Pregabalin: Its Pharmacology and Use in Pain Management

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Pregabalin is a new synthetic molecule and a structural derivative of the inhibitory neurotransmitter γ-aminobutyric acid. It is an α_2-δ (α_2-δ) ligand that has analgesic, anticonvulsant, anxiolytic, and sleep-modulating activities. Pregabalin binds potently to the α_2-δ subunit of calcium channels, resulting in a reduction in the release of several neurotransmitters, including glutamate, noradrenaline, serotonin, dopamine, and substance P. In this review, I will discuss the pharmacology of pregabalin and available efficacy studies in pain management. This review will focus on the advances in pregabalin pharmacology since my previous review in 2005.
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This review will focus on the advances in pregabalin pharmacology and the latest studies since my previous review in 2005 (1). Anticonvulsant medications are established treatments for neuropathic pain (2–11). Pregabalin (S-[+]-3-isobutylgaba) was designed as a lipophilic GABA (γ-aminobutyric acid) analog substituted at the 3′-position to facilitate diffusion across the blood-brain barrier (12–14). Pregabalin, like gabapentin, was shown to be effective in several models of neuropathic pain (15–17), incisional injury (18), inflammatory injury (13,19), and formalin-induced injury (13). It is also effective in the treatment of anxiety, and is also a sleep-modulating drug (18–32). Pregabalin increases the duration of nonrapid eye movement and also decreases rapid eye movement sleep in rats (20). In addition, pregabalin has been shown to increase slow-wave sleep in healthy volunteers. Slow-wave sleep has been correlated with the restorative aspects of sleep (33). Pregabalin treatment has been shown to significantly increase the time spent in stages III–IV sleep while decreasing nighttime awakenings (34).

The European Commission, granted Pfizer approval for pregabalin (Lyrica™, Pfizer, New York, NY) in July 2004 in all European Union member states for the treatment of peripheral neuropathic pain and as an adjunctive therapy for partial seizures in patients with epilepsy. The approval was based on results from 10 trials studying more than 9000 patients. In December 2004, the Food and Drug Administration approved pregabalin, for the treatment of neuropathic pain associated with diabetic peripheral neuropathy (DPN) and postherpetic neuralgia (PHN), under the trade name Lyrica. In June 2005, pregabalin was approved as an adjunctive treatment of partial onset epilepsy in adults. More recently, in March 2006, the European Commission approved pregabalin for the treatment of generalized anxiety disorder. The Drug Enforcement Administration has placed pregabalin into Schedule V of the Controlled Substances Act (35), based on results of a small study of 15 recreational "nondependent" drug users, reports of euphoria in controlled clinical trials, and adverse events that were observed when pregabalin was abruptly discontinued.

MECHANISM OF ACTION

The precise mode of action of pregabalin has not been fully elucidated, but it does interact with the same binding site, and has a similar pharmacologic profile, as gabapentin (1-[aminomethyl] cyclohexane acetic acid) (36–39). Its main site of action appears to be on the α_2-δ subunit of presynaptic, voltage-dependent calcium channels (Fig. 1) that are widely distributed throughout the peripheral and central nervous system (40–47). Binding affinity for the α_2-δ subunit, and potency, is six times more than that of gabapentin (48). Up-regulation of the α_2-δ subunit may play an important role in hypersensitization processes (49). Pregabalin appears to produce an inhibitory modulation of neuronal excitability (50), particularly in areas of the central nervous system dense in synaptic connections such as the neocortex, amygdala, and hippocampus (51,52). Ectopic activity is reduced while normal nerve function is unchanged (53). As with gabapentin, pregabalin is inactive at $GABA_A$ and $GABA_B$ receptors, is not converted metabolically into GABA or a GABA antagonist, and it does not alter GABA uptake or degradation (54–56).

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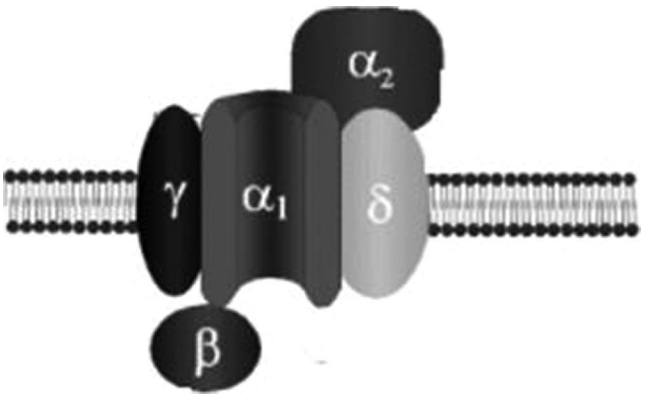


Figure 1. Structure of the calcium channel.

Voltage-dependent calcium channels have been divided into six classes, based on their voltage dependence, kinetics, and sensitivity to a range of drugs (57,58). The molecular structure of these functionally identified P-, Q-, N-, L-, R-, and T-type calcium channels has now been determined (59). N-type calcium channels are thought to have a role in pain sensitization processes (60,61). Calcium channels are made up of five subunits. Pregabalin binds potently to the α_2-δ subunit and modulates calcium influx at nerve terminals, and, thereby, reduces the release of several neurotransmitters, including glutamate, noradrenaline, serotonin, dopamine, and substance P (62–68). Dihydopyridines, such as verapamil, are selective for L-type calcium channels (69). In contrast to these medications, pregabalin has no effect on arterial blood pressure or cardiac function.

Studies have been conducted using the R217A mutant mouse that has a single amino acid substitution of arginine to alanine at position 217 in the α_2-δ subunit, which is presumed to alter its conformation. In these mutant mice, pregabalin binding at the α_2-δ subunit is reduced as is its analgesic action, supporting the hypothesis that the analgesic actions of pregabalin are mediated through its binding to the α_2-δ subunit of voltage-gated calcium channels (70). The mutant mice had otherwise typical responses to analgesic drugs, such as amitriptyline and morphine, and normal pain thresholds.

DOSAGE AND ADMINISTRATION

For painful DPN, the maximum recommended dose of pregabalin is 100 mg thrice a day (300 mg/day). Dosing should begin at 50 mg thrice a day (150 mg/day) and may be increased to 300 mg/day within 1 wk based on efficacy and tolerability. Because pregabalin is eliminated primarily by renal excretion, the dose should be adjusted for patients with reduced renal function. Although pregabalin was also studied at 600 mg/day, which was less well tolerated, there is no evidence that this dose confers additional significant benefit. In view of the dose-dependent adverse effects, treatment of DPN patients with doses larger than 300 mg/day is not recommended.

For PHN, dosing should begin at 75 mg twice a day, or 50 mg thrice times a day (150 mg/day) and may be increased to 300 mg/day within 1 wk based on efficacy and tolerability. Patients who do not experience sufficient pain relief after 2–4 wk of treatment with 300 mg/day, and who are able to tolerate pregabalin, may be treated with up to 300 mg twice a day, or 200 mg thrice a day (600 mg/day).

Converting patients from gabapentin to pregabalin has not been studied. Gabapentin should be discontinued over a minimum of 1 wk before starting pregabalin at a dose of 150 mg/day. There is no contraindication to adding pregabalin to gabapentin, but side effects may be additive.

PHARMACOKINETICS

Absorption of gabapentin is limited by saturable, active, dose-dependent transport in the gastrointestinal tract (71). Therefore, smaller doses, given more frequently, may be required to optimize absorption. Absorption of pregabalin is not saturable, resulting in a linear pharmacokinetic profile (72,73). In healthy volunteers, pregabalin is rapidly absorbed with peak blood concentrations within 1 h (74–76). Average bioavailability exceeds 90% and is independent of dose, which may produce a more predictable patient response. The elimination half-life of pregabalin ranges from 5.5 to 6.7 h, and is independent of dose and repeated dose administration. In contrast to pregabalin, the rate of gabapentin absorption is relatively slow, with peak plasma concentrations occurring around 3 h postdose.

Pregabalin does not undergo hepatic metabolism and is not bound to plasma proteins. It is renally excreted, and 98% of the absorbed dose is excreted unchanged in the urine. Pregabalin elimination is nearly proportional to creatinine clearance. Pregabalin clearance is reduced in subjects with impaired renal function. A 50% reduction in pregabalin daily dose is recommended for patients with creatinine clearance (CLcr) between 30 and 60 mL/min compared with those with CLcr >60 mL/min (77). After a 4-h hemodialysis treatment, plasma pregabalin concentrations are reduced by approximately 50%.

No pharmacokinetic drug-drug interactions have been identified in formal interaction studies and, based on the pharmacokinetic profile, none is expected (78,79).

SIDE EFFECTS AND PRECAUTIONS

Pregabalin is well tolerated (80) and associated with dose-dependent adverse effects that are mild-to-moderate and are usually transient (Table 1). In clinical trials, dizziness and somnolence are the most frequently reported adverse events, with dizziness experienced by 29% of pregabalin-treated patients compared with 9% with placebo and somnolence, experienced by 22% of pregabalin-treated patients

Table 1. Incidence of Adverse Events with Pregabalin in all Controlled Studies

Somnolence	29.2
Dizziness	22.2
Dry mouth	9.1
Peripheral edema	6.1
Blurred vision	6.4
Weight gain	5.6
Thinking abnormal[a]	5.4

All values are given in percentages.

[a] Primarily difficulty with concentration or attention.

compared with 8% with placebo (81). Dose-dependent weight gain has been reported (82). There have been case reports of myoclonus (83) aterixis (84), gynecomastia (85), and a single case report has described encephalopathy and edema of the corpus callosum after abrupt discontinuation of pregabalin (86).

As with all antiepileptic drugs, pregabalin should be withdrawn gradually to minimize the potential of increased seizure frequency in patients with seizure disorders. If pregabalin is discontinued, the dose should be gradually tapered over a minimum of 1 wk. There are no head-to-head studies comparing the side effects of pregabalin versus gabapentin. The trials involving gabapentin have usually used variable doses (87,88), whereas the trials with pregabalin used fixed dosing without titration. Differences in study design may influence the reported incidence of side effects. Nonetheless, comparing available studies, side effect profiles appear similar, with the exception perhaps of a more frequent incidence of nausea and diarrhea with gabapentin (89). Pregabalin is contraindicated in patients with a known hypersensitivity to pregabalin or any of its components.

STUDIES

Volunteer Studies

Thirty-two healthy volunteers received either oral pregabalin (titrated to 300 mg) or aprepitant, an NK_1 antagonist (titrated to 320 mg), or matching placebo over 6 days (50). Aprepitant was used as an example of a drug class active in animal models, but not in neuropathic pain patients. Central sensitization was then invoked by repetitive stimulation of the skin. Sensitization was assessed over 3 h. At 2 h, subjects received either parecoxib (40 mg) or IV saline. Pregabalin significantly reduced the areas of punctate mechanical hyperalgesia and dynamic touch allodynia versus placebo. No significant reduction in the area of hyperalgesia or allodynia versus placebo was observed with aprepitant. In the pregabalin and parecoxib-treated group, the area of allodynia was significantly reduced and the area of hyperalgesia insignificantly attenuated versus placebo and parecoxib. No efficacy improvement was observed with aprepitant and parecoxib.

Painful DPN

Rosenstock et al. (90) evaluated the effectiveness of pregabalin in alleviating pain associated with DPN. Patients were randomized to receive placebo or pregabalin 100 mg TID, without an initial titration phase. The primary efficacy measure was end-point mean pain score from daily patient diaries (11-point numerical pain rating scale). Secondary measures included Short Form McGill Pain Questionnaire (SF-MPQ) scores; sleep interference scores; Patient and Clinical Global Impression of Change (PGIC and CGIC); Short Form-36 (SF-36) Health Survey scores; and Profile of Mood States scores. Safety assessment included incidence and intensity of adverse events, physical and neurologic examinations, and laboratory evaluations. Pregabalin produced significant improvements versus placebo for mean pain scores, mean sleep interference scores, total SF-MPQ score, SF-36 Bodily Pain subscale, PGIC, and Total Mood Disturbance and Tension–Anxiety components of Profile of Mood States. Pain relief and improved sleep began during week 1 and remained significant throughout the 8-wk study. Pregabalin was well tolerated despite a more frequent incidence of dizziness and somnolence than placebo. Most adverse events were mild-to-moderate and did not result in patient withdrawal.

In a study by Lesser et al. (91), patients were randomized to receive pregabalin 300 or 600 mg/day or placebo. Pregabalin 600 mg/day was titrated over 6 days; smaller doses were initiated on day 1. Patients in the pregabalin 300 and 600 mg/day pregabalin groups showed improvements in end-point mean pain score compared with those in the placebo. Improvements were also seen in weekly pain score, sleep interference score, PGIC, CGIC, SF-MPQ, and multiple domains of the SF-36 Health Survey. Improvements in pain and sleep were seen as early as week 1 and were sustained throughout the 5-wk study period. Responders (50% reduction in pain compared with baseline) were 46% (300 mg/day), 48% (600 mg/day), and 18% (placebo). For this responder rate analysis, patients who did not complete the study were assigned a 0% improvement, known as baseline observation carried forward analysis. There was no evidence of a greater effect on pain scores of the 200 mg TID dosing compared with 100 mg TID, but there was evidence of dose-dependent adverse events. Pregabalin was well tolerated with a low discontinuation rate. The most common adverse events were dizziness and somnolence.

A 6-wk, randomized, double-blind, multicenter study evaluated the efficacy of pregabalin in the treatment of painful DPN (92). Patients with DPN received pregabalin (50 mg or 200 mg TID) or placebo. The primary efficacy variable was mean pain score at the end of treatment. Pregabalin 600 mg/day significantly decreased mean pain score to 4.3 (versus 5.6 for placebo) and increased the proportion of patients who had a ≥50% decrease from baseline pain (39% vs 15% for placebo). Pregabalin also significantly reduced sleep

interference, past week and present pain intensity, sensory and affective pain scores, and bodily pain and decreased by ≥50% the number of patients describing their pain as gnawing, sickening, fearful, and punishing-cruel. More patients receiving pregabalin 600 mg/day than placebo showed improvement, as rated on the PGIC/CGIC scales, 73% vs 45% and 85% vs 47%, respectively. Pregabalin 150 mg/day was essentially no different from placebo. Dizziness was the most common side effect.

PHN

Sabatowski et al. (82) assessed the efficacy and safety of pregabalin for treating neuropathic pain in patients with PHN. Patients were randomized to receive pregabalin 150 mg/day, pregabalin 300 mg/day, or placebo for 8 wk. Those who had failed to respond to previous treatment with gabapentin at doses of 1200 mg/day or more were excluded. Patients were allowed to continue a stable treatment regime of acetaminophen (up to 3 g/day), nonsteroidal antiinflammatory drugs, opioid or non-opioid analgesics, or antidepressants. End-point mean pain scores were significantly reduced in patients receiving pregabalin 150 mg/day or 300 mg/day compared with placebo. Efficacy was observed as early as week 1, and was maintained throughout the study. Significantly, more patients in both pregabalin groups (150 mg, 26%; 300 mg, 28%) were responders (50% or more decrease in mean pain score from baseline to end point) than in the placebo group (10%). Additionally, by week 1 and for the study's duration, pregabalin 150 and 300 mg/day significantly reduced weekly mean sleep interference scores. More patients in the pregabalin group reported that they were "much improved" or "very much improved" compared with patients in the placebo group. Health-related quality-of-life measurements using the SF-36 Health Survey demonstrated improvement in the mental health domain for both pregabalin dosages, and bodily pain and vitality domains were improved in the 300 mg/day group. The most frequent adverse events were dizziness, somnolence, peripheral edema, headache, and dry mouth.

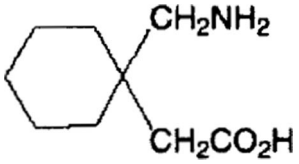
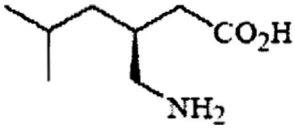
Dworkin et al. (93) conducted a multicenter, parallel-group, double-blind, placebo-controlled, 8-wk, randomized clinical trial in PHN, defined as pain for three or more months after herpes zoster rash healing. Patients were randomized to receive pregabalin either 600 mg/day (CLcr >60 mL/min) or 300 mg/day (CLcr 30–60 mL/min). The primary efficacy measure was the mean of the last seven daily pain ratings. Secondary end points included additional pain ratings, sleep interference, quality-of-life, mood, and patient and clinician ratings of global improvement. Pregabalin-treated patients had greater decreases in pain than patients treated with placebo (end-point mean scores 3.60 vs 5.29). Pain was significantly reduced in the pregabalin-treated patients after the first full day of treatment and throughout the study, and significant improvement on the SF-MPQ total, sensory, and affective pain scores was also found. The proportions of patients with 30% or more and 50% or more decreases in mean pain scores were larger in the pregabalin than in the placebo group (63% vs 25% and 50% vs 20%). Sleep also improved in patients treated with pregabalin compared with placebo. Both patients and clinicians were more likely to report global improvement with pregabalin than with placebo. The number needed to treat (NNT) is the number of patients needed to be treated by an intervention to obtain a defined outcome (94). In this study, the NNT for pregabalin-associated decreases in end-point mean pain scores ≥30% was 2.7 and for decreases in end-point mean pain scores ≥50% was 3.4. These NNT are comparable to previous studies of gabapentin, tricyclic antidepressants, and opioid analgesics (95–99). Also, although few systematic comparisons of differences in side effects among the medications used in the treatment of PHN have been conducted (97), the number needed to harm for pregabalin based on all side effects was 4.3, which is also comparable to previous studies of gabapentin, tricyclic antidepressants, and opioid analgesics (97,99,100). Thirty-two percent of subjects discontinued pregabalin because of dizziness, somnolence, or other side effects, compared with 5% receiving placebo.

van Seventer et al. (31) evaluated the efficacy and safety of pregabalin 75, 150, or 300 mg given BID compared with placebo in patients with PHN. Patients with pain for ≥3 mo after skin rash healing were randomized in a multicenter, 13-wk, double-blind, placebo-controlled study. Compared with placebo, all dosages of pregabalin were significantly more effective at relieving pain. Weekly mean pain scores in each pregabalin group were also significantly improved, compared with placebo, by week 1, and improvement was maintained through week 13. Most adverse events were mild or moderate, and only 13% of patients treated with pregabalin and 4% of patients in the placebo group withdrew because of treatment-related adverse events. Among pregabalin-treated patients, the adverse events that most often led to discontinuation were dizziness, somnolence, and ataxia.

Other Neuropathic Pain Studies

A12-wk randomized, double-blind, multicenter, placebo-controlled, parallel-group study evaluated the efficacy and safety of pregabalin in patients with PHN or painful DPN (101). Patients were randomized to receive placebo or 1 of 2 pregabalin regimens: a flexible schedule of 150, 300, 450, and 600 mg/day with weekly dose escalation based on patients' individual responses and tolerability or a fixed schedule of 300 mg/day for 1 wk, followed by 600 mg/day for 11 wk. Both flexible- and fixed-dose pregabalin significantly reduced end-point mean pain score versus placebo. The NNT for at least a 50% reduction in pain was

Table 2. Comparision of Gabapentin and Pregabalin

Structure	Gabapentin	Pregabalin
		
Bioavailability	27%–60%	90%
T_{max} (hrs)	2–3	1
Plasma protein binding	<3%	0
Potency	+	++++++
$t_{½}$ (hrs)	5–7	5.5–6.7
Metabolism	None	None
Elimination	Renal (100% unchanged)	Renal (92–99% unchanged)
Dosing Schedule	TID	BID/TID
Controlled Substance	No	Schedule V
Neuropathic pain dose	1800–3600 mg/day	150–600 mg/day
Time to effective dose	9 days[a]	1 day

[a] Recommended titration.

calculated to be 3.6 for patients in the fixed-dose arm, 4.2 for patients in the flexible-dose arm, and 3.8 for all pregabalin-treated patients. The most common adverse events for pregabalin-treated patients were dizziness, peripheral edema, weight gain, and somnolence.

D'Urso De Cruz et al. (102) evaluated the long-term efficacy and safety of pregabalin for the treatment of neuropathic pain associated with DPN or PHN in treatment-refractory patients. All patients had previously participated in double-blind or open-label trials. Patients had documented inadequate pain relief or intolerable adverse events to a tricyclic antidepressant (≥75 mg/d, ≥2 wk); gabapentin (≥1800 mg/d, ≥2 wk); and a third-line pain treatment (≥2 wk). Patients received pregabalin 150–600 mg/day titrated to effectiveness and tolerability. Concomitant analgesics, including gabapentin, were allowed as needed. Pregabalin was discontinued during a drug holiday at 3-mo intervals to evaluate the continuing presence of neuropathic pain and the continuing need for treatment. Only patients whose pain relapsed during a drug holiday (i.e., pain became moderately, much, or very much worse) resumed trial participation. Baseline visual analog scale scores for DPN and PHN patients were 73 and 75 mm. At the end of the first 15 study months, mean visual analog scale scores for DPN and PHN patients were 47 and 48 mm. At 3 mo, 45% and 36% of DPN and PHN patients reported pain reductions ≥50%, and at 15 mo, 36% and 38% of patients reported similar reductions. The median duration of drug holidays was 3 days. All but four patients experienced pain exacerbation during drug holidays. Most common adverse events were dizziness, somnolence, and peripheral edema. Ten patients withdrew because of adverse events. It is noteworthy that two studies did not exclude gabapentin nonresponders (31,101).

A 12-wk, multicenter study randomized patients to receive flexible-dose pregabalin 150–600 mg/day or placebo administered BID (103). Patients were allowed to continue on existing, stable pain therapy. The primary efficacy variable was the end-point mean pain score, derived from patients' last 7 days daily pain diary entries. Key secondary end points included pain responder rates, the SF-MPQ, sleep interference, mood, and the PGIC. The mean end-point pain score was lower in the pregabalin group (4.62) than in the placebo group (6.27; $P < 0.001$), with efficacy observed as early as week 1 and maintained for the duration of the study. The average pregabalin dose after the 3-wk stabilization phase was 460 mg/day. Pregabalin was significantly superior to placebo in end-point assessments on the SF-MPQ. The 30% and 50% pain responder rates were higher with pregabalin than with placebo (42% and 22%, respectively). Pregabalin was associated with improvements in disturbed sleep and anxiety, and more patients reported global improvement at end-point assessments in the pregabalin group. Somnolence and dizziness were the most common adverse events and were mild or moderate, and typically transient.

Fibromyalgia

The efficacy and safety of pregabalin up to 450 mg/day (150 mg thrice daily) were evaluated for reducing pain and associated symptoms in patients with fibromyalgia (104). Patients were randomized to receive 150, 300, or 450 mg/day of pregabalin or placebo. Compared with those receiving placebo, patients treated with pregabalin 450 mg/day showed significant improvement in pain scores at week 1, and this was maintained throughout week 7. However, there was no statistically significant improvement from placebo at week 8. Reasons for the loss of a statistically significant difference at week 8 may include reduced statistical power at later time points or lack of durability of analgesic effect. Patients receiving 300 and 450 mg/day pregabalin also experienced reduced fatigue and improved sleep quality compared

Table 3. Analgesia Studies: Prospective, Randomized, Double-Blind, Placebo-Controlled Trials

Authors	Diagnosis	No. patients	Groups	Efficacy/NNT	Comments
DPN					
Rosenstock et al. (90)	Diabetic neuropathy	146	Placebo Pregabalin 100 TID	14.4% 40.0% (NNT 3.92)	8 wk study Acetaminophen and aspirin only allowed
Lesser et al. (91)	Diabetic neuropathy	337	Placebo Pregabalin 300 mg Pregabalin 600 mg	18% 46% (NNT 3.55) 48% (NNT 3.27)	5 wk study
Richter et al. (92)	Diabetic neuropathy	246	Placebo Pregabalin 150 mg Pregabalin 600 mg	15% 18% 39% (NNT 4.24)	6 wk study
PHN					
Sabatowski et al. (82)	PHN	238	Placebo Pregabalin 50 mg TID Pregabalin 100 mg TID	10% 26% (NNT 6.3) 28% (NNT 5.6)	8 wk study Other analgesics allowed
Dworkin et al. (93)	PHN	173	Placebo Pregabalin 100 mg TID Pregabalin 200 mg TID	20% 50% (NNT 3.4)	8 wk study Other analgesics allowed
van Seventer et al. (31)	PHN	370	Placebo Pregabalin 75 mg TID Pregabalin 150 mg TID Pregabalin 300 mg TID	7.5% 26.4% 26.5% (NNT 5.26) 37.5% (NNT 3.31)	13 wk study
Other neuropathic pain studies					
Freynhagen et al. (101)	Diabetic neuropathy and PHN	338	Placebo Pregabalin 150–600 mg/d Pregabalin 600 mg/d	 NNT 4.2 NNT 3.6	12 wk study flexible and fixed doses
D'Urso De Cruz et al. (102)	Refractory neuropathic pain (DPN and PHN)	81	Pregabalin 300–600 mg/d	DPN 36.4% PHN 32.4%	15 mo open label extension study
Siddall et al. (103)	Spinal cord injury	137	Placebo Pregabalin 150–600 mg/d	42% (>30% pain reduction) 22% (>50% pain)	Flexible dosing 12 wk study
Fibromyalgia					
Crofford et al. (104)	Fibromyalgia	529	Placebo Pregabalin 150 mg/d Pregabalin 300 mg/d	 Pregabalin 450 mg superior to placebo	8 wk study
Acute pain studies					
Hill et al. (116)	Postoperative dental pain	189	Placebo Ibuprofen 400 mg Pregabalin 50 mg Pregabalin 300 mg	 Pregabalin 300 mg superior to pregabalin 50 mg and placebo	Single dose study
Reuben et al. (118)	Postoperative spinal fusion surgery	35	Placebo Celecoxib 400 mg Pregabalin 150 mg Celecoxib 400 mg/ pregabalin 150 mg	 Celecoxib 400 mg/pregabalin 150 mg combination more effective then either alone	

PHN = postherpetic neuralgia; DPN = diabetic peripheral neuropathy; NNT = number needed to treat.

with those receiving pregabalin 150 mg/day or placebo. Forty-eight patients (9%) withdrew because of adverse events, and 44 patients (8%) withdrew because of lack of efficacy. The most common adverse events were dizziness and somnolence.

Acute Pain

Sensitization of dorsal horn neurons has been demonstrated in acute pain models (105,106) and may also play a role in the development of chronic pain after surgery (107,108). By reducing the hyperexcitability of dorsal horn neurons induced by tissue damage, gabapentin and pregabalin may have roles in the treatment of postoperative pain (109–111). However, the optimal doses of these medications still require further study (112). Since patients may be anxious in the perioperative period, the anxiolytic effects of gabapentin and pregabalin may be beneficial. In addition, gabapentin, and perhaps pregabalin, may prevent opioid tolerance (113,114). Interestingly, gabapentin and pregabalin may have some therapeutic use in the treatment of opioid dependence (115).

A randomized, double-blind, placebo-controlled, parallel-group trial was performed to compare pregabalin 50 and 300 mg with placebo and ibuprofen 400 mg using a dental pain model (116). Study medication was administered postoperatively to patients who had undergone elective surgery to remove one- or two-third molars, at least one of which was mandibular and fully or partially impacted in bone. Primary efficacy variables included pain relief, pain intensity difference, pain relief intensity difference, time to onset of analgesia, and duration of analgesia. The patient's global impression of the study medication was used as a secondary efficacy variable. There were statistically significant differences in pain relief, pain intensity difference, and pain relief intensity difference between the 300 mg pregabalin group and placebo. In addition, the 300 mg pregabalin group had a significantly longer duration of analgesia than the ibuprofen group and had the highest score on the patient global impression of study medication. The median time to onset of analgesia was shorter for patients treated with ibuprofen (16 min) than for those receiving pregabalin 300 mg (23.5 min), although this difference was not statistically significant. Adverse events were reported more often in the pregabalin 300 mg group. Of the 50 patients receiving pregabalin 300 mg, 24 (48%) experienced side effects, most commonly dizziness, somnolence, and vomiting. Interestingly, another study in a rat model suggested that the use of gabapentin or pregabalin in small-dose combinations with naproxen may afford therapeutic advantages for clinical treatment of persistent inflammatory pain (117).

In a recent study, 80 patients undergoing elective spinal fusion surgery were randomized to receive placebo, celecoxib 400 mg, pregabalin 150 mg, or a combination of celecoxib 400 mg and pregabalin 150 mg orally 1 h before induction of anesthesia (118). Patients underwent general anesthesia. Postoperatively, patients received patient-controlled analgesia using morphine. Twelve hours after initial study drug administration, patients were given placebo, celecoxib 200 mg, pregabalin 150 mg, or a combination of celecoxib 200 mg and pregabalin 150 mg orally. The combination of pregabalin and celecoxib significantly reduced pain and opioid use compared with the use of either analgesic alone.

SUMMARY AND FUTURE DIRECTIONS

Pregabalin is a new synthetic molecule with a favorable pharmacokinetic profile compared with gabapentin (Table 2). Analgesic efficacy for neuropathic pain has been well studied and significant decreases in pain scores are typically seen by day 2 (119) (Table 3). Pregabalin is a valuable addition to the still-limited options for the treatment of neuropathic pain (120–129) and may be more cost-effective than high doses of gabapentin (130,131). It can be effective in patients who have previously failed to respond to gabapentin (102). Studies are required to define outcomes, benefits, and side effects compared with gabapentin as well as other therapies for neuropathic pain (132,133). The mechanism of action of pregabalin also requires further study. Pregabalin will likely be studied as part of a multimodal approach to pain management and, like gabapentin, is likely to prove useful for the treatment of a wide variety of chronic pain (134–154) syndromes as well as for acute postoperative pain (155) and inflammatory pain. Other uses of pregabalin also need to be more clearly defined (156,157).

REFERENCES

1. Gajraj NM. Pregabalin for pain management. Pain Pract 2005;5:95–102
2. Tremont-Lukats I, Megeff C, Backonja M. Anticonvulsants for neuropathic pain syndromes: mechanisms of action and place in therapy. Drugs 2000;60:1029–52
3. Dickenson AH, Matthews EA, Suzuki R. Neurobiology of neuropathic pain: mode of action of anticonvulsants. Eur J Pain 2002;6:51–60
4. Dubinsky RM, Kabbani H, El-Chami Z, Boutwell C, Ali H. Practice parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2004; 63:959–65
5. Beydoun A, Backonja M. Mechanistic stratification of antineuralgic agents. J Pain Symptom Manage 2003;25:S18–S30
6. Gilron I, Watson C, NP, Cahill CM, Moulin DE. Neuropathic pain: a practical guide for the clinician. CMAJ 2006;175:265–75
7. Mellegers M, Furlan A, Mailis A. Gabapentin for neuropathic pain: systematic review of controlled and uncontrolled literature. Clin J Pain 2001;17:284–95
8. Attal N, Cruccu G, Haanpaa M, Hansson P, Jensen TS, Nurmikko T, Sampaio C, Sindrup S, Wiffen P. EFNS guidelines on pharmacological treatment of neuropathic pain. Eur J Neurol 2006;13:1153–69
9. Stefan H, Feuerstein TJ. Novel anticonvulsant drugs. Pharmacol Ther 2006;113:165–83
10. Dickenson A, Ghandehari J. Anti-convulsants and anti-depressants. Handb Exp Pharmacol 2007;177:145–77
11. Forde G. Adjuvant analgesics for the treatment of neuropathic pain: evaluating efficacy and safety profiles. J Fam Pract 2007;56:3–12
12. Lauria-Horner B, Pohl R. Pregabalin: a new anxiolytic. Expert Opin Investig Drugs 2003;12:663–72
13. Field M, Oles R, Lewis A, McCleary S, Hughes J, Singh L. Gabapentin (neurontin) and S-(+)-3-isobutylgaba represent a novel class of selective antihyperalgesic agents. Br J Pharmacol 1997;121:1513–22
14. Feng M, Turluck D, Burleigh J, Lister R, Fan C, Middlebrook A, Taylor C, Su T. Brain microdialysis and PK/PD correlation of pregabalin in rats. Eur J Drug Metab Pharmacokinet 2001;26:123–8
15. Partridge B, Chaplan S, Sakamoto E, Yaksh T. Characterization of the effects of gabapentin and 3-isobutyl-γ-aminobutyric acid on substance P-induced thermal hyperalgesia. Anesthesiology 1998;88:196–205
16. Jun J, Yaksh T. The effect of intrathecal gabapentin and 3-isobutyl γ-aminobutyric acid on the hyperalgesia observed after thermal injury in the rat. Anesth Analg 1998;86:348–54
17. Nozaki-Taguchi N, Chaplan SR, Higuera ES, Ajakwe RC, Yaksh TL. Vincristine-induced allodynia in the rat. Pain 2001;93:69–76
18. Field MJ, Holloman EF, McCleary S, Hughes J, Singh L. Evaluation of gabapentin and S-(+)-3-isobutylgaba in a rat model of postoperative pain. J Pharmacol Exp Ther 1997; 282:1242–6
19. Houghton AK, Lu Y, Westlund KN. S-(+)-3-Isobutylgaba and its stereoisomer reduces the amount of inflammation and hyperalgesia in an acute arthritis model in the rat. J Pharmacol Exp Ther 1998;285:533–8

20. Kubota T, Fang J, Meltzer LT, Krueger JM. Pregabalin enhances nonrapid eye movement sleep. J Pharmacol Exp Ther 2001;299:1095–105
21. Field M, McCleary S, Hughes J, Singh L. Gabapentin and pregabalin, but not morphine and amitriptyline, block both static and dynamic components of mechanical allodynia induced by streptozocin in the rat. Pain 1999;80:391–8
22. Stahl S. Anticonvulsants and the relief of chronic pain: pregabalin and gabapentin as α(2)δ ligands at voltage-gated calcium channels. J Clin Psychiatry 2004;65:596–7
23. Diop L, Raymond F, Fargeau H, Petoux F, Chovet M, Doherty AM. Pregabalin (CI-1008) inhibits the trinitrobenzene sulfonic acid-induced chronic colonic allodynia in the rat. J Pharmacol Exp Ther 2002;302:1013–22
24. Wallin J, Cui J-G, Yakhnitsa V, Schechtmann G, Meyerson BA, Linderoth B. Gabapentin and pregabalin suppress tactile allodynia and potentiate spinal cord stimulation in a model of neuropathy. Eur J Pain 2002;6:261–72
25. Eutamene H, Coelho A-M, Theodorou V, Toulouse M, Chovet M, Doherty A, Fioramonti J, Bueno L. Antinociceptive effect of pregabalin in septic shock-induced rectal hypersensitivity in rats. J Pharmacol Exp Ther 2000;295:162–7
26. Stahl S. Mechanism of action of α-2-δ ligands: voltage sensitive calcium channel (VSCC) modulators. J Clin Psychiatry 2004;65:1033–4
27. Pande AC, Crockatt JG, Feltner DE, Janney CA, Smith WT, Weisler R, Londborg PD, Bielski RJ, Zimbroff DL, Davidson JRT, Liu-Dumaw M. Pregabalin in generalized anxiety disorder: a placebo-controlled trial. Am J Psychiatry 2003;160:533–40
28. Pande A, Feltner D, Jefferson J, Davidson J, Pollack M, Stein M, Lydiard R, Futterer R, Robinson P, Slomkowski M. Efficacy of the novel anxiolytic pregabalin in social anxiety disorder: a placebo-controlled, multicenter study. Clin Psychopharmacol 2004;24:141–9
29. Rickels K, Pollack M, Feltner D, Lydiard R, Zimbroff D, Bielski R, Tobias K, Brock J, Zornberg G, Pande A. Pregabalin for treatment of generalized anxiety disorder: a 4-week, multicenter, double-blind, placebo-controlled trial of pregabalin and alprazolam. Arch Gen Psychiatry 2005;62:1022–30
30. Frampton J, Scott L. Pregabalin : in the treatment of painful diabetic peripheral neuropathy. Drugs 2004;64:2813–20
31. van Seventer R, Feister H, Young J, Stoker M, Versavel M, Rigaudy L. Efficacy and tolerability of twice-daily pregabalin for treating pain and related sleep interference in postherpetic neuralgia: a 13-week, randomized trial. Curr Med Res Opin 2006;22:375–84
32. Frampton J, Foster R. Pregabalin: in the treatment of postherpetic neuralgia. Drugs 2005;65:119–20
33. Hindmarch I, Dawson J, Stanley N. A double-blind study in healthy volunteers to assess the effects on sleep of pregabalin compared with alprazolam and placebo. Sleep 2005;28:187–93
34. Freeman R, van Seventer R, Murphy T, Sharma U, Young J. Pregabalin rapidly and significantly improves sleep disturbances in chronic pain syndromes and is associated with sleep improvements in healthy volunteers. American Academy of Neurology 58th. Annual Meeting. April 1–8, 2005;P04.010
35. Drug Enforcement Administration, Department of Justice. Schedules of controlled substances: placement of pregabalin into schedule V. Final rule. Fed Regist 2005;43633–5
36. Chesler EJ, Ritchie J, Kokayeff A, Lariviere WR, Wilson SG, Mogil JS. Genotype-dependence of gabapentin and pregabalin sensitivity: the pharmacogenetic mediation of analgesia is specific to the type of pain being inhibited. Pain 2003;106:325–35
37. Martin DJ, McClelland D, Herd MB, Sutton KG, Hall MD, Lee K, Pinnock RD, Scott RH. Gabapentin-mediated inhibition of voltage-activated Ca^{2+} channel currents in cultured sensory neurones is dependent on culture conditions and channel subunit expression. Neuropharmacology 2002;42:353–66
38. Sills GJ. The mechanisms of action of gabapentin and pregabalin. Curr Opin Pharmacol 2006;6:108–13
39. Rose M, Kam P. Gabapentin: pharmacology and its use in pain management. Anaesthesia 2002;57:451–62
40. Arikkath J, Campbell KP. Auxiliary subunits: essential components of the voltage-gated calcium channel complex. Curr Opin Neurobiol 2003;13:298–307
41. Gee NS, Brown JP, Dissanayake VUK, Offord J, Thurlow R, Woodruff GN. The novel anticonvulsant drug, gabapentin (Neurontin), binds to the α-2-δ subunit of a calcium channel. J Biol Chem 1996;271:5768–76
42. Taylor C. The biology and pharmacology of calcium channel α2-δ proteins. CNS Drug Rev 2004;10:183–8
43. Bryans J, Wustrow D. 3-substituted GABA analogs with central nervous system activity: a review. Med Res Rev 1999;19:149–77
44. Field M, Bramwell S, Cox P, Melrose H, Offord J, Richardson E, Su T, Williams D. The analgesic actions of pregabalin are mediated through its binding to the δ-2–1 subunit of voltage gated calcium channels. American Pain Society Annual Meeting 2004; Poster 802
45. Bian F, Li Z, Offord J, Davis M, McCormick J, Taylor C. Calcium channel α(2)-δ type 1 subunit is the major binding protein for pregabalin in neocortex, hippocampus, amygdala, and spinal cord: an ex vivo autoradiographic study in α(2)-δ type 1 genetically modified mice. Brain Res 2006;1:1–6
46. Belliotti T, Capiris T, Ekhato I, Kinsora J, Field M, Heffner T, Meltzer L, Schwarz J, Taylor C, Thorpe A, Vartanian M, Wise L, Zhi-Su T, Weber M, Wustrow D. Structure-activity relationships of pregabalin and analogues that target the α(2)-δ protein. J Med Chem 2005;48:2294–307
47. Gazulla J, Tintore M. The P/Q-type voltage-dependent calcium channel as pharmacological target in spinocerebellar ataxia type 6: Gabapentin and pregabalin may be of therapeutic benefit. Med Hypotheses 2007;68:131–6
48. Jones D, Sorkin L. Systemic gabapentin and S(+)-3-isobutyl-γ-aminobutyric acid block secondary hyperalgesia. Brain Res 1998;810:93–9
49. Luo ZD, Chaplan SR, Higuera ES, Sorkin LS, Stauderman KA, Williams ME, Yaksh TL. Upregulation of dorsal root ganglion α-2-δ calcium channel subunit and its correlation with allodynia in spinal nerve-injured rats. J Neurosci 2001;21:1868–75
50. Chizh BA, Gohring M, Troster A, Quartey GK, Schmelz M, Koppert W. Effects of oral pregabalin and aprepitant on pain and central sensitization in the electrical hyperalgesia model in human volunteers. Br J Anaesth 2007;98:246–54
51. McClelland D, Evans R, Barkworth L, Martin D, Scott R. A study comparing the actions of gabapentin and pregabalin on the electrophysiological properties of cultured DRG neurones from neonatal rats. BMC Pharmacology 2004;4:14
52. Hill D, Suman-Chauhan N, Woodruff G. Localization of [3H]gabapentin to a novel site in rat brain: autoradiographic studies. Eur J Pharmacol 1993;244:303–9
53. Chen S, Xu Z, Pan H. Stereospecific effect of pregabalin on ectopic afferent discharges and neuropathic pain induced by sciatic nerve ligation in rats. Anesthesiology 2001;95:1473–9
54. Bialer M, Johannessen SI, Kupferberg HJ, Levy RH, Loiseau P, Perucca E. Progress report on new antiepileptic drugs: a summary of the fourth Eilat conference (EILAT IV). Epilepsy Res 1999;34:1–41
55. Welty D, Wang Y, Busch J, Taylor C, Vartanian M, Radulovic L. Pharmacokinetics and pharmacodynamics of CI-1008 (pregabalin) and gabapentin in rats with maximal electroshock [abstract]. Epilepsia 1997;388(suppl):Abstract 1.110
56. Lanneau C, Green A, Hirst W, Wise A, Brown J, Donnier E, Charles K, Wood M, Davies C, Pangalos M. Gabapentin is not a $GABA_B$ receptor agonist. Neuropharmacology 2001;41:965–75
57. Catterall WA. Structure and regulation of voltage-gated Ca^{2+} channels. Annu Rev Cell Dev Biol 2000;16:521–55
58. Jarvis SE, Zamponi GW. Interactions between presynaptic Ca^{2+} channels, cytoplasmic messengers and proteins of the synaptic vesicle release complex. Trends Pharmacol Sci 2001;22:519–25
59. Ertel EA, Campbell KP, Harpold MM, Hofmann F, Mori Y, Perez-Reyes E, Schwartz A, Snutch TP, Tanabe T, Birnbaumer L. Nomenclature of voltage-gated calcium channels. Neuron 2000;25:533–5
60. Matthews EA, Dickenson AH. Effects of spinally delivered N- and P-type voltage-dependent calcium channel antagonists on dorsal horn neuronal responses in a rat model of neuropathy. Pain 2001;92:235–46

61. Cizkova D, Marsala J, Lukacova N, Marsala M, Jergova S, Orendacova J, Yaksh T. Localization of N-type Ca^{2+} channels in the rat spinal cord following chronic constrictive nerve injury. Exp Brain Res 2002;147:456–63
62. Dooley D, Donovan C, Pugsley T. Stimulus-dependent modulation of [3H]norepinephrine release from rat neocortical slices by gabapentin and pregabalin. J Pharmacol Exp Ther 2000;295:1086–93
63. Dooley DJ, Mieske CA, Borosky SA. Inhibition of K^+-evoked glutamate release from rat neocortical and hippocampal slices by gabapentin. Neurosci Lett 2000;280:107–10
64. Fink K, Dooley DJ, Meder WP, Suman-Chauhan N, Duffy S, Clusmann H, Gothert M. Inhibition of neuronal Ca^{2+} influx by gabapentin and pregabalin in the human neocortex. Neuropharmacology 2002;42:229–36
65. Maneuf YP, Hughes J, McKnight AT. Gabapentin inhibits the substance P-facilitated K^+-evoked release of [3H]glutamate from rat caudal trigeminal nucleus slices. Pain 2001;93:191–6
66. Errante L, Petroff OAC. Acute effects of gabapentin and pregabalin on rat forebrain cellular GABA, glutamate, and glutamine concentrations. Seizure 2003;12:300–6
67. Cunningham M, Woodhall G, Thompson S, Dooley D, Jones R. Dual effects of gabapentin and pregabalin on glutamate release at rat entorhinal synapses in vitro. Eur J Neurosci 2004;20:1566–76
68. Micheva KD, Taylor CP, Smith SJ. Pregabalin reduces the release of synaptic vesicles from cultured hippocampal neurons. Mol Pharmacol 2006;70:467–76
69. Triggle D. Calcium-channel antagonists: mechanisms of action, vascular selectivities, and clinical relevance. Cleve Clin J Med 1992;59:617–27
70. Field MJ, Cox PJ, Stott E, Melrose H, Offord J, Su T-Z, Bramwell S, Corradini L, Engl S, Winks J, Kinloch RA, Hendrich J, Dolphin AC, Webb T, Williams D. Identification of the α-2δ-1 subunit of voltage-dependent calcium channels as a molecular target for pain mediating the analgesic actions of pregabalin. PNAS 2006;103:17537–42
71. Stewart B, Kugler A, Thompson P, Bockbrader H. A saturable transport mechanism in the intestinal absorption of gabapentin is the underlying cause of the lack of proportionality between increasing dose and drug levels in plasma. Pharm Res 1993;10:276–81
72. Bockbrader H, Hunt T, Strand J, Posvar E, Sedman A. Pregabalin pharmacokinetics and safety in healthy volunteers: results from two phase 1 studies. Neurology 2000;54:A421
73. Su TZ, Feng MR, Weber ML. Mediation of highly concentrative uptake of pregabalin by L-type amino acid transport in chinese hamster ovary and Caco-2 cells. J Pharmacol Exp Ther 2005;313:1406–15
74. Ben-Menachem E. Pregabalin pharmacology and its relevance to clinical practice. Epilepsia 2004;45:13–8
75. Piyapolrungroj N, Li C, Bockbrader H, Liu G, Fleisher D. Mucosal uptake of gabapentin (neurontin) vs. pregabalin in the small intestine. Pharm Res 2001;18:1126–30
76. Busch J, Strand J, Posvar E, Bockbrader H, Radulovic L. Pregabalin (CI-1008) multiple-dose pharmacokinetics and safety/tolerence in healthy volunteers. Pharm Sci 1999;1:2033
77. Randinitis EJ, Posvar EL, Alvey CW, Sedman AJ, Cook JA, Bockbrader HN. Pharmacokinetics of pregabalin in subjects with various degrees of renal function. J Clin Pharmacol 2003;43:277–83
78. Brodie MJ, Wilson EA, Wesche DL, Alvey CW, Randinitis EJ, Posvar EL, Hounslow NJ, Bron NJ, Gibson GL, Bockbrader HN. Pregabalin drug interaction studies: lack of effect on the pharmacokinetics of carbamazepine, phenytoin, lamotrigine, and valproate in patients with partial epilepsy. Epilepsia 2005;46:1407–13
79. Perucca E. Clinically relevant drug interactions with antiepileptic drugs. Br J Clin Pharmacol 2006;61:246–55
80. Hindmarch I, Trick L, Ridout F. A double-blind, placebo- and positive-internal-controlled (alprazolam) investigation of the cognitive and psychomotor profile of pregabalin in healthy volunteers. Psychopharmacology 183:133–43
81. Lyrica® (pregabalin) [package insert]. New York, NY: Pfizer Inc.; 2005
82. Sabatowski R, Galvez R, Cherry DA, Jacquot F, Vincent E, Maisonobe P, Versavel M, The 1008–045 Study Group. Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic neuralgia: results of a randomised, placebo-controlled clinical trial. Pain 2004;109:26–35
83. Huppertz H-J, Feuerstein TJ, Schulze-Bonhage A. Myoclonus in epilepsy patients with anticonvulsive add-on therapy with pregabalin. Epilepsia 2001;42:790–2
84. Heckmann J, Ulrich K, Dutsch M, Neundorfer B. Pregabalin associated asterixis. Am J Phys Med Rehabil 2005;84:724
85. Malaga I, Sanmarti FX. Two cases of painful gynecomastia and lower extremity pain in association with pregabalin therapy. Epilepsia 2006;47:1576–9
86. Anne Louise Oaklander BRB. Pregabalin-withdrawal encephalopathy and splenial edema: a link to high-altitude illness? Ann Neurol 2005;58:309–12
87. Rowbotham M, Harden N, Stacey B, Bernstein P, Magnus-Miller L, for the Gabapentin Postherpetic Neuralgia Study Group. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. JAMA 1998;280:1837–42
88. Rice ASC, Maton S. Gabapentin in postherpetic neuralgia: a randomised, double blind, placebo controlled study. Pain 2001;94:215–24
89. Neurontin® (gabapentin) [package insert]. New York, NY: Parke-Davis Inc.; 2005
90. Rosenstock J, Tuchman M, LaMoreaux L, Sharma U. Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. Pain 2004;110:628–38
91. Lesser H, Sharma U, LaMoreaux L, Poole RM. Pregabalin relieves symptoms of painful diabetic neuropathy: a randomized controlled trial. Neurology 2004;63:2104–10
92. Richter RW, Portenoy R, Sharma U, Lamoreaux L, Bockbrader H, Knapp LE. Relief of painful diabetic peripheral neuropathy with pregabalin: a randomized, placebo-controlled trial. J Pain 2005;6:253–60
93. Dworkin RH, Corbin AE, Young JP Jr, Sharma U, LaMoreaux L, Bockbrader H, Garofalo EA, Poole RM. Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial. Neurology 2003;60:1274–83
94. Cook R, Sackett D. The number needed to treat: a clinically useful measure of treatment effect. BMJ 1995;310:452–4
95. Raja SN, Haythornthwaite JA, Pappagallo M, Clark MR, Travison TG, Sabeen S, Royall RM, Max MB. Opioids versus antidepressants in postherpetic neuralgia: a randomized, placebo-controlled trial. Neurology 2002;59:1015–21
96. Sindrup SH, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. Pain 1999;83:389–400
97. Collins SL, Moore RA, McQuay HJ, Wiffen P. Antidepressants and anticonvulsants for diabetic neuropathy and postherpetic neuralgia: a quantitative systematic review. J Pain Symptom Manage 2000;20:449–58
98. Jensen TS. Anticonvulsants in neuropathic pain: rationale and clinical evidence. Eur J Pain 2002;6:61–8
99. McQuay HJ. Neuropathic pain: evidence matters. Eur J Pain 2002;6:11–8
100. Watson C, Babul N. Efficacy of oxycodone in neuropathic pain: a randomized trial in postherpetic neuralgia. Neurology 1998;50:1837–41
101. Freynhagen R, Strojek K, Griesing T, Whalen E, Balkenohl M. Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens. Pain 2005;115:254–63
102. D'Urso De Cruz E DR, Stacey B, Siffert J, Emir B. Long-term treatment of painful DPH and PHN with pregabalin in treatment-refractory patients. Poster presented at: American Diabetes Association 64th Scientific Sessions; June 10–14, 2005; San Diego, California
103. Siddall PJ, Cousins MJ, Otte A, Griesing T, Chambers R, Murphy TK. Pregabalin in central neuropathic pain associated with spinal cord injury: a placebo-controlled trial. Neurology 2006;67:1792–800
104. Crofford L, Rowbotham M, Mease P, Russell I, Dworkin R, Corbin A, Young J, LaMoreaux L, Martin S, Sharma U. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2005;52:1264–73

105. Woolf C, Chong M. Preemptive analgesia-treating postoperative pain by preventing the establishment of central sensitization. Anesth Analg 1993;77:362–79
106. Lascelles BDX, Waterman AE, Cripps PJ, Livingston A, Henderson G. Central sensitization as a result of surgical pain: investigation of the pre-emptive value of pethidine for ovariohysterectomy in the rat. Pain 1995;62:201–12
107. Perkins F, Kehlet H. Chronic pain as an outcome of surgery. A review of predictive factors. Anesthesiology 2000;93: 1123–33
108. Aasvang E, Kehlet H. Chronic postoperative pain: the case of inguinal herniorrhaphy. Br J Anaesth 2005;95:69–76
109. Dahl JB, Mathiesen O, Moiniche S. 'Protective premedication': an option with gabapentin and related drugs? A review of gabapentin and pregabalin in the treatment of post-operative pain. Acta Anaesthesiol Scand 2004;48:1130–6
110. Rowbotham DJ. Gabapentin: a new drug for postoperative pain? Br J Anaesth 2006;96:152–5
111. Turan A, Kaya G, Karamanlioglu B, Pamukcu Z, Apfel C. Effect of oral gabapentin on postoperative epidural analgesia. Br J Anaesth 2006;96:242–6
112. Adam F, Menigaux C, Sessler DI, Chauvin M. A single preoperative dose of gabapentin (800 milligrams) does not augment postoperative analgesia in patients given interscalene brachial plexus blocks for arthroscopic shoulder surgery. Anesth Analg 2006;103:1278–82
113. Gilron I, Biederman J, Jhamandas K, Hong M. Gabapentin blocks and reverses antinociceptive morphine tolerance in the rat paw-pressure and tail-flick tests. Anesthesiology 2003;98: 1288–92
114. Hansen C, Gilron I, Hong M. The effects of intrathecal gabapentin on spinal morphine tolerance in the rat tail-flick and paw pressure tests. Anesth Analg 2004;99:1180–4
115. Andrews N, Loomis S, Blake R, Ferrigan L, Singh L, McKnight A. Effect of gabapentin-like compounds on development and maintenance of morphine-induced conditioned place preference. Psychopharmacology 2001;157:381–7
116. Hill C, Balkenohl M, Thomas D, Walker R, Mathe H, Murray G. Pregabalin in patients with postoperative dental pain. Eur J Pain 2001;5:119–24
117. Hurley R, Chatterjea D, Rose Feng M, Taylor C. Gabapentin and pregabalin can interact synergistically with naproxen to produce antihyperalgesia. Anesthesiology 2002;97:1263–73
118. Reuben SS, Buvanendran A, Kroin JS, Raghunathan K. The analgesic efficacy of celecoxib, pregabalin, and their combination for spinal fusion surgery. Anesth Analg 2006;103: 1271–7
119. Portenoy R, D'Urso de Cruz E, Young J, Griesing T. Pregabalin for painful diabetic peripheral neuropathy and postherpetic neuralgia: onset and duration of analgesia in combined analyses of clinical studies. American Pain Society 25th Annual Meeting. Poster 777. May 3–6, 2006; San Antonio, Texas
120. Kinloch RA, Cox PJ. New targets for neuropathic pain therapeutics. Expert Opin Ther Targets 2005;9:685–98
121. Dworkin RH, Backonja M, Rowbotham MC, Allen RR, Argoff CR, Bennett GJ, Bushnell MC, Farrar JT, Galer BS, Haythornthwaite JA, Hewitt DJ, Loeser JD, Max MB, Saltarelli M, Schmader KE, Stein C, Thompson D, Turk DC, Wallace MS, Watkins LR, Weinstein SM. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. Arch Neurol 2003;60:1524–34
122. Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Algorithm for neuropathic pain treatment: an evidence based proposal. Pain 2005;118:289–305
123. Guay DRP. Pregabalin in neuropathic pain: a more "pharmaceutically elegant" gabapentin? Am J Geriatr Pharmacother 2005;3:274–87
124. Shneker B, McAuley J. Pregabalin: a new neuromodulator with broad therapeutic indications. Ann Pharmacother 2005;39: 2029–37
125. Raja SN, Haythornthwaite JA. Combination therapy for neuropathic pain – which drugs, which combination, which patients? N Engl J Med 2005;352:1373–5
126. Argoff C, Backonja M, Belgrade M, Bennett G, Clark M, Cole B, Fishbain D, Irving G, McCarberg B, McLean MAS. Consensus guidelines: treatment planning and options. Diabetic peripheral neuropathic pain. Mayo Clin Proc 2006;81(4 suppl): S12–S25
127. Gilron IF, Flatters S. Gabapentin and pregabalin for the treatment of neuropathic pain: a review of laboratory and clinical evidence. Pain Res Manag 2006;11(suppl A):16A–29A
128. Kavoussi R. Pregabalin: from molecule to medicine. Eur Neuropsychopharmacology 2006;2006:S128–S133
129. Gidal B. New and emerging treatment options for neuropathic pain. Am J Manag Care 2006;12:S269–S278
130. Smith K, Roberts M. Sequential medication strategies for postherpetic neuralgia: a cost-effectiveness analysis. J Pain 2007;8:396–404
131. Tarride J, Gordon A, Vera-Llonch M, Dukes E, Rousseau CN. Cost-effectiveness of pregabalin for the management of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia: a Can perspective. Clin Ther 2006;28:1922–34
132. Walia KS, Khan EA, Ko DH, Raza SS, Khan YN. Side effects of antiepileptics. Pain Pract 2004;4:194–203
133. Turk DC, Dworkin RH, Allen RR, Bellamy N, Brandenburg N, Carr DB, Cleeland C, Dionne R, Farrar JT, Galer BS. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. Pain 2003;106:337–45
134. Fassoulaki A, Patris K, Sarantopoulos C, Hogan Q. The analgesic effect of gabapentin and mexiletine after breast surgery for cancer. Anesth Analg 2002;95:985–91
135. Dirks J, Fredensborg B, Christensen D, Fomsgaard J, Flyger H, Dahl J. A randomized study of the effects of single-dose gabapentin versus placebo on postoperative pain and morphine consumption after mastectomy. Anesthesiology 2002;97: 560–4
136. Turan A, Memis D, Karamanlioglu B, Yagiz R, Pamukcu Z, Yavuz E. The analgesic effects of gabapentin in monitored anesthesia care for ear-nose-throat surgery. Anesth Analg 2004;99:375–8
137. Turan A, Karamanlioglu B, Memis D, Usar P, Pamukcu Z, Ture M. The analgesic effects of gabapentin after total abdominal hysterectomy. Anesth Analg 2004;98:1370–3
138. Turan A, Karamanlioglu B, Memis D, Hamamcioglu M, Tukenmez B, Pamukcu Z, Kurt I. Analgesic effects of gabapentin after spinal surgery. Anesthesiology 2004;100:935–8
139. Dierking G, Duedahl TH, Rasmussen ML, Fomsgaard JS, Moiniche S, Romsing J, Dahl JB. Effects of gabapentin on postoperative morphine consumption and pain after abdominal hysterectomy: a randomized, double-blind trial. Acta Anaesthesiol Scand 2004;48:322–7
140. Pandey CK, Priye S, Singh S, Singh U, Singh RB, Singh PK. Preemptive use of gabapentin significantly decreases postoperative pain and rescue analgesic requirements in laparoscopic cholecystectomy. Can J Anaesth 2004;51:358–63
141. Rorarius M, Mennander S, Suominen P, Rintala S, Puura A, Pirhonen R, Salmelin R, Haanpaa M, Kujansuu E, Yli-Hankala A. Gabapentin for the prevention of postoperative pain after vaginal hysterectomy. Pain 2004;110:175–81
142. Spira PJ, Beran RG. Gabapentin in the prophylaxis of chronic daily headache: a randomized, placebo-controlled study. Neurology 2003;61:1753–9
143. Turan A, White PF, Karamanlioglu B, Memis D, Tasdogan M, Pamukcu Z, Yavuz E. Gabapentin: an alternative to the cyclooxygenase-2 inhibitors for perioperative pain management. Anesth Analg 2006;102:175–81
144. Mathew NT, Rapoport A, Saper J, Magnus L, Klapper J, Ramadan N, Stacey B, Tepper S. Efficacy of gabapentin in migraine prophylaxis. Headache 2001;41:119–28
145. Berry J, Petersen K. A single dose of gabapentin reduces acute pain and allodynia in patients with herpes zoster. Neurology 2005;65:444–7
146. Bone M, Critchley P, Buggy DJ. Gabapentin in postamputation phantom limb pain: a randomized, double-blind, placebo-controlled, cross-over study. Reg Anesth Pain Med 2002;27: 481–6
147. Caraceni A, Zecca E, Bonezzi C, Arcuri E, Tur RY, Maltoni M, Visentin M, Gorni G, Martini C, Tirelli W, Barbieri M, De Conno F. Gabapentin for neuropathic cancer pain: a randomized controlled trial from the Gabapentin Cancer Pain Study Group. J Clin Oncol 2004;22:2909–17
148. Pandey CK, Bose N, Garg G, Singh N, Baronia A, Agarwal A, Singh PK, Singh U. Gabapentin for the treatment of pain in Guillain-Barre syndrome: a double-blinded, placebo-controlled, crossover study. Anesth Analg 2002;95:1719–23

149. Ulrich K, Gunreben B, Lang E, Sittl R, Griessinger N. Pregabalin in the therapy of hypnic headache. Cephalalgia 2006;26: 1031–2
150. Hahn K, Arendt G, Braun JS, von Giesen H-J, Husstedt IW, Maschke M, Straube ME, Schielke E. A placebo-controlled trial of gabapentin for painful HIV-associated sensory neuropathies. J Neurol 2004;251:1260–6
151. Levendoglu, Ogun C, Ozerbil O, Ogun T, Ugurlu H. Gabapentin is a first line drug for the treatment of neuropathic pain in spinal cord injury. Spine 2004;29:743–51
152. Lawson K. Emerging pharmacological therapies for fibromyalgia. Curr Opin Investig Drugs 2006;7:631–6
153. Guido M, Specchio LM. Glossopharyngeal neuralgia responding to pregabalin. Headache 2006;46:1307–8
154. Yokoyama T, Maeda Y, Audette KM, Sluka KA. Pregabalin reduces muscle and cutaneous hyperalgesia in two models of chronic muscle pain in rats. J Pain 2007;8:422–9
155. Gilron I. The role of anticonvulsant drugs in postoperative pain management: a bench-to-bedside perspective: [Le role des anticonvulsivants dans le traitement de la douleur postoperatoire: perspective d'une application]. Can J Anaesth 2006;53: 562–71 (review article)
156. Zesiewicz T, Ward C, Hauser R, Pease Campbell J, Sullivan KN. Pregabalin (Lyrica) in the treatment of essential tremor. Mov Disord 2007;22:139–41
157. Vandemergel X, Mbeufet M, Renneboog B. Intractable hiccups successfully treated with pregabalin. Eur J of Internal Med 2006;17:522