA_A$ or $GABA_B$ receptors (31-33) and neither does pregabalin (34). The antinociceptive effects of gabapentin in models of neuropathic pain were unaltered by administration of either a $GABA_A$ receptor antagonist (7) or a $GABA_B$ receptor antagonist (7,35). Therefore, it is doubtful that gabapentin exerts its analgesic properties via GABA receptors, and current data indicate this is probably also true for pregabalin (34). The mechanisms of action of gabapentin and pregabalin have also been linked to the L-amino acid transporter, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, N-methyl-D-aspartate (NMDA) receptors and ATP-sensitive potassium channels (for review see [36]). However, conclusive data demonstrating definitive roles for these targets in the analgesic effects of gabapentin and pregabalin are lacking or contradictory.

Currently, the most likely mechanism underlying the analgesic effects of gabapentin and pregabalin involves the ubiquitous $\alpha_2\delta$ calcium channel subunit. It was first recognized that gabapentin could bind to a novel site in the brain (31), which was later identified to be the $\alpha_2\delta$ calcium channel subunit (37). In general, native neuronal voltage-gated calcium channels (VGCCs) consist of a main α_1 pore-forming subunit (on which VGCC classification is based) with $\alpha_2\delta$ and β subunits (38). There are four isoforms of the $\alpha_2\delta$ subunit with differential expression (33); of importance to sensory processing, $\alpha_2\delta$-1 and $\alpha_2\delta$-2 are highly expressed in small dorsal root ganglion (DRG) cells and $\alpha_2\delta$-3 is highly expressed in large DRG cells and the brain (33,39). It has been shown that gabapentin and pregabalin bind with high affinity to $\alpha_2\delta$-1 and $\alpha_2\delta$-2 isoforms, but not $\alpha_2\delta$-3 and $\alpha_2\delta$-4 isoforms (40,41) and, in addition, gabapentin binds with greater affinity to the $\alpha_2\delta$-1 subunit compared with the $\alpha_2\delta$-2 subunit (40).

There is substantial evidence for the role of the $\alpha_2\delta$-1 subunit of VGCCs, but not currently $\alpha_2\delta$-2, in the generation of neuropathic pain, and that gabapentin and pregabalin exert their analgesic effects through interaction with this subunit. There is a marked upregulation of $\alpha_2\delta$-1 expression in ipsilateral DRGs following both SNL (42) and PSL (43). Antisense oligonucleotides directed to $\alpha_2\delta$-1 blocked $\alpha_2\delta$-1 upregulation in the spinal cord and inhibited mechanical allodynia induced by SNL (44). Importantly, the upregulation of $\alpha_2\delta$-1 expression can be correlated to the antinociceptive effects of gabapentin (45). Specifically, in neuropathic pain models in which gabapentin was effective, (CCI, SNL and diabetic) an upregulation of $\alpha_2\delta$-1 expression was evident in the DRG or the spinal cord. In comparison, there was no such $\alpha_2\delta$-1 upregulation and gabapentin was ineffective in vincristine-induced neuropathic pain (45). However, others have reported a significant inhibition of vincristine-induced pain following repeated gabapentin administration (22) and a single dose pregabalin treatment (30), perhaps suggesting that the analgesic effects of these drugs do not occur via $\alpha_2\delta$-1 binding alone. The 217th amino acid, arginine, of the recombinant $\alpha_2\delta$ protein was found to be essential for gabapentin binding, because its substitution for alanine (R217A) markedly reduced gabapentin binding in brain membranes (33). Furthermore, R217A mutant mice developed mechanical allodynia following CCI, which was insensitive to pregabalin treatment, but was inhibited by morphine and amitriptyline (33).

The proposed consequence of gabapentin/pregabalin binding to $\alpha_2\delta$ subunits of VGCCs is a reduction in neurotransmitter release resulting in a decrease in neuronal hyperexcitability. Gabapentin has been shown to inhibit the evoked release of glutamate (46) and substance P (47) in the spinal cord of neuropathic rats. Spontaneous (ectopic) discharge occurs following peripheral nerve injury and, using electrophysiological techniques, studies have examined the effect of gabapentin/pregabalin on this phenomenon. In vitro, gabapentin has been shown to inhibit spontaneous discharges of A-fibres in chronically compressed DRG (48). In vivo, systemic gabapentin had no effect on the ectopic discharge from injured afferents (18,47), yet inhibited the spontaneous activity of spinal (wide dynamic range [WDR]) neurons (49) in SNL rats. Following PSL, both systemic gabapentin and pregabalin inhibited the spontaneous discharge from injured afferents (20,28).

Gabapentin's site of action is thought to occur at the spinal level, because analgesia following nerve injury is produced by systemic or spinal gabapentin administration, but not with an administration into the brain or periphery (24,26). There is evidence to suggest that the spinal site of action has a presynaptic location (50). However, one study reported antinociceptive effects in PSL mice following intracerebroventricular gabapentin, suggesting an additional supraspinal site of action (51). In addition, this study demonstrated a significant role for the descending noradrenergic system and spinal α_2-adrenergic receptors in the antinociceptive effects of gabapentin following nerve injury (51). Recently, it was elegantly demonstrated that the efficacy of gabapentin in neuropathic rats is dependent upon the integrity of a spino-bulbo-spinal circuit (52), which originates with neurokinin-1 (NK-1) expressing superficial dorsal horn neurons projecting to the brain and terminates with the activation of excitatory 5-hydroxytryptamine 3 ($5\text{-}HT_3$) receptors in the spinal cord via descending 5-HT pathways. These pivotal studies (51,52) demonstrate that the analgesic mechanism of gabapentin/pregabalin is unlikely to be solely due to $\alpha_2\delta$ interaction and further studies are required to determine its precise nature.

CLINICAL EVIDENCE OF ANALGESIC EFFICACY IN NEUROPATHIC PAIN SYNDROMES

Pain reduction during treatment with gabapentin or pregabalin has been reported in a wide variety of human neuropathic conditions, including diabetic polyneuropathy (DPN), PHN, various radiculopathies, complex regional pain syndrome (CRPS), phantom limb pain, central pain syndromes and trigeminal neuralgia (53). In the mid- to late 1990s, early evidence for gabapentin came in the form of uncontrolled case reports, case series, retrospective reviews and open-label trials (53,54). Since 1998, however, more than two dozen prospective, double-blind, randomized, controlled trials (RCTs) have been published supporting analgesic efficacy of both gabapentin and pregabalin in many, but not all, neuropathic pain syndromes. Four gabapentin RCTs and seven pregabalin RCTs were industry-initiated or included authors from the drugs' manufacturers, Parke-Davis or Pfizer. We conducted a literature search using the Cochrane Central Register of Controlled Trials (2006, Issue 1) and MEDLINE database (1966 to January 2005). The database search strategies involved Boolean searches of: (gabapentin OR pregabalin) AND (neuropathic OR neuropathy OR neuralgia OR sciatica OR radiculopathy OR causalgia OR reflex sympathetic

TABLE 2
Published randomized, controlled trials of gabapentin and pregabalin for painful diabetic neuropathy

	Gabapentin (TID dosing) (rerference)				Pregabalin (reference)		
	8	66	62	65	67	68	69
Study design	Parallel	Crossover	Crossover	Parallel	Parallel	Parallel	Parallel
Patients in each category (n)	Gabapentin 84; Placebo 81	40	25	Gabapentin 30; Placebo 30	Pregabalin 75 mg/day: 77, 300 mg/day: 81, 600 mg/day: 82; Placebo 97	Pregabalin: 76; Placebo: 70	Pregabalin 150 mg/day: 79, 600 mg/day: 82; Placebo 85
Treatment control(s)	Placebo	Placebo	Amitriptyline (no placebo)	Part I: placebo; Part II: venlafaxine + combination	Placebo	Placebo	Placebo
Allowed concomitant medications	Acetaminophen, ASA, SSRIs	NSAIDs, opioids	Acetaminophen	None	Acetaminophen, SSRIs, gabapentin treatment failures excluded	Acetaminophen, ASA, SSRIs, gabapentin treatment failures excluded	ASA, acetaminophen, SSRIs
Starting dose	900 mg/day	Not specified	300 mg/day	300 mg/day	75 mg/day: 75 mg/day, 300 mg/day: 300 mg/day, 600 mg/day: 75 mg/day	100 mg TID	150 mg/day–25 mg/day 600 mg/day–100 mg/day
Target maintenance dose	3600 mg/day (reached by 67% of patients)	900 mg/day	1800 mg/day	3600 mg/day	75 mg/day: 75 mg/day; 300 mg/day: 300 mg/day; 600 mg/day: 600 mg/day; (TID dosing)	100 mg TID	150 mg/day–150 mg/day 600 mg/day–600 mg/day (TID dosing)
Titration method	To MTD	Not specified	To MTD	To MTD	Forced to target	Forced to target	Forced?
Titration duration	4 weeks	Not specified	Not specified	4 weeks	1 week	None	2 weeks
Treatment duration	8 weeks	6 weeks	6 weeks	8 weeks	5 weeks	8 weeks	6 weeks
Primary outcome measure	0–10 NRS	0–10 cm VAS	Verbal pain descriptors	0–10 NRS	0–10 NRS	0–10 NRS	0–10 NRS
Study results* (comments)	Gabapentin > placebo	Gapapentin vs placebo NS (gabapentin > placebo for MPQ scores)	Gabapentin vs amytriptyline NS	Part I: Gabapentin > placebo; Part II: Gabapentin/venlafaxine > gabapentin	Pregabalin > placebo for 300 mg/day and 600 mg/day only	Pregabalin > placebo	600 mg/day > placebo; 150 mg/day vs placebo NS
Patients who dropped out due to AEs (%)	8.3	Not specified	16.7	Not specified	75 mg/day: 2.6 300 mg/day: 3.7 600 mg/day: 12.2	10.5	150 mg/day: 2.5 600 mg/day: 8.5
Trial quality score†	5	2	4	3	5	5	5

**The symbol '>' denotes 'analgesic efficacy greater'; listed differences were reported as statistically significant unless otherwise stated; †See text for details. AEs Adverse events; ASA Acetylsalicylic acid; MPQ McGill Pain Questionnaire; MTD Maximally tolerated dose; NRS Numerical rating scale; NS Not statistically significant; NSAIDs Nonsteroidal anti-inflammatory drugs; SSRIs Selective serotonin reuptake inhibitors; TID Three times daily; VAS Visual analogue scale; vs Versus*

dystrophy OR crps OR rsd OR complex regional pain syndrome); Field: All Fields; Limits: Randomized Controlled Trial, English language. Tables 2 to 5 list the RCTs included for review and the Appendix lists excluded publications along with reasons for exclusion. All included RCTs were evaluated by one of the authors (IG) and rated using a three-item (1 to 5) quality scale (55).

Diabetic neuropathy

DPN or distal symmetrical sensorimotor neuropathy is the most common neuropathy in patients with diabetes mellitus (56), and affects approximately 750 per 100,000 population in developed countries (57). DPN is associated with loss of peripheral neurons due to a variety of metabolic, autoimmune and ischemic causes (58). These disturbances are thought to cause pain by various possible mechanisms, including acute and ongoing neuronal degeneration (59), hyperexcitability of dysfunctional nociceptive afferent neurons (eg, C fibres) (60) or aberrant interactions between nociceptive (eg, C fibres) and non-nociceptive (eg, A-beta fibres) sensory afferent neurons (61). However, it is currently unclear why these changes lead to pain symptoms in only some diabetic neuropathy patients. In addition to antidepressants, opioids and other anticonvulsant drugs, gabapentin and pregabalin have been studied in multiple DPN RCTs. Table 2 includes three gabapentin and three pregabalin placebo-controlled RCTs in DPN. Table 2 also describes one nonplacebo-controlled trial comparing gabapentin with amitriptyline only (62). In addition to these,

one gabapentin RCT (63) and one pregabalin RCT (64) involved mixed populations of DPN (60% to 70%) and PHN (30% to 40%) (Table 3).

Gabapentin: In two of the four placebo-controlled gabapentin RCTs, analgesic efficacy was statistically superior to placebo and accompanied by improvements in several secondary measures of quality of life, mood and sleep (8,65). Backonja et al (8) reported a 39% pain reduction from baseline with gabapentin, significantly greater than the 22% pain reduction seen with placebo. Simpson (65) reported a 38% pain reduction from baseline with gabapentin, significantly greater than the 8% pain reduction seen with placebo. However, the gabapentin RCT by Gorson et al (66), which involved a maximum dose of 900 mg/day, yielded no significant gabapentin-placebo difference for pain intensity but a significant difference for McGill Pain Questionnaire total scores in favour of gabapentin. Gilron et al (63) also reported no significant gabapentin-placebo difference for the primary efficacy measure (0 to 10 numerical rating scale) at a mean maximally tolerated gabapentin dose of 2207 mg/day. This RCT employed an active placebo (lorazepam) which provides more effective blinding and may have resulted in a narrower gabapentin-placebo treatment difference than one might observe with an inert placebo. However, in this RCT, gabapentin was statistically superior to active placebo for several secondary outcome measures including the short-form McGill Pain Questionnaire, Brief Pain Inventory, Short Form-36 Health Survey and Beck Depression Inventory (63).

Pregabalin: Four large RCTs of pregabalin for DPN have been reported as completed (67-70), however, one of these is unpublished as yet and cited here as a meeting abstract (70). The three published RCTs (Table 2) reported statistically significant analgesic efficacy versus placebo with 34% to 40% pain reductions from baseline at pregabalin target doses of at least 300 mg/day (67-69). In these RCTs, pain reduction was accompanied by improvements in sleep over similar dosage ranges and with a similar temporal profile (67-69). The mixed DPN/PHN pregabalin RCT reported similar results (Table 3) (64).

TABLE 3
Published randomized, controlled trials of gabapentin and pregabalin in mixed populations of painful diabetic neuropathy and postherpetic neuralgia

	Gabapentin (63)	Pregabalin (64)
Study design	Crossover	Parallel
Patients (n)	57	Flex: 141; fixed: 132; placebo: 65
Treatment control(s)	Active placebo (lorazepam) Morphine-gabapentin in combination	Placebo
Allowed concomitant medications	All allowed	SSRIs, ASA, benzodiazepines, acetaminophen; previous gabapentin allowed
Starting dose	400 mg/day	Flex: 150 mg/day; Fixed: 300 mg/day
Target maintenance dose	3200 mg/day (mean MTD: 2207 mg/day)	Flex: 150–600 mg/day; Fixed: 600 mg/day (BID dosing)
Titration method	To MTD	Flex: MTD; Fixed: forced
Titration duration	3 weeks	Flex: 5 weeks; Fixed: 2 weeks
Treatment duration	4 weeks	12 weeks
Primary outcome	0–10 NRS	0–10 NRS
Study results* (comments)	Gabapentin vs active placebo NS (gabapentin > active placebo for SF-MPQ); gabapentin-morphine > gabapentin	Flex and Fixed > placebo; trend for fewer AEs (NS) in Flex group
Patients dropped out due to AEs (%)	5.3	Flex: 17.0; Fixed: 25
Trial quality score†	5	4

**The symbol '>' enotes 'analgesic efficacy greater'; listed differences were reported as statistically significant unless otherwise stated; †See text for details. AEs Adverse events; ASA Acetylsalicylic acid; BID Twice daily; Fixed Forced titration to maximal target dose; Flex Flexible dose titration to maximally tolerated dose (MTD); NRS Numerical rating scale; NS Not statistically significant; SFMPQ Short Form McGill Pain Questionnaire; SSRIs Selective serotonin reuptake inhibitors; vs Versus*

PHN

PHN affects approximately 300 per 100,000 of the population and affects 25% to 50% of adults (older than 50 years) with herpes zoster reactivation (57). PHN is perhaps the most dreaded complication of acute herpes zoster infection, which causes destruction of sensory neurons (71). A postmortem study of five patients who had previously experienced a herpes zoster infection described spinal cord dorsal horn damage, as well as peripheral nerve pathology, in the three patients who had developed PHN, but only peripheral nerve pathology in the two patients who did not develop PHN (72). Quantitative sensory testing studies in living patients (73) have described heterogeneous mechanisms of PHN, which may result in sensory loss, spontaneous pain and touch-evoked pain (allodynia). Furthermore, these heterogeneous mechanisms may even coexist in the same patient. In addition to antidepressants, opioids and other anticonvulsants, gabapentin and pregabalin have been studied in multiple PHN RCTs. Table 4 describes two gabapentin and three pregabalin RCTs in PHN.

Gabapentin: A total of 336 PHN patients received gabapentin in two well-powered RCTs; gabapentin demonstrated analgesic efficacy at target doses of 1800 mg/day, 2400 mg/day or 3600 mg/day (Table 4) (9,74). Pain reduction from baseline was reported to be 33% to 35% in all three of these dose groups. Improvements in sleep and several Short Form-36 quality of life domains were also reported (9,74).

Pregabalin: Three large RCTs have demonstrated analgesic efficacy in PHN (75-77) (Table 4) with pain reductions from baseline which varied from 18% at 150 mg/day (77) to 37% at 600 mg/day (75). Again, pain relief was accompanied by improved sleep over similar dosage ranges and with a similar temporal profile.

Other neuropathic pain syndromes

The great majority of neuropathic pain RCTs of drug treatments have been conducted in patients with DPN or PHN. However, it has been recognized that not all drugs effective against DPN or PHN are effective in other neuropathic pain

TABLE 4
Published randomized, controlled trials of gabapentin and pregabalin for postherpetic neuralgia

	Gabapentin (reference)		Pregabalin (reference)		
	9	74	75	76	77
Study design	Parallel	Parallel	Parallel	Parallel	Parallel
Patients in each category (n)	Gabapentin 113; placebo 116	2400 mg/day 108; 1800 mg/day 115; placebo 111	Pregabalin 89; placebo 84	Pregabalin 150 mg/day 81; pregabalin 300 mg/day 76; placebo 81	Pregabalin 150 mg/day 87; pregabalin 300 mg/day 98; pregabalin 600 mg/day 90
Treatment control(s)	Placebo	Placebo	Placebo	Placebo	Placebo
Allowed concomitant medications	TCAs, opioids	NSAIDs, weak opioids, antidepressants, ASA	Opioids, antidepressants, NSAIDs, acetaminophen; gabapentin treatment failures excluded	All but benzodiazepines and AEDs prohibited; gabapentin treatment failures excluded	NSAIDs, acetaminophen, opioids, antidepressants
Starting dose	900 mg/day	300 mg/day	50 mg TID	150 mg/day–50 mg TID, 300 mg/day–100 mg TID	Titration not described
Target maintenance dose	3600 mg/day (reached by 65%)	1 group: 1800 mg/day; 1 group: 2400 mg/day	200 mg TID (CrCl>60) 100 mg TID (CrCl≤60)	150 mg/day–150 mg/day 300 mg/day–300 mg/day (TID dosing)	Titration not described (BID dosing)
Titration method	To MTD	Forced to target dose	Forced to target dose	Forced to target dose	Titration not described
Titration duration	4 weeks	2–3 weeks	1–2 weeks	1 week	Titration not described
Treatment duration	8 weeks	7 weeks	8 weeks	8 weeks	13 weeks
Primary outcome	0–10 NRS	0–10 NRS	0–10 NRS	0–10 NRS	0–10 NRS
Study results* (comments)	Gabapentin > placebo	Gabapentin > placebo at both 1800 mg/day and 2400 mg/day	Pregabalin > placebo	Pregabalin > placebo; minimal difference 150 mg/day vs 300 mg/day	150 mg/day–600 mg/day > placebo, dose response apparent but not statistically reported
Patients dropped out due to AEs (%)	18.6	1800 mg/day 13; 2400 mg/day 17.6	31.5	150 mg/day 11.1; 300 mg/day 15.4	150 mg/day 8.0 300 mg/day 15.3 600 mg/day 21.1
Trial quality score†	5	5	5	5	3

**The symbol '>' denotes 'analgesic efficacy greater'; listed differences were reported as statistically significant unless otherwise stated; †See text for details. AEs Adverse events; ASA Acetylsalicylic acid; BID Twice daily; CrCl Creatinine clearance; MTD Maximally tolerated dose; NRS Numerical rating scale; NSAIDs Nonsteroidal anti-inflammatory drugs; TCAs Tricyclic antidepressants; vs Versus*

syndromes (78,79). Thus, several clinical investigators have attempted to evaluate the efficacy of gabapentin (but not pregabalin, as yet) in other neuropathic pain syndromes. Table 5 lists eight published RCTs of gabapentin in other neuropathic pain syndromes (80-87). Pain reduction with gabapentin was reported to be superior to placebo in single RCTs of phantom limb pain (81), Guillain-Barré Syndrome (83), cancer-related neuropathic pain (85) and mixed neuropathies (82). Levendoglu et al (84) reported a positive result in SCI patients, whereas a smaller SCI trial failed to show significant differences in pain intensity, possibly due to inadequate statistical power (80). Gabapentin appeared to demonstrate slight, statistically insignificant superiority over placebo in a single RCT of patients with CRPS type I (86). In a small RCT (n=11 to 15 per group) of HIV-associated neuropathy, pain reduction from baseline was reported as 44.1% with gabapentin and 29.8% with placebo. However, the gabapentin versus placebo difference in pain reduction was not statistically significant (87).

Comparative and combination trials

In addition to placebo controls, few RCTs have compared gabapentin with other drugs. At the time of writing, no comparative RCTs of pregabalin have been published. Gilron et al (63) demonstrated that neuropathic pain intensity was significantly lower during treatment with morphine and gabapentin combination than with gabapentin alone. In addition, a trend favouring morphine alone over gabapentin alone was observed (63). In 11 gabapentin nonresponders, Simpson (65) conducted a second-stage trial and reported that a venlafaxine and gabapentin combination was superior to gabapentin alone in this group. Finally, in a nonplacebo-controlled trial, Morello et al (62) observed a slight trend suggesting superior pain reduction with amitriptyline versus gabapentin; however, this difference was not statistically significant.

Pooled efficacy estimates

Finnerup et al (78) recently conducted a systematic review of pharmacological treatments for neuropathic pain that calculated numbers needed to treat (NNT – the number of patients that need to be treated with a certain drug [compared with placebo] to obtain one patient with at least 50% pain relief) and that included 10 of the 15 gabapentin RCTs and five of the seven pregabalin RCTs reviewed here (78). Their initial NNT estimate for all doses of gabapentin was 5.1 (4.1 to 6.8); however, after excluding the low-dose RCT (900 mg/day) by Gorson et al (66) and the lower dose arm (1800 mg/day) of the Rice et al (74) RCT, a revised NNT estimate for gabapentin was reported as 3.8 (3.1 to 5.1) (78). The NNT for pregabalin, including doses ranging from 150 mg/day to 600 mg/day, was estimated to be 4.2 (3.4 to 5.4) (78). These NNT values suggest that approximately four patients with neuropathic pain need to be treated with gabapentin or pregabalin to achieve one patient with at least 50% pain relief. Comparison with estimates for other drugs suggest that the efficacy of gabapentin and pregabalin is perhaps slightly less than that of tricyclic antidepressants (NNT=2 to 3) or morphine (NNT=2.5) (78).

TABLE 5
Published randomized, controlled trials of gabapentin for other neuropathic pain syndromes

	References							
	80	81	82	83	84	85	86	87
Pain syndrome	SCI	PLP	Mixed	Guillain-Barre	SCI	Ca-NP	CRPS-1	HIV-NP
Study design	Crossover	Crossover	Parallel	Crossover	Crossover	Parallel	Crossover	Parallel
Patients (n)	14	19	Gabapentin: 153; placebo:152	18	20	Gabapentin: 79, placebo 41	58	Gabapentin: 15; placebo: 11
Treatment control(s)	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
Allowed concomitant medications	None prohibited	TCAs	TCAs, SSRIs, ASA, NSAIDs, weak opioids	Fentanyl	None allowed	None prohibited	None prohibited	NSAIDs, acetaminophen
Starting dose	300 mg/day	300 mg/day	300 mg/day	15 mg/kg/day	Not specified	600 mg/day	600 mg/day	400 mg/day
Target maintenance dose	1800 mg/day	2400 mg/day	2400 mg/day	15 mg/kg/day?	3600 mg/day (mean MTD 2850 mg/day)	1800 mg/day	1800 mg/day	2400 mg/day
Titration method	To MTD	To MTD	To MTD	Not specified	To MTD	To MTD	Not specified	To MTD
Titration duration	Not specified	Not specified	5 weeks	none	4 weeks	Not specified	Not specified	2-3 weeks
Treatment duration	4 weeks	6 weeks	8 weeks	1 week	8 weeks	10 days	3 weeks	4 weeks
Primary outcome measure	Neuropathic pain scale	VAS 0–10 cm	0–10 NRS	0–10 NRS	VAS 0–100 mm	0–10 NRS	VAS 0–100 mm	VAS 0–10 cm
Study results* (comments)	Gabapentin vs placebo NS; (gabapentin > placebo for "unpleasant sensation" only)	Gabapentin > placebo	Gabapentin > placebo	Gabapentin > placebo	Gabapentin > placebo (minimal placebo response)	Gabapentin > placebo	Gabapentin vs placebo NS (apparent reversal of quantitative sensory deficit by gabapentin)	Gabapentin vs placebo NS
Patients dropped out due to AEs (%)	Not specified	Not specified	15.7	Not specified	None	7.6	5.2	7.1
Trial quality score†	4	5	5	3	4	5	5	5

**The symbol '>'denotes 'analgesic efficacy greater'; listed differences were reported as statistically significant unless otherwise stated; †See text for details. AEs Adverse events; ASA Acetylsalicylic acid; Ca-NP Cancer-related neuropathic pain; CRPS-1 Complex regional pain syndrome type 1; HIV-NP Human immunodeficiency-related neuropathic pain; Mixed Mixed population of various different neuropathic pain syndromes; MTD Maximally tolerated dose; NRS Numerical rating scale; NS Not statistically significant; NSAIDs Nonsteroidal anti-inflammatory drugs; PLP Phantom limb pain; SCI Spinal cord injury; SSRIs Selective serotonin reuptake inhibitors; TCAs Tricyclic antidepressants; VAS Visual analogue scale; vs Versus*

SAFETY AND TOLERABILITY

Gabapentin

After more than one decade of marketing and widespread international use, gabapentin appears to be a considerably safe and well-tolerated drug. Of interest, one case of gabapentin overdose did not result in serious toxicity (88). While it is often very difficult to demonstrate treatment-related causality with individual adverse events, several adverse event reports involving gabapentin bear mentioning. First, multiple case reports have described various adverse events following abrupt (89-92) or even tapered (93) gabapentin discontinuation, including tachycardia, diaphoresis, headache, gastrointestinal cramps, catatonia and, in one case, status epilepticus in the absence of a pre-existing seizure disorder (91). Several reports have suggested that gabapentin may induce various movement disorders, including myoclonus, dystonia and asterixis (94-98), which may be a cause of falls (98). Two different case reports (99,100) have suggested that gabapentin may exacerbate myasthenia gravis, and individual case reports have implicated gabapentin as contributing to psychomotor agitation (101), renal allograft dysfunction (102), amenorrhea (103), arthralgia (104), aggressive behaviour in children (105), painful gynecomastia (106), cutaneous leukocytoclastic vasculitis (107) and neutropenia (108).

In the setting of neuropathic pain treatment, Table 6 describes adverse event frequencies from published gabapentin RCTs in neuropathic pain. Similar to the setting of epilepsy treatment (109), these data indicate that the most common adverse effects of gabapentin are somnolence and dizziness or ataxia. These symptoms are generally dose-related and reversible following dose reduction. Various other adverse events have been reported in more than 10% of patients, in at least two RCTs, including peripheral edema, lethargy, headache and diarrhea (Table 6). However, these events were not necessarily significantly more frequent than with placebo. Gabapentin treatment did not appear to adversely affect glycemic control in diabetic patients (8). Parsons et al (110) conducted a pooled analysis of adverse events in 603 PHN patients (358 received gabapentin and 245 received placebo) from three different RCTs. The results of this analysis indicated that the three most common adverse events were dizziness, somnolence and peripheral edema. Peripheral edema was significantly more frequent at doses of 1800 mg/day or greater. Dizziness and somnolence, however, were most often first reported at doses less than 1800 mg/day and, in patients ultimately titrated to doses 1800 mg/day or greater, new-onset or worsening dizziness or somnolence were not more frequent than with placebo at

TABLE 6
Adverse event frequencies from neuropathic pain randomized, controlled trials (RCTs) of gabapentin

	References														
	9	8	66	62	65	74 (2400 mg/day)	80	81	82	83	84	85	86	87	63
Dizziness	24	24*		28	22	33	NR	11	24			9	37*	80*	6
Somnolence	27	23*	15	48	22	20	NR	37	14		15	23	28*	60	10
Ataxia	7		8	20		11	NR							47	2
Peripheral edema	10			12		11	NR				15				2
Lethargy				16			NR						20*		
Headache		11		8	12		NR	11	9		5	1	15	7	2
Diarrhea		11		8	12	5	NR		5			1			
Postural hypotension				24			NR								
Constipation				16			NR								4
Asthenia						6	NR				25				
Fatigue			10				NR								
Accidental injury			10				NR		6						
Abnormal gait							NR						7		
Confusion		8			7		NR								
Cognitive dysfunction							NR								4
Nausea		8		8	7		NR	5	9	6		6	19	33	2
Vertigo							NR				15				
Infection	8		10				NR		9			3			
Dry mouth						5	NR								8
Blurry vision							NR								2

*Data presented indicate percentage of patients receiving drug and reporting the listed adverse event. Note: Reported adverse event may differ across RCTs, in part, due to differences in adverse event evaluation which may vary from spontaneous patient reporting to open-ended patient questioning by researchers to specific questioning about each listed adverse event. Original percentages are rounded up. *Incidence of adverse event significantly more frequent than with placebo. NR Not reported*

doses 1800 mg/day or greater (110). This may suggest that tolerable dizziness or somnolence occurring early during gabapentin dose titration does not necessarily preclude further dose increases. The recent systematic review by Finnerup et al (78) estimated gabapentin's number needed to harm (the number of patients that need to be treated with a certain drug [compared with placebo] for one patient to drop out due to adverse effects) at 26.1 (14.1 to 170).

Pregabalin

Pregabalin has only recently been approved in several countries. Therefore, substantially fewer postmarketing safety data are available compared with gabapentin, and current estimates of safety come largely from RCTs of neuropathic pain, epilepsy and generalized anxiety disorder. Quite similar to gabapentin, the most frequent adverse events described with pregabalin include somnolence, dizziness, ataxia and peripheral edema (111). Early case reports have suggested that pregabalin, like gabapentin, may induce movement disorders such as myoclonus (112) and asterixis (113), and a single case report has described encephalopathy and edema of the splenium of the corpus callosum following abrupt discontinuation of pregabalin (114). Finally, limited evidence suggesting subjective drug 'liking' in a study of pregabalin in recreational sedative or hypnotic drug users as well as withdrawal symptoms upon pregabalin discontinuation has led the United States Drug Enforcement Administration to list pregabalin as a Schedule V narcotic of the Controlled Substances Act (low potential for abuse) (111). However, less than 5% of patients from all pregabalin RCTs reported euphoria as an adverse event.

In the setting of neuropathic pain treatment, Table 7 describes adverse event frequencies from published pregabalin RCTs in neuropathic pain. These data indicate that the most common adverse effects of pregabalin, similar to gabapentin, are somnolence, dizziness and peripheral edema. Various other adverse events have been reported in more than 10% of patients, in at least two RCTs, including headache, weight gain and dry mouth (Table 7). However, these events were not necessarily significantly more frequent than with placebo. Pregabalin treatment did not appear to adversely affect glycemic control in diabetic patients (68). The recent systematic review by Finnerup et al (78) estimated pregabalin's number needed to harm at 11.7 (8.3 to 19.9) suggesting considerably higher study withdrawal rates than for gabapentin.

PRESCRIBING CONSIDERATIONS FOR GABAPENTIN AND PREGABALIN IN NEUROPATHIC PAIN

Treatment of neuropathic pain should be individualized to each patient concurrent with ongoing diagnostic evaluation, patient education and reassurance (79). Current clinical thinking supports multimodal, multidisciplinary therapy which includes drug treatment (115,116). Gabapentin and pregabalin have been recommended as first-line drugs for neuropathic pain along with topical lidocaine, tricyclic antidepressants and serotonin-noradrenaline reuptake inhibitors (78,79). While comparative estimates suggest that tricyclic antidepressants may be more efficacious than gabapentin or pregabalin, the drug interaction and side effect profiles of gabapentin and pregabalin appear to be more favourable (78).

Table 8 lists some basic information regarding the clinical pharmacology of gabapentin and pregabalin; however, clinicians

TABLE 7
Adverse event frequencies from neuropathic pain randomized, controlled trials (RCTs) of pregabalin

	References						
	67 (600 mg/day)	68	69 (600 mg/day)	75	76 (300 mg/day)	77 (600 mg/day)	64
Dizziness	39	36	38	28	28	37	24
Somnolence	27	20	22	25	24	26	12
Peripheral edema	13	11	17	19	13		12
Headache	10	7	16	8	11	4	4
Weight gain			10			9	13
Dry mouth	5		9	11	7	12	4
Ataxia	9			7		12	
Constipation	9	5	6			9	
Lethargy							
Diarrhea	4	4	2	7	5		
Asthenia	7	4	12		3	6	8
Fatigue							
Accidental injury	5	4	10				
Abnormal gait				8		4	
Confusion	9			7		3	
Cognitive dysfunction						4	
Nausea		8				2	8
Vertigo							9
Infection	1	15	6		7		
Blurry vision	9	5	9	11		6	

*Data presented indicate percentage of patients receiving drug and reporting the listed adverse event. Note: Reported adverse event may differ across RCTs, in part, due to differences in adverse event evaluation that may vary from spontaneous patient reporting to open-ended patient questioning by researchers to specific questioning about each listed adverse event. Original percentages are rounded up. *Incidence of adverse event significantly more frequent than with placebo*

TABLE 8
Clinical pharmacology of gabapentin and pregabalin

	Gabapentin (117,128)	Pregabalin (34,129)
Time to maximal absorption	2 h to 3 h	0.8 h to 1.4 h
Oral bioavailability	57% after single 300 mg dose, 42% after single 600 mg dose	>90% independent of dose
Metabolism and elimination	• Negligible metabolism • Renally excreted unchanged • Elimination half-life 5 h to 9 h	• Negligible metabolism • Renally excreted unchanged • Elimination half-life 4 h to 7 h
Drug interactions	• Oral antacids reduce bioavailability by 20% to 30%	• No significant drug interactions described to date
Starting dose	• 100 mg/day to 900 mg/day • Dose reduction required with renal insufficiency	• 75 mg/day to 150 mg/day • Dose reduction required with renal insufficiency
Titration	• Titrate toward MTD over several weeks • Increaseweekly by 300 mg/day to 900 mg/day	• Titrate toward MTD over several weeks • Increase weekly by 50 mg/day to 150 mg/day
Dosage frequency	Every 8 h	Every 8 h to 12 h
Usual effective dose	1200 mg/day to 2400 mg/day	150 mg/day to 600 mg/day
Maximum dose	3600 mg/day	600 mg/day

MTD Maximally tolerated dose

are urged to consult the product monograph before prescribing these medications. Advantages of gabapentin and pregabalin include negligible metabolism, no hepatic enzyme inhibition or induction and, thus, no clinically important drug interactions (34,117). However, the bioavailability of gabapentin is known to diminish by 20% to 30% with concomitant oral antacid administration (117). Both drugs are excreted unchanged in the urine and, therefore, dose should be reduced proportionally to creatinine clearance in the presence of renal insufficiency (34,117). Absorption of pregabalin is quite fast (approximately 1 h to maximal absorption) and oral bioavailability remains very high (greater than 90%) regardless of dose. In contrast, absorption of gabapentin is slightly slower (2 h to 3 h to maximal absorption) and occurs through a saturable transport system in the gastrointestinal tract such that bioavailability decreases with increasing doses (118). Therefore, gabapentin dose increases in higher dose ranges should be expected to lead to incrementally smaller increases in plasma drug concentrations. RCTs of gabapentin and pregabalin have used starting doses of at least 300 mg/day and 75 mg/day, respectively (Tables 2 to 5). However, in elderly patients, patients with renal insufficiency or patients already receiving sedating drugs, one should consider starting with even lower doses than these and be titrated very slowly to minimize the risk of falling and related trauma. Evidence suggests that flexible dose titration toward individual maximally tolerated doses leads to fewer adverse events than fixed titration to a specific target dose (64). The elimination half-lives of gabapentin and pregabalin (5 h to 9 h and 4 h to 7 h, respectively) lend themselves to three times daily dosing. Two recent

pregabalin RCTs have demonstrated superiority over placebo with twice daily dosing (64,77). However, these trials used a retrospective 24 h pain intensity measure each morning, so the possibility of important breakthrough pain with twice daily dosing has not been ruled out. Gabapentin and pregabalin RCT results collectively suggest that analgesic efficacy is dose-dependent across the doses studied (Tables 2 to 5). Usual effective, and tolerable, doses range from 1200 mg/day to 2400 mg/day for gabapentin and 150 mg/day to 600 mg/day for pregabalin; doses greater than 3600 mg/day and 600 mg/day, respectively, have not been studied (Table 8).

CONCLUSIONS

Gabapentin and pregabalin represent a relatively novel class of drugs for the treatment of neuropathic pain. Laboratory evidence demonstrates that gabapentin and pregabalin can inhibit different neuropathic pain behaviours in a broad range of neuropathic pain models. Their analgesic effects are thought to be elicited via their binding to the $\alpha_2\delta$ subunit of VGCCs which is considered to decrease neurotransmitter release, thus reducing neuronal hyperexcitability. The majority of clinical evidence supports analgesic efficacy in DPN and PHN and limited evidence suggests that this efficacy extends to other, but not necessarily all, neuropathic pain syndromes. Early comparative RCTs and pooled estimates from meta-analyses suggest that analgesic efficacy of gabapentin and pregabalin is perhaps slightly lower than that of tricyclic antidepressants or opioids. However, the most attractive aspects of these two drugs include their tolerability, lack of serious toxicity and ease of use. Future research efforts are warranted to fully understand the mechanism of action of these drugs, to clearly characterize the safety and efficacy of gabapentin and pregabalin in all clinical neuropathic pain syndromes and to further explore the role of these drugs in the rational polypharmacy of neuropathic pain.

ACKNOWLEDGEMENT: This work was supported by Canadian Institutes of Health Research Grant #69422 and Queen's University Grant #383-861.

APPENDIX: PUBLICATIONS EXCLUDED FROM REVIEWED RANDOMIZED CONTROLLED TRIALS

Reason for exclusion: Not a neuropathic pain treatment trial

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