

# Gabapentin and pregabalin for chronic neuropathic and early postsurgical pain: current evidence and future directions

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## Purpose of review

Gabapentin and pregabalin bind to the alpha-2-delta calcium channel subunit and represent a novel analgesic drug class. The evidence base supporting their use for chronic neuropathic and early postsurgical pain is reviewed.

## Recent findings

Multiple, large, high-quality trials have demonstrated the safety and efficacy of gabapentin and pregabalin in neuropathic pain. Treatment-related improvement of pain and sleep positively impact upon quality of life. Sedation, dizziness and ataxia are important and relatively common adverse effects, however. Accumulating evidence indicates that gabapentin, and possibly pregabalin, also exert important effects following surgery. Multiple high-quality trials have demonstrated analgesic and opioid-sparing efficacy with gabapentin following various surgical procedures. Gabapentin and pregabalin reduce movement-evoked pain and this can lead to enhanced functional postoperative recovery. Postoperative opioid sparing is of questionable relevance since few trials have shown reduced opioid-related adverse effects. Sedation, dizziness and ataxia have been reported in only a few trials. Future larger-scale perioperative trials focused on safety assessment are needed, however.

## Summary

Gabapentin and pregabalin are efficacious treatments for neuropathic and postsurgical pain. Future research addressing several specific questions would serve to better delineate their optimal roles in treating these and other pain conditions.

## Keywords

gabapentin, neuropathic pain, postoperative pain, pregabalin

## Abbreviations

<b>DPN</b>	diabetic peripheral neuropathy
<b>GABA</b>	gamma-aminobutyric acid
<b>NNH</b>	number needed to harm
<b>NNT</b>	number needed to treat
<b>PHN</b>	postherpetic neuralgia
<b>RCT</b>	randomized controlled trial

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0952-7907

## Introduction

Two anticonvulsants, gabapentin and pregabalin, have been studied as treatments for a wide variety of disorders including pain [1], epilepsy [2], spasticity [3] and anxiety [4]. The basic and clinical pharmacology of these drugs has become an intense field of research. Simple MEDLINE searches of these drugs in May 2007 have yielded more than 2500 citations, 200 randomized controlled trials (RCTs) and, in the area of pain management alone, over a dozen systematic reviews and meta-analyses (see Table 1). Furthermore, recent searches on 'www.clinicaltrials.gov' and 'www.controlled-trials.com' show over 70 ongoing trials. In the dynamic setting of ongoing research, this article attempts to provide an up-to-date evidence-based qualitative review that delineates the evolving role of gabapentin and pregabalin in treating chronic neuropathic and early postsurgical pain. The reader should keep in mind possible limitations of such a review of published evidence, which include heterogeneity across studies with respect to quality, design and outcome measures, as well as the potential for publication bias since many 'negative' trials are not published and may even stay out of the public domain [17].

A literature search was conducted using the Cochrane Central Register of Controlled Trials (2007, Issue 2) and the MEDLINE Database (1966 to May 2007). All RCTs were evaluated by the author of this review and rated using a three-item (1–5) quality scale [18].

## Historical perspective

In 1977, gabapentin (Neurontin [1-(aminomethyl)cyclohexaneacetic acid]) – an alkylated analogue of gamma-aminobutyric acid (GABA) – was synthesized [19] and subsequently developed as an anticonvulsant drug in the late 1980s [20]. Initial interest in the potential of gabapentin as an analgesic drug was stimulated by early case reports in neuropathic pain in the mid 1990s [21–23],

Curr Opin Anaesthesiol 20:456–472. © 2007 Lippincott Williams & Wilkins.

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Current Opinion in Anaesthesiology 2007, 20:456–472

**Table 1 Selected meta-analyses and systematic reviews of gabapentin and pregabalin for pain management**

	Drug	Therapeutic area	No. of RCTs included for review
Bennett, 2004 [5]	Gabapentin	Neuropathic	7
Finnerup, 2005 [1]	Gabapentin/ pregabalin	Neuropathic	14
Gilron, 2006 [6*]	Gabapentin/ pregabalin	Neuropathic	22
Mellegers, 2001 [7]	Gabapentin	Neuropathic	6
Jensen, 2002 [8]	Gabapentin	Neuropathic	4
Wiffen, 2005 [9]	Gabapentin	Neuropathic and postsurgical	14
Dahl, 2004 [10]	Gabapentin/ pregabalin	Postsurgical	8
Gilron, 2006 [11*]	Gabapentin/ pregabalin	Postsurgical	16
Ho, 2006 [12*]	Gabapentin	Postsurgical	16
Hurley, 2006 [13*]	Gabapentin	Postsurgical	12
Peng, 2007 [14*]	Gabapentin	Postsurgical	18
Seib, 2006 [15*]	Gabapentin	Postsurgical	8
Tiippana, 2007 [16*]	Gabapentin/ pregabalin	Postsurgical	22

RCT, randomized controlled trial.

which led to more formal pain investigations concurrently conducted in both laboratory [24,25] and clinical [26,27] settings. Pregabalin (Lyrica [(S)-(+)-3-(aminomethyl)-5-methylhexanoic acid]) is a pharmacologically similar alkylated GABA analogue that was synthesized over a decade after gabapentin [28] and has been recently marketed in several countries for the treatment of neuropathic pain [6\*]. Although gabapentin and pregabalin were first identified as treatments for neuropathic pain, a condition previously thought to be entirely distinct from inflammatory pain [29], early preclinical studies suggesting analgesic efficacy following tissue injury [30] have led to the development of gabapentin and pregabalin as treatments for postsurgical pain [10]. With the first published gabapentin analgesic RCTs in 1998 [26,27] and the first published pregabalin analgesic RCT in 2001 [31], it should be noted that the evidence base supporting the use of gabapentin and pregabalin for pain management is less than a decade old, with many important questions yet to answer.

### Pharmacological effects and analgesic mechanisms

Previous studies suggest that gabapentin may have important actions at peripheral [32], primary afferent neuron [33], spinal cord [34] and supraspinal [35] sites. Reviews based upon numerous laboratory investigations indicate that gabapentin and pregabalin produce several pharmacological effects, including competition with other amino acids for membrane transport across the 'L-alpha-amino acid transporter system', increasing the concentration of GABA in the brain, activation of ATP-sensitive K<sup>+</sup> channels and hyperpolarization-activated cation channels, activation of heterodimeric GABA-B

receptors, and binding to the alpha-2-delta subunit of N-type voltage-gated calcium channels [36,37\*\*]. Recent compelling evidence suggests that binding of gabapentin and pregabalin to the alpha-2-delta subunit of N-type voltage-gated calcium channels is likely the most important analgesic mechanism of these drugs [37\*\*–39\*\*]. In particular, nerve injury in rats results in upregulation of alpha-2-delta-1 calcium channel subunits in dorsal root ganglion neurons [40,41] and this upregulation has been shown to correlate with the antinociceptive effects of gabapentin [42]. More recent work suggests that, unlike normal 'wild-type' mice, 'R217A' mutant mice – that exhibit decreased pregabalin binding at alpha-2-delta-1 calcium channel subunits – show no antinociceptive response to gabapentin or pregabalin following nerve injury, but do respond to treatment with amitriptyline [38\*\*]. Of further interest, pregabalin (but not morphine) was ineffective in reducing pain behaviors in 'R217A' mutant mice following formalin injection, which is a nociceptive pain model [38\*\*]. Taken together, these results suggest that – in both neuropathic and posttissue injury pain – binding to alpha-2-delta calcium channel subunits is likely an important mechanism for the analgesic effects of gabapentin and pregabalin. Alpha-2-delta calcium channel subunit binding is thought to then result in a reduction in the release of neurotransmitters such as glutamate [43] and substance P [44], thus suppressing neuronal excitability following nerve or tissue injury. It should be emphasized that one of the key features of these drugs is that their antinociceptive effects occur primarily in the setting of neural sensitization after nerve or tissue injury and that they have minimal effects on normal physiological pain transmission [39\*\*].

While 'alpha-2-delta' binding is currently thought to be the most important mechanism, one cannot rule out the possibility that other important analgesic mechanisms of gabapentin and pregabalin have yet to be described. For example, a recent translational study demonstrated important interactions between gabapentin and spinal alpha-2-adrenergic receptor systems in the rat and, furthermore, that gabapentin administration reduces cerebrospinal fluid norepinephrine levels in humans [45\*]. Taken together, results from these and other studies suggest the possibility of important interactions between gabapentin or pregabalin and modulators of adrenergic neurotransmission. Readers are encouraged to consult previous reviews on the antinociceptive effects of gabapentin and pregabalin described in various preclinical pain models [6\*,37\*\*,39\*\*].

### Clinical pharmacology

Basic information about the clinical pharmacology of gabapentin and pregabalin is listed in Table 2 but, of course, health professionals are urged to review the product monographs before prescribing these

**Table 2 Clinical pharmacology of gabapentin and pregabalin**

	Gabapentin [46,47]	Pregabalin [48,49]
Time to maximal absorption ( $T_{max}$ )	2–3 h	0.8–1.4 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 5–9 h	Negligible metabolism Renally excreted unchanged Elimination half-life 4–7 h
Clinically important drug interactions	Oral antacids reduce bioavailability by 20–30%	No significant drug interactions described to date
Starting dose	Can potentiate sedative effects of ethanol and benzodiazepines 100–900 mg/day Dose reduction required with renal insufficiency	Can potentiate sedative effects of ethanol and benzodiazepines 75–150 mg/day Dose reduction required with renal insufficiency
Titration	Over several weeks towards maximal tolerated dose Weekly increases of 300–900 mg/day	Over several weeks towards maximal tolerated dose Weekly increases of 50–150 mg/day
Dosage frequency	Every 8 h	Every 8–12 h
Usual effective dose	1200–2400 mg/day	150–600 mg/day
Maximum dose	3600 mg/day	600 mg/day

Modified from [6\*].

medications. The lack of hepatic enzyme inhibition or induction and the lack of clinically important drug interactions are major perceived advantages of gabapentin and pregabalin [46,48]. Oral antacids, however, are known to diminish the bioavailability of gabapentin by 20–30% [46]. As with other sedating drugs, gabapentin and pregabalin can potentiate the effects of other sedatives such as ethanol and benzodiazepines. Doses of both drugs should be reduced proportional to creatinine clearance in the presence of renal insufficiency since they are normally excreted unchanged in the urine [46,48]. Absorption of pregabalin is quite fast (approximately 1 h to maximal absorption) and oral bioavailability remains very high (>90%) regardless of dose. In contrast, absorption of gabapentin is slightly slower (2–3 h to maximal absorption) and occurs through a saturable transport system in the gastrointestinal tract, such that bioavailability decreases with increasing doses [50]. Therefore, gabapentin dose increases in higher dose ranges should be expected to lead to incrementally smaller increases in plasma drug concentrations (i.e. nonlinear pharmacokinetics). RCTs of gabapentin and pregabalin have used starting doses of at least 300 mg/day and 75 mg/day, respectively (see below). In the elderly, however, in patients with renal insufficiency, or in patients already receiving sedating drugs, one should consider starting with even lower doses than these and titrating the dose very slowly in order to minimize the risk of falling and related trauma. Usual effective, and tolerable, doses for neuropathic pain range from 1200 to 2400 mg/day for gabapentin and 150 to 600 mg/day for pregabalin, and doses greater than 3600 mg/day and 600 mg/day, respectively, have not been studied (Table 2).

### Neuropathic pain

The topic of neuropathic pain can be further considered under the headings diabetic neuropathy, postherpetic neuralgia, and other neuropathic pain syndromes.

### Diabetic neuropathy

Three gabapentin and three pregabalin placebo-controlled RCTs in diabetic peripheral neuropathy (DPN), as well as one nonplacebo-controlled trial comparing gabapentin only to amitriptyline, have been published (Table 3). Also, one gabapentin RCT and one pregabalin RCT involving a mixed population of 60–70% DPN and 30–40% postherpetic neuralgia (PHN) patients are outlined in Table 4.

In two of the four placebo-controlled gabapentin RCTs, analgesic efficacy was statistically superior to placebo and was accompanied by improvements in several secondary measures of quality of life, mood and sleep [26,53]. In an industry-sponsored RCT, Backonja *et al.* reported a 39% pain reduction from baseline with gabapentin, significantly greater than the 22% pain reduction seen with placebo [26]. Another trial reported a 38% pain reduction from baseline with gabapentin, significantly greater than the 8% pain reduction seen with placebo [53]. The gabapentin RCT by Gorson *et al.*, however, which involved a maximum dose of only 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 [51]. Gilron *et al.* [57] also reported no significant gabapentin-placebo difference for the primary efficacy measure (0–10 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. In this RCT, however, gabapentin was statistically superior to active placebo for several secondary outcome measures, including the short-form McGill Pain Questionnaire, Brief Pain Inventory, SF-36 Health Survey and Beck Depression Inventory [57].

**Table 3 Published randomized controlled trials of gabapentin and pregabalin for painful diabetic neuropathy**

	Gabapentin (TID dosing)				Pregabalin		
	Backonja, 1998 [26]	Gorson, 1999 [51]	Morello, 1999 [52]	Simpson, 2001 [53]	Lesser, 2004 [54]	Rosenstock, 2004 [55]	Richter, 2005 [56]
Study design, no. patients (N)	Parallel, Gbp-84, Plc-81	Crossover, 40	Crossover, 25	Parallel, Gbp-30, Plc-30	Parallel, Pgb 75-77, Pgb 300-81, Pgb 600-82, Plc-97	Parallel, Pgb-76, Plc-70	Parallel, Pgb 150-79, Pgb 600-82, Plc-85
Treatment control(s)	Placebo	Placebo	Amitriptyline (no placebo)	Part I: placebo, Part II: venlafaxine + gabapentin in combination	Placebo	Placebo	Placebo
Allowed concomitant medications	Acetaminophen, ASA, SSRIs	NSAIDs, opioids	Acetaminophen	None	Acetaminophen, SSRIs, gabapentin failures excluded	Acetaminophen, ASA, SSRIs	ASA, acetaminophen, SSRIs
Starting dose	900 mg/day	Not specified	300 mg/day	300 mg/day	75–75 mg/day, 300–300 mg/day, 600–75 mg/day	100 mg TID	150–25 mg/day, 600–100 mg/day
Target maintenance dose	3600 mg/day (reached by 67% of patients)	900 mg/day	1800 mg/day	3600 mg/day	75–75 mg/day, 300–300 mg/day, 600–600 mg/day (TID dosing)	100 mg TID	150–150 mg/day, 600–600 mg/day (TID dosing)
Titration method	To MTD 4 weeks	Not specified	To MTD	To MTD 4 weeks	Forced to target 1 week	Forced to target	Forced?
Titration duration	4 weeks	Not specified	Not specified	4 weeks	5 weeks	None	2 weeks
Treatment duration	8 weeks	6 weeks	6 weeks	8 weeks	0–10 NRS	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 <sup>a</sup> (comments)	Gbp > Plc	Gbp compared with Plc: NS (Gbp > Plc for MPQ scores)	Gbp compared with Plc: NS (Gbp > Plc for MPQ scores)	Part I: Gbp > Plc, Part II: Gbp + Vifx > Gbp	Pgb > Plc For 300 and 600 only	Pgb > Plc	600 > Plc, 150 compared with Plc NS
% patients dropped out due to AEs	8.3%	Not specified	16.7%	Not specified	75–2.6%, 300–3.7%, 600–12.2%	10.5%	150–2.5%, 600–8.5%
Trial quality score	5	2	4	3	5	5	5

TID, three times daily; Gbp, gabapentin; Plc, placebo; Pgb, pregabalin; ASA, aspirin; SSRIs, selective serotonin reuptake inhibitors; MTD, maximally tolerated dose; NRS, numerical rating scale; VAS, visual analog scale; MPQ, McGill Pain Questionnaire; Ami, amitriptyline; NS, not statistically significant; Vifx, venlafaxine; AEs, adverse events. Trial quality score, see text for details. Modified from [6].

<sup>a</sup>The symbol '>' denotes 'analgesic efficacy greater'; listed differences were reported as statistically significant unless otherwise stated.

**Table 4 Published randomized controlled trials of gabapentin and pregabalin in mixed populations of painful diabetic neuropathy and postherpetic neuralgia**

	Gabapentin	Pregabalin
	Gilron, 2005 [57]	Freyenhagen, 2005 [58]
Study design, no. patients (N)	Crossover, 57	Parallel, flex-141, fixed-132, Plc-65
Treatment control(s)	Active placebo (lorazepam) Morphine–gabapentin in combination	Placebo
Allowed concomitant medications	All allowed	SSRIs, ASA, benzodiazepines, acetaminophen, Prev Gbp allowed
Starting dose	400 mg/day	Flex-150 mg/day, Fixed-300 mg/day
Target maintenance dose	Target 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 <sup>a</sup> (comments)	Gabapentin compared with active placebo NS (gabapentin > active placebo for SF-MPQ) Gabapentin-morphine > gabapentin	Flex and Fixed > Plc, 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

Flex, flexible dose titration to maximally tolerated dose; Fixed, forced titration to maximal target dose; Plc, placebo; SSRIs, selective serotonin reuptake inhibitors; ASA, aspirin; Prev Gbp, previous gabapentin exposure; MTD, maximally tolerated dose; BID, twice daily; NRS, numerical rating scale; NS, not statistically significant; SF-MPQ, Short Form McGill Pain Questionnaire; AEs, adverse events. Trial quality score, see text for details. Modified from [6<sup>\*</sup>].

<sup>a</sup>The symbol '>' denotes 'analgesic efficacy greater'; listed differences were reported as statistically significant unless otherwise stated.

Three industry-sponsored RCTs of pregabalin for pain in DPN have been published. These RCTs (see Table 3) report superiority over placebo with 34–40% pain reductions from baseline at pregabalin target doses of at least 300 mg/day [54–56]. In these RCTs, pain reduction was accompanied by improvements in sleep over similar dosage ranges and with a similar temporal profile [54–56]. The mixed DPN/PHN pregabalin RCT reported similar results [58] (Table 4).

### Postherpetic neuralgia

In the setting of PHN treatment, two gabapentin and three pregabalin RCTs, as well as one nonplacebo-controlled trial comparing gabapentin only to nortriptyline, have been published (Table 5).

Gabapentin was studied in 336 PHN patients in two industry-sponsored RCTs that demonstrated analgesic efficacy at target doses of 1800, 2400 or 3600 mg/day [27,59] (see Table 5). Pain reduction from baseline was reported to be 33–35% in all three of these dose groups. Improvements in sleep and several SF-36 quality of life domains were also reported [27,59].

Efficacy of pregabalin in PHN was reported in three large industry-sponsored RCTs [61,62,63<sup>\*</sup>] (see Table 5), with pain reductions from baseline that varied from 18% at 150 mg/day [63<sup>\*</sup>] to 37% at 600 mg/day [61]. Pain relief, again, was accompanied by improved sleep over similar dosage ranges and with a similar temporal profile.

### Other neuropathic pain syndromes

Since not all drugs effective in DPN or PHN are effective in other neuropathic syndromes [1,64<sup>\*</sup>], investigators

have formally evaluated gabapentin and pregabalin in other neuropathic pain conditions (Table 6).

Pain reduction with gabapentin was reported to be superior to placebo in RCTs of phantom limb pain [68], Guillain–Barré syndrome [72,73], cancer-related neuropathic pain [74] and mixed neuropathies [71]. Levendoglu *et al.* [66] reported a positive result in spinal cord injured (SCI) patients whereas a smaller SCI trial failed to show significant differences in pain intensity, possibly due to inadequate statistical power [65]. Gabapentin appeared to demonstrate slight, statistically insignificant superiority over placebo in a single RCT of patients with complex regional pain syndrome (CRPS) type I [67]. In a small RCT ( $n=11–15$  per group) of human immunodeficiency virus (HIV)-associated neuropathy, pain reduction from baseline was reported as 44.1% with gabapentin and 29.8% with placebo. The gabapentin–placebo difference in pain reduction was not statistically significant, however [69]. In a recent randomized, open-label spinal stenosis study, gabapentin in addition to standard therapy (exercise, corset brace and NSAIDs) resulted in greater walking distance and less pain compared with standard therapy alone [70<sup>\*</sup>].

In a recent industry-sponsored trial of pregabalin for central neuropathic pain following spinal cord injury, analgesic efficacy was superior to placebo, and additional reported benefits included reduced anxiety and improved sleep [75<sup>\*</sup>].

### Comparative and combination trials

A small number of RCTs have compared gabapentin with other drugs for neuropathic pain. At the time of writing,

**Table 5 Published randomized controlled trials of gabapentin and pregabalin for postherpetic neuralgia**

	Gabapentin			Pregabalin		
	Rowbotham, 1998 [27]	Rice, 2001 [59]	Chandra, 2006 [60*]	Dworkin, 2003 [61]	Sabatowski, 2004 [62]	van Seventer, 2006 [63*]
Study design, no. patients (N)	Parallel, Gbp-113, Plc-116	Parallel, 2400 mg/day-108, 1800 mg/day-115, Plc-111	Parallel, gabapentin-34, nortriptyline-36	Parallel, Pgb-89, Plc-84	Parallel, Pgb 150-81, Pgb 300-76, Plc-81	Parallel, Pgb 150-87, Pgb 300-98, Pgb 600-90
Treatment control(s)	Placebo	Placebo	Nortriptyline	Placebo	Placebo	Placebo
Allowed concomitant medications	TCA, opioids	NSAIDs, weak opioids, antidepressants, ASA	All but muscle relaxants, anticonvulsants and topical analgesics	Opioids, antidepressants, NSAIDs, acetaminophen, note gabapentin treatment failures excluded	All but benzodiazepines and AEDs prohibited, Gbp treatment failures excluded	NSAIDs, acetaminophen, opioids, antidepressants
Starting dose	900 mg/day	300 mg/day	900 mg/day	50 mg TID	150–50 mg TID, 300–100 mg TID	Titration not described
Target maintenance dose	3600 mg/day (reached by 65%)	1 group-1800 mg/day, 1 group-2400 mg/day	2700 mg/day	200 mg TID (CrCl > 60), 100 mg TID (CrCl ≤ 60)	150–150 mg/day, 300–300 mg/day (TID dosing)	Titration not described (BID dosing)
Titration method	To MTD	Forced to target dose	Flexible dose titration to 'acceptable relief'	Forced to target	Forced to target	Titration not described
Titration duration	4 weeks	2–3 weeks	6 weeks	1–2 weeks	1 week	Titration not described
Treatment duration	8 weeks	7 weeks	8 weeks	8 weeks	8 weeks	13 weeks
Primary outcome	0–10 NRS	0–10 NRS	0–10 NRS	0–10 NRS	0–10 NRS	0–10 NRS
Study results <sup>a</sup> (comments)	Gbp > Plc	Gbp > Plc at both 1800 and 2400 mg/day	Gbp compared with nortriptyline NS (Gbp better tolerated)	Pgb > Plc	Pgb > Plc Minimal difference 150 compared with 300	150–600 > Plc, dose response apparent but not statistically reported
% patients dropped out due to AEs	18.6%	1800: 13%, 2400: 17.6%	Five trial dropouts but none attributed to AEs	31.5%	150–11.1%, 300–15.4%	150–8.0%, 300–15.3%, 600–21.1%
Trial quality score	5	5	5	5	5	3

Gbp, gabapentin; Plc, placebo; Pgb, pregabalin; TCAs, tricyclic antidepressants; ASA, aspirin; AEDs, antiepileptic drugs; TID, three times daily; BID, twice daily; CrCl, creatinine clearance; NRS, numerical rating scale; AEs, adverse events. Trial quality score, see text for details. Modified from [6\*].

<sup>a</sup>The symbol '>' denotes 'analgesic efficacy greater'; listed differences were reported as statistically significant unless otherwise stated.

Table 6 Published randomized controlled trials of gabapentin and pregabalin for other neuropathic pain syndromes

Diagnosis Study design, no. patients (N)	Gabapentin										Pregabalin
	Tai, 2002 [65]	Levendoglu, 2004 [66]	van de Vusse, 2004 [67]	Bone, 2002 [68]	Hahn, 2004 [69]	Yaksi, 2007 [70*]	Serpelli, 2002 [71]	Pandey, 2002 [72]	Pandey, 2005 [73]	Caraceni, 2004 [74]	Siddall, 2006 [75*]
	SCI	SCI	CRPS-1	PLP	HIV-NP	Spinal stenosis	Mixed	Guilain-Barré	Guilain-Barré	Ca-NP	SCI
	Crossover, 14	Crossover, 20	Crossover, 58	Crossover, 19	Parallel, Gbp-15, Plic-11	Parallel, Gbp-28, Standard Rx-27 (*unblinded*)	Parallel, Gbp-153, Plic-152	Parallel, Gbp-12, Cbz-12, Plic-12	Parallel, Gbp-79, Plic-41	Parallel, Gbp-79, Plic-67	
Treatment control(s)	Placebo	Placebo	Placebo	Placebo	Placebo	'Standard treatment'	Placebo	Placebo	Placebo	Placebo	Placebo
Allowed concomitant medications	None prohibited	None allowed	None prohibited	TCAs	NSAIDs, acetaminophen	NSAIDs	TCAs, SSRIs, ASA, opioids, weak	Fentanyl	Fentanyl	None prohibited	NSAIDs, opioids, AEDs, TCAs
Starting dose	300 mg/day	Not specified	600 mg/day	300 mg/day	400 mg/day	900 mg/day	300 mg/day	900 mg/day	600 mg/day	600 mg/day	(Gbp prohibited)
Target maintenance dose	1800 mg/day	3600 mg/day (mean MTD, 2850 mg/day)	1800 mg/day	2400 mg/day	2400 mg/day	2400 mg/day	2400 mg/day	900 mg/day	1800 mg/day	1800 mg/day	600 mg/day
Titration method	To MTD	To MTD	Not specified	To MTD	To MTD	To MTD	To MTD	Not specified	Not specified	To MTD	To MTD
Titration duration	Not specified	4 weeks	Not specified	Not specified	2–3 weeks	Not specified	5 weeks	Not specified	Not specified	Not specified	3 weeks
Treatment duration	4 weeks	8 weeks	3 weeks	6 weeks	4 weeks	16 weeks	8 weeks	1 week	10 days	10 days	12 weeks
Primary outcome	Neuropathic pain scale	VAS 0–100 mm	VAS 0–100 mm	VAS 0–10 cm	VAS 0–10 cm	Not specified	0–10 NRS	0–10 NRS	0–10 NRS	0–10 NRS	0–10 NRS
Study results <sup>a</sup>	Gbp compared with Plic NS	Gbp > Plic	Gbp compared with Plic NS	Gbp > Plic	Gbp compared with Plic NS	Gbp > standard Rx for walking distance and pain	Gbp > Plic	Gbp > Cbz = Plic	Gbp > Plic	Gbp > Plic	Pgb > Plic
% dropouts due to AEs	Not specified	None	5.2%	Not specified	7.1%	None	15.7%	Not specified	7.6%	21%	
Trial quality score	4	4	5	5	5	1	5	3	5	5	5

SCI, spinal cord injury; PLP, phantom limb pain; Mixed, mixed population of various different neuropathic pain syndromes; Ca-NP, cancer-related neuropathic pain; CRPS-1, complex regional pain syndrome type 1; HIV-NP, human immunodeficiency-related neuropathic pain; Gbp, gabapentin; Plic, placebo; TCAs, tricyclic antidepressants; SSRIs, selective serotonin reuptake inhibitors; ASA, aspirin; MTD, maximally tolerated dose; VAS, visual analog scale; NRS, numerical rating scale; NS, not statistically significant; Aes, adverse events. Trial quality score, see text for details. Modified from [6\*].

\* The symbol > denotes 'analgesic efficacy greater'; listed differences were reported as statistically significant unless otherwise stated.

no comparative RCTs of pregabalin have been published. Gilron *et al.* [57] demonstrated that neuropathic pain intensity was significantly lower during treatment with morphine-gabapentin combination than with gabapentin alone. In addition, a trend favoring morphine alone over gabapentin alone was observed, and the efficacy of morphine, but not gabapentin, was statistically superior to placebo [57]. In a small second-phase study of 11 gabapentin nonresponders, a venlafaxine-gabapentin combination was superior to gabapentin alone [53]. In a nonplacebo-controlled trial, Morello *et al.* [52] reported a nonsignificant trend favoring amitriptyline slightly over gabapentin. Finally, in a more recent PHN trial, efficacy of gabapentin was reported to be comparable with that of nortriptyline; however, gabapentin was reportedly better tolerated [60\*].

### Early postsurgical pain

At the time of writing, gabapentin has been studied in 901 surgical patients as described in 11 RCTs of abdominal or pelvic surgery (Table 7), 10 RCTs of musculoskeletal surgery (Table 8), and six RCTs of head, neck and breast surgery (Table 9). Seventeen of all presented trials evaluated only single preoperative doses of gabapentin and the remaining 10 evaluated repeated doses of gabapentin over periods of 1–10 days. Most trials started gabapentin administration before surgery; however, a recent trial in donor nephrectomy patients showed no statistically significant difference in pain scores upon comparing preoperative with postincisional administration [81]. Presented RCTs evaluated variable gabapentin doses from as low as single doses of 300 mg to as high as 1800 mg/day. Although further work is needed to better define the optimal gabapentin dose for specific surgical procedures and at different postoperative timepoints, it is useful to note that Pandey and colleagues conducted a dose-response trial of gabapentin single-dose pretreatment in lumbar discectomy patients. This study demonstrated an analgesic ceiling at 600 mg, that is, pain reduction with 600 mg was better than with 300 mg but no additional benefits were observed at doses of 900 or 1200 mg [89]. Five RCTs evaluated only pain at rest [80,81,87,89,93\*], six RCTs did not specify whether pain was measured at rest or with movement [88,92,94\*–96\*,99], and the remaining 16 RCTs evaluated pain both at rest and with movement. Gabapentin was superior to placebo for analgesic efficacy in 19 of the 27 published RCTs, and opioid sparing in 21 of the 27 RCTs. Five studies reported no effects on pain scores or opioid sparing [84\*,85\*,90,93\*,94\*]; three studies reported opioid sparing only [77,92,102\*]; one study reported pain reduction only [76], and one study reported pain reduction but did not use postoperative opioids [95\*]. Of the 16 RCTs measuring pain with movement, 11 demonstrated significantly reduced movement-related pain with gabapentin [76,78,79,82,83\*,86\*,91,97,98,100,101\*].

**Table 7 Perioperative RCTs of gabapentin for abdominal or pelvic surgery**

	Yoon, 2001 [76]	Dierking, 2004 [77]	Turan, 2004 [78]	Rorarius, 2004 [79]	Pandey, 2004 [80]	Pandey, 2005 [81]	Gilron, 2005 [82]	Turan, 2006 [83]	Fassoulaki, 2006 [84]	Bartholdy, 2006 [85]	Durmus, 2007 [86]
Trial quality score	4	5	4	5	3	5	5	4	5	5	5
Procedure	Hysterectomy	Abdominal hysterectomy Multi (24 h)	Abdominal hysterectomy Single	Vaginal hysterectomy Single	Laparoscopic cholecystectomy Single	Donor nephrectomy Single	Abdominal hysterectomy Multi (72 h)	Abdominal hysterectomy Multi (72 h)	Abdominal hysterectomy Multi (18 h preop + 5 days postop)	Laparoscopic sterilization Single	Abdominal hysterectomy Single
Single compared with multidose	Multi (preop night & 30 min preop)	Multi (24 h)	Single	Single	Single	Single	Multi (72 h)	Multi (72 h)	Multi (18 h preop + 5 days postop)	Single	Single
Dose (mg)	400 mg	1200 1 h pre 600 TID × 1d	1200 1 h pre	1200 2.5 h pre	300 2 h pre	600 2 h pre	600 TID × 3d	1200 mg/d × 2d	400 mg every 6 h	1200 mg 30 min pre	1200 mg 1 h pre
Treatment control(s)	Placebo	Placebo	Placebo	Oxazepam	Tramadol; placebo	Placebo; g:post	Placebo; rofecoxib; gr combo	Placebo; rofecoxib; gr combo	Placebo	Placebo	Placebo; gabapentin; paracetamol combo
N (Gbp/Plc)	16/16	39/32	25/25	38/37	153/153	40/20	23/24	25/25	25/27	38/38	25/25
Nonopioid analgesic	?	None	None	None	None	None	None	None	Paracetamol	Lornoxicam	None
Significant pain <sup>a</sup>	+ (movement pain)	0	+ (resting & sitting)	+ (in first 2 h)	+	+	+ (at rest & with movement)	+	0 (in 1 <sup>st</sup> 2d) (more pain-free patients at 1 month)	0	+
reduction compared with placebo	0	+	+	+	+	+	+	+	0	0	+
Significant opioid sparing <sup>a</sup> compared with placebo	ns	ns	ns	ns	More sedation and nausea	ns	More sedation	ns	Not reported	ns	ns
Adverse effects	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns

ns, not statistically significant; + indicates significant pain intensity difference between gabapentin and placebo groups; 0 indicates no significant pain intensity difference between gabapentin and placebo groups. <sup>a</sup> Refers only to gabapentin-placebo comparison and refers to pain at rest unless otherwise specified.

Several RCTs compared gabapentin with other treatments. Fassoulaki *et al.* reported analgesia and opioid sparing with gabapentin that was comparable with that of the sodium channel blocker, mexiletine [98]. Pandey *et al.* reported lower pain intensity and fentanyl consumption with gabapentin as compared with tramadol [80]. Furthermore, Gilron *et al.* compared gabapentin with rofecoxib and with these two drugs in combination [82]. Cumulative morphine consumption was similarly reduced in both single agent gabapentin and rofecoxib groups, with even further significant reductions seen in the combination group. Pain evoked by cough was roughly similar in both gabapentin and rofecoxib groups. Finally, Durmus and colleagues have recently shown that combining acetaminophen with gabapentin significantly reduces postoperative pain and opioid consumption when compared with gabapentin alone [86\*].

In light of gabapentin's known anxiolytic effects [103, 104], it is also interesting to note that one perioperative trial showed an anxiolytic effect with gabapentin in the setting of knee surgery [91]. Also, whether related to opioid sparing or a specific antiemetic effect, one trial has suggested that gabapentin may reduce nausea and vomiting following laparoscopic cholecystectomy [105\*]. Following previous suggestions that lower movement-evoked pain correlates with improved postoperative function [106], it is interesting to note that, in the setting of anterior cruciate ligament repair, preoperative gabapentin administration resulted in greater knee flexion angles on postoperative days 1 and 2 [91]. Furthermore, Gilron *et al.* demonstrated that lung function during treatment with either gabapentin or rofecoxib, as assessed by peak expiratory flow rate, was significantly higher than with placebo, and these improvements were enhanced even further when both drugs were given in combination [82]. These observations indicate that gabapentin-induced reductions in movement-evoked pain may actually accelerate postoperative functional recovery. Future investigations with longer follow-up and more specific outcome measures are needed, however, in order to determine whether these benefits translate into lower complication rates, earlier hospital discharge or earlier return to work. Also, given the hypothesis that more effective pain management may prevent chronic postsurgical pain [107], a trial of 10 days of gabapentin treatment (1200 mg/day) following breast cancer surgery reporting lower chronic postsurgical pain may have generated much excitement [98]. A more recent RCT of 30 days of gabapentin treatment (up to 2400 mg/day) following lower limb amputation failed, however, to demonstrate any reduction in the incidence or intensity of postamputation pain [108\*\*].

Based on published RCTs at the time of writing, pregabalin has been studied in 173 surgical patients (Table 10).

**Table 8 Perioperative RCTs of gabapentin for musculoskeletal surgery**

	Pandey, 2004 [87]	Turan, 2004 [88]	Pandey, 2005 [89]	Radhakrishnan, 2005 [90]	Menigaux, 2005 [91]	Tuncer, 2005 [92]	Leung, 2006 [93]	Adam, 2006 [94]	Turan, 2006 [95]	Turan, 2007 [96]
Trial quality score	3	5	4	4	5	1	2	4	5	5
Procedure	Lumbar discectomy	Discectomy or fusion	Lumbar discectomy	Lumbar laminectomy/discectomy	Anterior cruciate ligament repair	'Major orthopedic surgery'	'Spine surgery'	Arthroscopic shoulder surgery	Lower extremity surgery	Hand surgery
Single compared with multidoses	Single	Single	Single	Single	Single	Single	Multi 3 d	Single	Multi - 2 d	Single
Dose (mg)	300 mg, 2 h preop	1200 mg, 1 h preop	300 mg; 600 mg; 900 mg; 1200 mg - 2 h preop	800 mg, 2 h preop	1200 1-2 h pre	800 mg; 1200 mg; 1 h preop	900 mg, 1-2 h preop; (repeated for 3 d)	800 mg, 2 h preop	1200 mg/d for 2 d	1200 mg, 1 h preop
Treatment control(s)	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
N (Gbp/Plc)	28/28	25/25	80/20	30/30	20/20	30/15	9/12	27/26	20/20	20/20
Nonopioid analgesic	None	None	None	None	Ketoprofen	None	Not specified	Acetaminophen; brachial plexus regional anesthesia	Epidural regional anesthesia; acetaminophen	Diclofenac
Significant pain <sup>a</sup> reduction compared with placebo	+	+	+	0	+	0	0	0	+	+
Significant opioid sparing <sup>a</sup> compared with placebo	+	+	+	0	+	+	0	0	No opioid used	+
Adverse effects	ns	less vomiting less urinary retention	ns	ns	ns	ns	Less postop delirium	Less headache	More dizziness	ns

ns, not statistically significant; + indicates significant pain intensity difference between gabapentin and placebo groups; 0 indicates no significant pain intensity difference between gabapentin and placebo groups.  
<sup>a</sup> Refers only to gabapentin-placebo comparison and refers to pain at rest unless otherwise specified.

**Table 9 Perioperative RCTs of gabapentin for head, neck and breast surgery**

	Dirks, 2002 [97]	Fassoulaki, 2002 [98]	Turan, 2004 [99]	Fassoulaki, 2005 [100]	Al-Mujadi, 2006 [101*]	Mikkelsen, 2006 [102*]
Trial quality score	5	4	4	5	5	5
Procedure	Radical mastectomy	Breast Ca surgery	Septoplasty	Breast Ca surgery	Thyroidectomy	Tonsillectomy
Single compared with multidose	Single	Multi (10 d)	Single	Multi (8 d)	Single	Multi (5 d)
Dose (mg)	1200 1 h pre	400 TID	1200 1 h pre	400 TID	1200 2 h pre	2400 mg on day of surgery; 1800 mg/d until postop day 5
Treatment control(s)	Placebo	Placebo mexiletine	Placebo	Placebo	Placebo	Placebo
N (Gbp/Plc)	31/34	22/24	25/25	23/23	37/35	22/27
Nonopioid analgesic	None	Acetaminophen	Diclofenac	Topical EMLA LA infiltration	None	Rofecoxib
Significant pain <sup>a</sup> reduction compared with placebo	+ (for movement pain)	+	+	+	+	0
Significant opioid sparing <sup>a</sup> compared with placebo	+	+	+	+	+	+
Adverse effects	ns	Not reported	More sedation	Not reported	ns	More dizziness, gait disturbance and vomiting

ns, not statistically significant; + indicates significant pain intensity difference between gabapentin and placebo groups; 0 indicates no significant pain intensity difference between gabapentin and placebo groups.

<sup>a</sup>Refers only to gabapentin-placebo comparison and refers to pain at rest unless otherwise specified.

In an oral surgery analgesic trial, 300 mg of pregabalin provided a significantly higher pain intensity difference than placebo [31], with a slightly lower peak effect but longer duration of action than the trial's active comparator, ibuprofen 400 mg [31]. Doses of 150 mg of pregabalin reduced both pain and opioid consumption (compared with placebo) following spinal surgery and observed efficacy was further enhanced with the addition of celecoxib [109\*]. In a recent RCT of patients receiving oxycodone, paracetamol and ibuprofen following laparoscopic hysterectomy, pregabalin 600 mg (but not 300 mg) resulted in significantly less opioid consumption than the active placebo, diazepam, but mean pain scores were similar across all treatment groups and varied between only 0.5 and 1.5 on an 11-point VAS scale [110\*].

### Gabapentin and pregabalin for the treatment of other pain syndromes

Although the focus of this review and the great majority of pain-related treatment studies deal with chronic neuropathic and early postsurgical pain, gabapentin and pregabalin are being studied for the treatment of various other pain conditions. Examples of other pain conditions that may respond to these drugs include chronic daily headache [111], fibromyalgia [112,113\*], acute herpes zoster pain [114], chronic pelvic pain [115] and orofacial muscle pain [116\*].

### Safety and tolerability of gabapentin in chronic neuropathic pain

Gabapentin is considered a relatively safe and well tolerated drug after over a decade of marketing and widespread international use. Despite the challenges in

demonstrating treatment-related causality with observed adverse events, several adverse event reports involving gabapentin bear mentioning. Several case reports have described various adverse events following abrupt [117–120] or even tapered [121] withdrawal of gabapentin, including tachycardia, diaphoresis, headache, gastrointestinal cramps, catatonia and, in one case, status epilepticus in the absence of a preexisting seizure disorder [119]. Other reports suggest the possibility that gabapentin induces various movement disorders, including myoclonus, dystonia and asterixis [122–126], which may be a cause of falls [126]. Two different case reports have suggested that gabapentin may exacerbate myasthenia gravis [127,128]. Single case reports have implicated gabapentin as contributing to psychomotor agitation [129], renal allograft dysfunction [130], amenorrhea [131], arthralgia [132], aggressive behavior in children [133], painful gynecomastia [134], cutaneous leukocytoclastic vasculitis [135] and neutropenia [136].

Table 11 describes adverse event frequencies from several published gabapentin RCTs in neuropathic pain. As with the treatment of epilepsy [137], these data indicate that the most common adverse effects of gabapentin are somnolence, dizziness and ataxia. These symptoms are generally dose-related and reversible following dose reduction. Other signs or symptoms reported in more than 10% of patients, in at least two RCTs, include peripheral edema, lethargy, headache and diarrhea (see Table 11). These events were not, however, necessarily significantly more frequent than with placebo. Of relevance to patients with painful diabetic neuropathy, gabapentin treatment did not appear to adversely affect glycemic control in diabetic patients [26].

**Table 10 Perioperative RCTs of pregabalin**

	Hill, 2001 [31]	Reuben, 2006 [109*]	Jokela, 2007 [110*]
Trial quality score	3	4	5
Procedure	Third molar extraction	Spinal fusion	Laparoscopic hysterectomy
Single compared with multidose	Single	Multi	Multi
Dose (mg)	50; 300	150 mg (1 h preop & 12 h postop)	300; 600 (1 h preop & 12 h postop)
Treatment control(s)	Placebo; ibuprofen	Placebo; celecoxib; p-c combo	Diazepam (1 h preop)/placebo (12 h postop)
N (Pgb/Plc)	99/50	20/20	54/29
Nonopioid analgesic	None	None	Paracetamol ibuprofen
Significant pain <sup>a</sup> reduction compared with placebo	+	+	0
Significant opioid sparing <sup>a</sup> compared with placebo	Not reported	+	+
Adverse effects	ns	ns	More dizziness, blurred vision & headache less pruritus

ns, not statistically significant; Pgb, pregabalin; Plc, placebo; + indicates significant pain intensity difference between gabapentin and placebo groups; 0 indicates no significant pain intensity difference between gabapentin and placebo groups.

<sup>a</sup>Refers only to gabapentin-placebo comparison and refers to pain at rest unless otherwise specified.

### Safety and tolerability of pregabalin in chronic neuropathic pain

Being a newer drug, fewer postmarketing safety data are available for pregabalin. As with gabapentin, the most frequent adverse events described with pregabalin include somnolence, dizziness, ataxia and peripheral edema [138]. Pregabalin, too, has been implicated in the onset of movement disorders such as myoclonus [139] and asterixis [140], and a single case report has described encephalopathy and edema of the splenium of the corpus callosum following abrupt discontinuation of pregabalin [141]. Limited evidence suggesting subjective drug 'liking' in a study of pregabalin in recreational sedative/hypnotic drug users, as well as withdrawal symptoms upon pregabalin discontinuation, have led the US Drug Enforcement Administration to list pregabalin as a Schedule V narcotic of the Controlled Substances Act (low potential for abuse) [138]. Less than 5% of patients from all pregabalin RCTs reported euphoria as an adverse event, however.

Table 12 shows reported frequencies of adverse effects from several pregabalin RCTs in neuropathic pain. Data suggest that, as with gabapentin, the most common adverse effects of pregabalin are somnolence, dizziness and peripheral edema. In at least two RCTs, various other adverse events have been reported in more than 10% of patients, including headache, weight gain and dry mouth (see Table 12). These events were not necessarily significantly more frequent than with placebo, however. Pregabalin, too, did not appear to adversely affect glycemic control in diabetic patients [55].

### Safety and tolerability of gabapentin and pregabalin in early postsurgical pain

Three gabapentin trials did not formally report on adverse effects [84\*,98,100], and 16 RCTs reported no significant difference in side effects between gabapentin and placebo (see Tables 7–9). It should be emphasized,

however, that given variable methods of assessment, most trials were not statistically powered to detect such differences in adverse effects. More frequent sedation was reported with gabapentin in three trials [80,82,99]; more nausea was reported with gabapentin in one trial [80], more dizziness in two RCTs [95\*,102\*], and gait disturbance and vomiting were reported more frequently with gabapentin in one trial [102\*]. Single RCTs reported that, compared with placebo, gabapentin was associated with less frequent vomiting [88], urinary retention [88], postoperative delirium [93\*] and headache [94\*]. It should be noted that only one of the 21 RCTs showing opioid sparing also reported a reduction in opioid-related side effects [88]. Several trials reported no significant differences between gabapentin and controls with respect to heart rate, blood pressure or respiratory rate during the postoperative period [78,86\*,88]. Fassoulaki *et al.* reported that 400 mg of gabapentin blunted the blood pressure, but not the heart rate, increase during laryngoscopy [142\*], whereas Memis *et al.* reported that 800 mg blunted both blood pressure and heart rate increases during laryngoscopy [143\*].

Of the three postoperative pregabalin RCTs, two reported no significant difference in adverse effects [31,109\*]. The third RCT of pregabalin 300 and 600 mg following laparoscopic hysterectomy reported more frequent headache, dizziness and blurred vision and less frequent pruritus [110\*]. Reuben *et al.* reported no significant differences between pregabalin and controls with respect to heart rate, blood pressure or respiratory rate during the postoperative period [109\*].

### Summary: chronic neuropathic pain

From the trials listed in Tables 3–6, gabapentin was studied in a total of 1022 patients and pregabalin was studied in a total of 1341 patients. Only five of the 18 gabapentin trials and none of the pregabalin trials presented were unable to demonstrate a difference

Table 11 Adverse event frequencies from neuropathic pain RCTs of gabapentin

	Rowbotham, 1998 [27]	Backonja, 1998 [26]	Gorson, 1999 [51]	Morello, 1999 [52]	Simpson, 2001 [53]	Rice, 2001 [59]	Tai, 2002 [65]	Bone, 2002 [68]	Serpelli, 2002 [71]	Pandey, 2002 [72]	Levendoglu, 2004 [66]	Caraceni, 2004 [74]	van de Vusse, 2004 [67]	Hahn, 2004 [67]	Gilron, 2005 [57]
Dizziness (%)	24	24 <sup>a</sup>		28	22	33	NR	11	24			9	37 <sup>a</sup>	80 <sup>a</sup>	6
Somnolence (%)	27	23 <sup>a</sup>	15	48	22	20	NR	37	14		15	23	28 <sup>a</sup>	60	10
Ataxia (%)	7		8	20		11	NR							47	2
Peripheral edema (%)	10			12		11	NR				15				2
Lethargy (%)				16			NR								
Headache (%)		11		8	12		NR	11	9		5	1	20 <sup>a</sup>	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								4
Cognitive dysfunction (%)							NR								
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 % of patients receiving drug and reporting the listed adverse event. 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. NR, not reported. Modified from [6].

<sup>a</sup> Incidence of adverse event significantly more frequent than with placebo.

**Table 12 Adverse event frequencies from neuropathic pain RCTs of pregabalin**

	Lesser, 2004 [54]	Rosenstock, 2004 [55]	Richter, 2005 [56]	Dworkin, 2003 [61]	Sabatowski, 2004 [62]	van Seventer, 2006 [63*]	Freyenhagen, 2005 [58]
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 % of patients receiving drug and reporting the listed adverse event. 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. Modified from [6\*].

between active treatment and control. Two of the negative gabapentin trials were very small studies [65,69]: one used only 900 mg/day [51]; one used lorazepam as an active placebo and showed important differences in multiple secondary pain outcomes [57], and one involved patients with CRPS type 1 [67]. Of note, all eight pregabalin trials published to date were large, multicenter, industry-sponsored RCTs. A recent systematic review by Finnerup *et al.* [1] 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] based on 10 of the 18 gabapentin RCTs and five of the eight pregabalin RCTs reviewed here [1]. Their initial NNT estimate for all doses of gabapentin was 5.1 (4.1–6.8); however, after excluding the low-dose RCT (900 mg/day) by Gorson *et al.* [51] and the lower dose arm (1800 mg/day) of the Rice *et al.* RCT [59], a revised NNT estimate for gabapentin was reported as 3.8 (3.1–5.1) [1]. The NNT for pregabalin, including doses ranging from 150 to 600 mg/day, was estimated to be 4.2 (3.4–5.4) [1]. 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 suggests that the efficacy of gabapentin and pregabalin is perhaps slightly less than that of tricyclic antidepressants (NNT = 2–3) or morphine (NNT = 2.5) [1]. The review by Finnerup *et al.* further reported a combined number needed to harm (NNH, the number of patients that need to be treated for one patient to drop out due to adverse effects) for gabapentin and pregabalin of 17.8, which suggests comparable tolerability with that of opioids

(NNH = 17.7) and somewhat better tolerability than tricyclic antidepressants (NNH = 14.7).

### Summary: early postsurgical pain

As can be appreciated by several recent postoperative meta-analyses (Table 1), drawing broad-ranging conclusions on the clinical utility of gabapentin and pregabalin for postoperative pain is currently very challenging, due to heterogeneity of available RCTs with respect to surgical procedure and patient population, trial design and quality, outcome measures used, drug dose and duration of treatment. Nevertheless, a majority (21 of 30) of published placebo-controlled, double-blind, randomized trials have demonstrated postoperative analgesic efficacy with gabapentin and pregabalin, and a small number of comparative trials suggest that their analgesic and opioid-sparing efficacy is roughly comparable with that of nonsteroidal anti-inflammatory drugs [82,83\*,109\*] and is perhaps superior to mexiletine [98], acetaminophen [98] and tramadol [80]. An important feature of gabapentin and pregabalin is their efficacy for movement-evoked pain which, in some studies, was associated with accelerated postoperative functional recovery [82,91]. Sedation or dizziness occurred more frequently with gabapentin or pregabalin in six of 30 trials [80,82,95\*,99,102\*,110\*]. Although the majority of trials (22 of 30) reported opioid-sparing effects with gabapentin or pregabalin, only one of these trials reported a concurrent reduction in opioid-related adverse effects [88].

### Conclusion

Multiple, large high-quality RCTs have demonstrated the safety and efficacy of gabapentin and pregabalin in

neuropathic pain, leading to their recommendation as first-line neuropathic pain treatments by several experts [1,64,144,145,146]. Improvement of neuropathic pain and sleep with gabapentin or pregabalin has been shown to positively impact upon quality of life. Sedation, dizziness and ataxia are important and relatively common adverse effects of these drugs, however. Patients suffering from neuropathic pain might benefit from additional research, which addresses several questions. For example, how do gabapentin and pregabalin compare with each other and to other neuropathic pain treatments? What is the efficacy of pregabalin in neuropathic pain conditions other than DPN and PHN? How do gabapentin and pregabalin interact with other neuropathic pain drugs in the setting of analgesic polypharmacy for neuropathic pain? What is the analgesic efficacy and safety of these drugs in special populations (e.g. children, pregnancy/lactation, elderly etc.)? Can novel preparations (e.g. sustained-release) of gabapentin/pregabalin or perhaps even other novel 'alpha-2-delta ligands' improve the current treatment of neuropathic pain? Are gabapentin and pregabalin effective analgesics for other nonneuropathic chronic pain conditions?

Contrary to previous beliefs that postinjury pain and chronic neuropathic pain are entirely separate entities, accumulating evidence indicates that anticonvulsants such as gabapentin and pregabalin actually have important analgesic effects following surgery [11]. Multiple high-quality (but relatively smaller-sized) RCTs have demonstrated analgesic and opioid-sparing efficacy following a wide variety of surgical procedures. An important benefit of treatment with gabapentin or pregabalin is the reduction of movement-evoked pain that has been related to acceleration of functional postoperative recovery. Postoperative opioid sparing with gabapentin/pregabalin is of questionable clinical relevance since very few RCTs have shown any reduction in opioid-related adverse effects. Sedation, dizziness and gait disturbances have been reported in only a small proportion of published RCTs. Broad-ranging conclusions on the perioperative safety of gabapentin/pregabalin cannot be made, however, because of the safety assessment methods and small RCT sizes available.

It is well recognized that selection of postoperative analgesic treatment regimens depends largely on the type of surgery [147]. Given the variable degrees of tissue injury, physiological impact and analgesic response across different surgical procedures, it has been suggested that pooled efficacy estimates for a given analgesic treatment (e.g. number-needed-to-treat) should be related to specific surgical procedures [148]. Thus, given the heterogeneity and relatively small sizes of published RCTs, future efforts should be directed towards larger multicenter trials of gabapentin or pregabalin, following

specific procedures where these drugs may have maximal impact with a major focus on safety, efficacy and functional recovery. Since the sedating effects of gabapentin/pregabalin may be partially mitigated by opioid sparing, administration of gabapentin/pregabalin would be best suited for procedures, and at postoperative timepoints, normally associated with substantial opioid administration. Surgical patients might benefit from additional research that addresses several other questions. For example, what is the optimal dose of, and duration of treatment with, gabapentin/pregabalin for the treatment of postoperative pain? Does gradual (i.e. over days to weeks) dose-titration towards maximal doses of gabapentin/pregabalin (e.g. 3600/600 mg/day) improve postoperative analgesic efficacy? How does preoperative gabapentin/pregabalin administration interact with intraoperative anesthetics and analgesics? How do gabapentin/pregabalin interact with other nonopioid analgesics in the setting of postoperative multimodal therapy? What is the feasibility and potential added benefit of human administration of gabapentin/pregabalin via other routes of administration (e.g. intravenous, intrathecal, epidural etc.)? How does perioperative administration of gabapentin/pregabalin affect postsurgical functional recovery? Can perioperative treatment with gabapentin/pregabalin reduce the incidence or severity of chronic postsurgical pain?

Gabapentin and pregabalin bind to the alpha-2-delta subunit of voltage-gated calcium channels and represent a novel class of drugs for the treatment of neuropathic and postsurgical pain. Perhaps the greatest advantage of these drugs is their relative safety, tolerability and ease of use, as well as lack of adverse interactions with other medications. Furthermore, emerging evidence suggests that gabapentin and pregabalin may also be useful for other acute and chronic pain conditions. Further research is needed to better delineate the optimal utility of these drugs for other indications.

### Acknowledgements

This work was supported by CIHR Grant no. 69422, PSI Foundation Grant no. 03-30 and Queen's University Grant no. 383-861. The author wishes to thank Dr Nicole R. Richardson for thoughtful comments made on previous versions of this article. I.G. has received research support from and/or consulted for Pfizer, Merck Frosst, Johnson & Johnson, Ortho-McNeill, and Janssen-Ortho.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 494–495).

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