Clinical Medicine Reviews in Therapeutics

Libertas Academica
FREEDOM TO RESEARCH

CMR
Clinical Medicine Reviews

REVIEW

A Review of Pregabalin for the Treatment of Peripheral and Central Neuropathic Pain and Its Place in the Treatment of Chronic Pain

C. Pérez[1], C. Margarit[2] and R. Gálvez[3]

[1]Pain Unit, Hospital Universitario de la Princesa, Madrid, Spain. [2]Pain Unit, Hospital General de Alicante, Spain. [3]Pain and Palliative Cara Unit, Hospital Virgen de las Nieves, Granada, Spain. Corresponding author email: cperez.hlpralud.madrid.org

Abstract: Pregabalin is an α2-δ ligand indicated for the treatment of peripheral and central neuropathic pain. In this article, we will review the pharmacodynamics, pharmacokinetics, randomized clinical trials supporting its efficacy for a wide array of neuropathic painful conditions, and the tolerability of this medication. We will comment the main differences with gabapentin, its parent compound, both from the pharmacological and clinical perspective. Our experience in the clinical practice setting with pregabalin, its use in patients with refractory neuropathic pain and its rational use in combination regimens will also be reviewed. With all this information in mind, the place of pregabalin in the pharmacotherapy of neuropathic pain is explored, mainly through the review of recent clinical guidelines which, in fact, place pregabalin among the first-line treatments for the management of most neuropathic painful conditions.

Keywords: pregabalin, peripheral neuropathic pain, diabetic neuropathy, postherpetic neuralgia, central neuropathic pain

Clinical Medicine Reviews in Therapeutics 2011:3 325–346

doi: 10.4137/CMRT.S7398

This article is available from http://www.la-press.com.

Introduction

Neuropathic pain is defined as pain arising from a lesion or disease affecting the somatosensory pathways within the peripheral or central nervous system.[1] Neuropathic pain is frequently encountered in clinical practice because it affects 7% to 8% of the population.[2,3] Due to its severity, chronicity, co-morbidities, and impact on the individual and society, neuropathic pain is particularly challenging. Neuropathic pain significantly reduces quality of life in affected patients,[4,5] and it is associated with high societal costs.[6,7] Anxiety, sleep and mood disorders are frequently present among patients with neuropathic pain,[8,9] and the presence of these symptoms may increase the severity of the pain.[10–12]

Neuropathic pain is difficult to treat because the patients are frequently resistant to treatment and/or unable to tolerate the medications.[13] Furthermore, patients with neuropathic pain often receive suboptimal treatment (ie, inappropriate drug therapy and/or use of subtherapeutic doses),[7,14,15] which increases the disease burden.[16–18] Although there are several treatments available for the management of neuropathic pain,[13] only the tricyclic antidepressants and calcium channel α_2-δ ligands (gabapentin and pregabalin) are considered for first-line treatment by most clinical guidelines.[19]

In this review, we will focus on pregabalin, an anticonvulsant that has been shown to be effective in randomized clinical trials for a wide array of painful neuropathic conditions. Pregabalin is indicated the USA for the treatment of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia; in Canada it is indicated for for the management of neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, and spinal cord injury; and in Europe it is indicated for the treatment of peripheral and central neuropathic pain.

Pharmacology

Pharmacodynamics

Pregabalin is the S-enantiomer of 3-(aminomethyl)-5-methylhexanoic acid. Although the mechanism of action of pregabalin has not been fully elucidated, it binds with high affinity to the α_2-δ site (an auxiliary subunit of voltage-gated calcium channels) in central nervous system tissue, and this binding is considered to be responsible for pregabalin's anti-nociceptive and antiseizure effects.[20] Recent research findings suggest that the α_2-δ_1 subunit plays an important role in neuropathic pain development.[21] The binding of pregabalin and gabapentin, its parent compound, to the α_2-δ_1 subunit of the voltage-gated calcium channels leads to a reduction in the release of multiple neurotransmitters (including glutamate, noradrenaline, serotonin, dopamine, and substance P), which, in turn, is responsible for the efficacy and tolerability of these drugs in patients with neuropathic pain.[21,22]

Despite pregabalin's structural similarity to gabapentin and identical mechanism of action, its affinity for the α_2-δ_1 subunit of the voltage-gated calcium channel is six-fold higher than that of gabapentin,[23] and this higher affinity may explain why pregabalin is clinically more effective at lower doses.[21,22]

Pharmacokinetics

Pregabalin is rapidly absorbed after oral administration, is eliminated largely by renal excretion, and has a relatively short elimination half-life (about 6 hours).[20] The oral bioavailability is ≥90%, independent of the dose. Following single- (25 to 300 mg) and multiple-dose (75 to 600 mg/day) administrations, the maximum plasma concentrations (Cmax) and area under the plasma concentration-time curve (AUC) values increase linearly.[20] Pregabalin also differs from gabapentin in its absorption. Both drugs are absorbed across the gastrointestinal tract using the system-L transporter. However, the absorption of gabapentin is only mediated by the system-L transporter and is limited by this saturable, active and dose-dependent transporter, which results in nonlinear pharmacokinetics;[22,24] therefore, higher doses and more frequent administration may be required to optimize the absorption of gabapentin. By contrast, pregabalin absorption appears to be mediated by an additional pathway, which is not saturable, and this results in linear pharmacokinetics.[22,24] The rate of absorption of pregabalin is 3-fold higher than that of gabapentin; it attains a peak blood concentration at 1 hour post-dose, compared to 3 hours for gabapentin.[22,24]

Pregabalin undergoes negligible metabolism in humans and is not bound to plasma proteins. Following a dose of radiolabeled pregabalin, approximately 90% of the administered dose is recovered in the urine as unchanged pregabalin. The N-methylated

derivative of pregabalin, the major metabolite of pregabalin found in urine, accounts for 0.9% of the dose.[20] Pregabalin is renally excreted, and its clearance is reduced in patients with renal function impairment; therefore, dose adjustments are required in this population (Table 1).

Pregabalin can be administered without regard to to timing of meals, and its pharmacokinetics are not significantly affected by race or gender.[20] Consistent with declining renal function, pregabalin's oral clearance tends to decrease with increasing age, and a dose reduction may be required in elderly patients.[20]

In vitro studies have shown that pregabalin does not inhibit or induce the major isoenzymes of the cytochrome P450 system.[20] Therefore, drug-drug interactions at this level are unlikely, and the genetic polymorphisms of these isoenzymes would not be expected to affect the pharmacokinetics of the compound.[24] In vivo studies suggest that the coadministration of pregabalin does not affect the pharmacokinetics of gabapentin, oral contraceptives, lorazepam, oxycodone, ethanol, and, with the possible exception of tiagabine, other antiepileptic drugs to a relevant extent.[20,25]

Clinical Efficacy

In this section we will review the efficacy of pregabalin in several neuropathic conditions using data from randomized clinical trials and metaanalysis. Then, we will discuss the information available on the use of pregabalin in patients with treatment-refractory neuropathic pain, its use in combination regimens, and the experience with pregabalin in the clinical practice setting. Although there are arguments favoring the notion that fibromyalgia is a neuropathic pain syndrome, this issue is still controversial.

Table 1. Pregabalin dosage adjustment based on renal function.

Creatinine clearance (CLcr) (mL/min)	Total pregabalin daily dose (mg/day)*				Dose regimen
≥60	150	300	450	600	BID or TID
30–60	75	150	225	300	BID or TID
15–30	25–50	75	100–150	150	QD or BID
<15	25	25–50	50–75	75	QD

Note: *Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose.[20]

Therefore, we have not included data on pregabalin and fibromyalgia in our review.

Painful diabetic peripheral neuropathy

Diabetic peripheral neuropathy (DPN) is a common and late complication of diabetes mellitus. It is estimated that DPN affects almost 30% of patients with diabetes.[26] Between 3% to 25% of patients with diabetes experience neuropathic pain,[27] which substantially impairs their quality of life and productivity.[28] The treatment of DPN includes tight glycemic control and the use of medication to manage pain.[29]

The efficacy and tolerability of pregabalin in patients with painful diabetic neuropathy have been investigated in seven randomized, double-blind clinical trials (Table 2). All but one were parallel, fixed-dose, placebo-controlled trials that evaluated pregabalin at doses of 75, 150, 300 and 600 mg/day. In one randomized study, pregabalin flexibly dosed at 150 to 600 mg/day was compared with amitriptyline (at 10 to 50 mg/day) using a cross-over design.[35] The main results of these trials are presented in Table 2. Fixed-dose, placebo-controlled trials indicate that pregabalin is effective for the treatment of painful diabetic neuropathy at doses of 300 and 600 mg/day. Doses of pregabalin of 150 mg/day or lower are consistently negative; although not identified in individual studies, the results of a pooled analysis (see below) has shown that doses of 150 mg/day of pregabalin are also better tha placebo.[37] The response rates (ie, the proportion of patients showing a reduction in their pain score of 50% or greater at the study endpoint) are over 40% in most trials, with pregabalin 600 mg/day showing slightly better response rates.

Although the proportion of responders was numerically higher with pregabalin (48% vs. 34%) in the only active-comparator trial, pregabalin (150–600 mg/day) did not significantly differ from amitriptyline (10–50 mg/day) in terms of efficacy.[35] In this trial, pregabalin was better tolerated than amitriptyline; the proportion of drop-outs due to adverse events was higher among the amitriptyline-treated patients (36.2% vs. 12.5%, a difference that, according to our estimation, is statistically significant and corresponds to a relative risk of 2.9 [95% CI, 1.3 to 6.7]). This trial also suggested that doses over 150 mg/day of pregabalin are usually required for treating patients with painful diabetic neuropathy since most patients

Table 2. Randomized clinical trials of pregabalin for the treatment of painful diabetic neuropathy.

Reference author	Design[1] and study duration	Study groups	No. randomized patients	Primary outcome measure
				Definition/analysis
Lesser[30]	DB 5-week	PGB 75 PGB 300 PGB 600 PBO	77 81 82 97	Mean pain score/ Difference from PBO (ANCOVA) ITT
Rosenstock[31]	DB 8-week	PGB 300 PBO	76 70	Mean pain score/ Difference from PBO (ANCOVA) ITT
Richter[32]	DB 6-week	PGB 150 PGB 600 PBO	79 82 85	Mean pain score/ Difference from PBO (ANCOVA) ITT
Tölle[33]	DB 12-week	PGB 150 PGB 300 PGB 300/600[2] PBO	99 99 101[2] 96	Mean pain score/ Difference from PBO (ANCOVA) ITT
Arezzo[34]	DB 13-week	PGB (150→600) PBO	82 85	Mean pain score/ Difference from PBO (ANCOVA) ITT
Bansal[35]	DB Cross-over 14-week	PGB (150→600) AMT (10→50)	48 47	Median pain score/ WILCOXON
Satoh[36]	DB 14-week	PGB 300 PGB 600 PBO	136 45 136	Mean pain score/ Difference from PBO (ANCOVA) ITT

(68%) from this study required doses of 300 mg/day of pregabalin.[35]

Three meta-analyses or pooled analyses have provided separate data for pregabalin in the treatment of painful diabetic neuropathy.[37–39] The first meta-analysis included data from only three clinical trials[30–32] and showed that pregabalin was associated with a significant decrease in pain scores compared to placebo. It also found that the response rate and patient's global impression of change were better than those for placebo (Hurley 2008).[38]

Freeman et al performed a pooled analysis using data from seven randomized clinical trials of pregabalin.[37] Six of these trials were from the 7 trials reviewed above, and the other trial[40] included both patients with diabetic neuropathy and patients with postherpetic neuralgia. This pooled analysis showed that pregabalin is superior to placebo for pain reduction at all the studied doses (150, 300, and 600 mg/day). The results for the secondary efficacy measures were similar, except for the response rate with pregabalin at 150 mg/day.[37] However, the clinical relevance of the pregabalin 150 mg/day results is doubtful; the number needed to treat (NNT) for the proportion of responders was 19.06 (CI not calculated), compared to NNTs of 4.04 (95% CI, 3.3 to 5.3) and 5.99 (95% CI, 4.2 to 10.4) for pregabalin 600 and 300 mg/day, respectively.[37] This pooled analysis also showed that the effect of pregabalin on pain seems to be dose-dependent and that the median time to onset of sustained improvement in pain is 4–5 days.[37] A retrospective analysis of nine placebo-controlled trials of pregabalin in patients with painful diabetic neuropathy or postherpetic neuralgia showed that patients who will respond to pregabalin usually obtain significant and sustained pain relief by the end of the second day of treatment.[41]

Results (95% CI) [*P*-value]	% Responders-50% (*P*-value)	% Drop-outs due to AEs (*P*-value)	Mean final dose
–0.15 (–0.76, 0.46) [0.6267]	–	2.6 (NA)	–
–1.26 (–1.86, –0.65) [0.0001]	46 (S)	3.7 (NA)	
–1.45 (–2.06, –0.85) [0.0001]	48 (S)	12.2 (NA)	
	18	3.1	
–1.47 (–2.19, –0.75) [0.0001]	40 (0.001)	10.5 (NA)	–
	14.5	2.9	
–0.440 (–1.080, 0.199) [0.1763]	20 (NS)	2.5 (NA)	–
–1.264 (–1.890, –0.639) [0.0002]	39 (0.002)	8.5 (NA)	
	15	4.7	
–0.27 (–0.87, 0.34) [0.7481]	34.4 (NS)	5.1 (NA)	–
–0.10 (–0.70, 0.50) [0.7481]	33.3 (NS)	11.1 (NA)	
–0.91 (–1.51, –0.31) [0.0093]	45.9 (0.036)	12.9 (NA)	
	30.1	3.1	
–1.36 (–2.20, –0.52) [<0.01]	49 (<0.001)	17.1 (NA)	–
	23	11.8	
40 (30–60)[3]	48 (NA)	12.5 (NA)	218
42.5 (30–57)[3]	34	36.2	16
[0.87]			
–0.63 (–1.09, –0.17) [0.0075]	29.1 (NS)	7.5	–
–0.74 (–1.39, –0.09) [0.0254]	35.6 (NS)	26.7	
	21.5	4.4	

Notes: [1]AMT, Amitriptyline; DB, double-blind; NA, not available; ITT, Intention to treat; NS, non-significant difference; OL, open-label; PBO, placebo; PGB, pregabalin; S, significant difference; [2]Patients with CLcr > 60 mL/min received PGB 600 (N = 88); patients with CLcr 30–60 mL/min received PGB 300 (N = 13); [3]Median pain score (IQR).

Finally, a recent meta-analysis provided data for an indirect comparison of pregabalin and duloxetine.[39] This meta-analysis included data from 3 trials with duloxetine and 6 trials with pregabalin and found no difference between the two drugs in the reduction of 24-hour pain severity, but pregabalin was superior to duloxetine when evaluated by the patient's global impression of change. Duloxetine produced a significantly lower incidence of dizziness.[39]

Aside from the improvement in pain, pregabalin provides other benefits in patients with painful diabetic neuropathy. Pregabalin improves pain-related sleep interference.[42] The improvement of sleep in pregabalin-treated patients may be, at least partially, a direct effect as it has been shown in patients with fibromyalgia[43] or patients with generalized anxiety disorder.[44] In addition, a placebo-controlled trial showed that pregabalin improves heart rate variability, a measure that is associated with a high risk of mortality and morbidity in patients with cardiovascular diseases.[45]

Postherpetic neuralgia

Postherpetic neuralgia is a common complication of herpes zoster infection. It refers to pain lasting longer than 3 months after the healing of a herpes zoster rash.[46] Using this definition, the proportion of patient with herpes zoster infection who develop postherpetic neuralgia ranges from 9% to 24%.[4] This condition is debilitating, has an important impact on quality of life, and is difficult to manage because no interventions reliably relieve the associated pain.[4,46]

Several randomized, controlled trials have been conducted with pregabalin in patients with postherpetic neuralgia, and the results are presented in Table 3. Four trials have compared pregabalin at fixed

Table 3. Randomized clinical trials of pregabalin for the treatment of postherpetic neuralgia.

Reference author	Design[1] and study duration	Study groups	No. randomized patients	Primary outcome measure
				Definition/analysis
Dworkin[47]	DB 8-week	PGB 300/600[2] PBO	89[2] 84	Mean pain score/ Difference from PBO (ANCOVA) ITT
Sabatowski[48]	DB 8-week	PGB 150 PGB 300 PBO	81 76 81	Mean pain score/ Difference from PBO (ANCOVA) ITT
Van Seventer[49]	DB 13-week	PGB 150 PGB 300 PGB 300/600[4] PBO	87 98 90[4] 93	Mean pain score/ Difference from PBO (ANCOVA) ITT
Stacey[50]	DB 4-week	PGB 150→600 PGB 300 PBO	91 88 90	Median time to onset pain relief/ Kaplan Meier ITT
Achar[51]	(–) 8-week	AMT 25 PGB 150 AMT 25 + PBG 150	15 15 15	% satisfactory improvement of pain (>75%)/ Chi-squared test
Barbarisi[52]	OL 4-week	(A) PGB 300 + TENS(B) PGB 300 + TENS-PBO (C) PGB 600 + TENS (D) PGB 600 + TENS-PBO	8 876	Mean pain score/ Difference between groups (Multiple pair comparisons; Bonferroni, $P < 0.05$)
Baron[53]	OL 4-week	5% LDC PGB (150→600)	50 48	Percentage of response (↓ from BL ≥ 2 points or score ≤4 points in NRS)/FAS[6]
Rehm[54]	OL 8-week[8]	5% LDC[8] 5% LDC + PGB (150→600)[8] PGB (150→600)[8] PGB (150→600) + 5% LDC[8]	25 18 14 17	Mean pain score (SF-MPQ)[9]/Difference from combination phase BL[8]

Results (95% CI) [*P*-value]	% Responders-50% (*P*-value)	% Drop-outs due to AEs (*P*-value)	Mean final dose
–1.69 (–2.33, –1.05) [0.0001]	50 (0.001) 20	31.5 (NA) 4.8	–
–1.20 (–1.81, –0.58) [0.0002] –1.57 (–2.20, –0.95) [0.0001]	26 (0.006) 28 (0.003) 10	11.1 (NA) 15.8 (NA) 9.9	–
–0.88 (–1.53, –0.23) [0.0077] –1.07 (–1.70, –0.45) [0.0016] –1.79 (–2.43, –1.15) [0.0003]	26.4 (0.001) 26.5 (0.001) 37.5 (0.001) 7.5	8.0 (NA) 15.3 (NA) 21.1 (NA) 5.4	–
3.5 days 1.5 days Not achieved [<0.0001]	46.7 (0.001) 39.8 (0.002) 18.4	4.4 (NA) 18.2 (NA) 4.4	396.1 mg/d 295.4 mg/d
13.4[5] 53.3[5] 73.3[5] [<0.05][5]	–	–	–
(A–B): –13.88 (–15.22; –12.55) [<0.0001] (A–C): 1.53 (0.15; 2.92) [0.02] (A–D): –7.55 (–8.99; –6.11) [<0.0001] (B–C): 15.42 (14.01; 16.84) [<0.0001] (B–D): 6.33 (4.85; 7.81) [<0.0001] (C–D): –9.09 (–10.61; –7.57) [<0.0001]	–	0 0 0 0	–
63.3 46.8	35.6 (NA) 20.9	6 (NA)[7] 6.25[7]	1.71 plasters
–11.8 (16.03)[3] –27.8 (21.60)[3] –5.4 (10.83)[3] –33.7 (22.75)[3]	–	4 (NA) 16.67 (NA) 7.14 (NA) 11.76 (NA)	

Notes: [1]AMT, Amitriptyline; BL, baseline; DB, double-blind; ITT, Intention to treat; LDC, lidocaine; NA, not available; NRS, Numerical rating scale; NS, non-significant difference; OL, open-label; PBO, placebo; PGB, pregabalin; S, significant difference; SF-MPQ, Short Form McGill Pain Questionnaire; TENS, transcutaneous electric nerve stimulation; [2]Patients with CLcr > 60 mL/min received PGB 600 (N = 59); patients with CLcr 30–60 mL/min received PGB 300 (N = 30); [3]Mean difference in pain score from baseline (Standard Deviation); [4]Patients with CLcr > 60 mL/min received PGB 600 (N = 64); patients with CLcr 30–60 mL/min received PGB 300 (N = 26); [5]Statistically significant satisfactory improvement (>75%) in pain perception was noticed in the combined group (AMT 50 + PBG 150) compared to the monotherapy groups (AMT 50 and PGB 150); [6]FAS, Full analysis set defined as all randomised patients who received at least one dose of the study medication and for whom at least one post-BL efficacy assessment was available; [7]Data obtained from Rehm 2010, where the extension phase of the trial (combination phase) was published; [8]Extension phase of Baron 2009 (combination phase): patients previously treated with monotherapy (either PGB or LDC) with NRS ≥ 4 continued in monotherapy, whereas those with NRS > 4 initiated combination therapy with either PGB or LDC (whatever drug they were not in); [9]For the combination phase the percentage of response based on NRS score is not provided. Instead the media and standard deviation of SF-MPQ, together with other scales, are provided.

doses of 150, 300 and 600 mg/day to placebo,[47–50] one trial used lidocaine 5% as active comparator,[53] and three trials evaluated the combination of pregabalin with other interventions, such as amitriptyline,[51] transcutaneous electric nerve stimulation[52] and 5% lidocaine.[54]

In the placebo-controlled trials, all tested doses of pregabalin were efficacious.[47–50] The response rates were 26% with 150 mg/day of pregabalin, 26%–39% with 300 mg/day, and 47%–50% with 300–600 mg/day (in some cases, the trial dose was adjusted to 300 or 600 mg of pregabalin depending on renal function, but most patients received 600 mg/day).[47–50] In the comparison with 5% lidocaine, the subgroup of patients with postherpetic neuralgia showed better efficacy results with lidocaine.[53] Combined treatment with pregabalin and amitriptyline,[51] transcutaneous electric nerve stimulation[52] or 5% lidocaine[54] was superior to treatment with pregabalin alone.

A recent meta-analysis of randomized, controlled trials of pregabalin for acute and chronic pain supports the efficacy of pregabalin for the treatment of postherpetic neuralgia and highlights that the lowest NNT to produce one patient with at least 50% pain relief was obtained with 600 mg pregabalin.[55] Other benefits observed with pregabalin in this population were significant improvements in the mental component of health-related quality of life[48] and in sleep.[47,49]

Low-back pain

Low-back pain is the most common form of chronic pain,[56] affecting 15%–45% of the general population.[57,58] Epidemiological studies have shown that there is a neuropathic component in 20%–35% of the patients with low-back pain.[59]

Two randomized, controlled trials evaluating the efficacy and tolerability of pregabalin in patients with low-back pain have been fully published.[60,61] In the first trial, the efficacy and tolerability of 12-week treatments with pregabalin, celecoxib or their combination in patients with chronic low-back pain secondary to a disc prolapse, lumbar spondylosis, and/or spinal stenosis were compared using a double-blind design.[60] Forty-two patients were randomly assigned to receive consecutive treatment with these three regimens in different orders: celecoxib-pregabalin-celecoxib+pregabalin, celecoxib+pregabalin-celecoxib-pregabalin, and pregabalin-celecoxib+pregabalin-celecoxib.[60] Pregabalin monotherapy significantly alleviated self-reported pain in the patients with greater severity, according to the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) pain scale, while celecoxib significantly reduced pain in those with less severe pain; overall, when the data were pooled according to LANSS score, the combination of celecoxib and pregabalin was more effective than either treatment alone.[60]

Using a double-blind, placebo-substitution design, Baron et al evaluated the time to loss of response in patients with low-back pain due to lumbosacral radiculopathy who had been responders to a single-blind, 4-week course of pregabalin.[61] In the double-blind phase of the study, pregabalin and placebo did not differ in the time to loss of response.[61]

Aside from these two trials, there are two other trials that have not been fully published and that did not find pregabalin to be effective in the treatment of chronic low-back pain, with or without radiculopathy (cited by Baron 2010).[61]

It has been suggested that low back pain in some patients with radiculopathy may be a mixed-pain syndrome that consists of both neuropathic and nociceptive pain.[59,62] This hypothesis may explain the positive results obtained with the combination of pregabalin and celecoxib in the trial mentioned above and the negative results with pregabalin monotherapy in other trials.

Central neuropathic pain

Central neuropathic pain arises from lesions of the central nervous system, such as those derived from spinal cord injury, multiple sclerosis or stroke.[63] In some instances, this type of chronic pain produces greater impairment of daily activities and quality of life than that caused by the disease itself.[64]

This pain is extremely difficult in its treatment. This difficult is maybe doubt to complex pathophysiology and numerous mechanisms, receptors, etc implicated. There are only few drugs and studies with positive results in this pain.

Two out of the three available studies have shown a significantly greater reduction in the mean pain scores of central neuropathic pain patients treated with pregabalin than in the mean scores of those receiving placebo (Table 4).[65,66] In both studies, pregabalin was flexibly dosed from 150 mg/day to 600 mg/day. One of the studies consisted of patients with spinal

Table 4. Randomized clinical trials of pregabalin for the treatment of central neuropathic pain.

Reference author	Design[1] and study duration diagnosis	Study groups	No. randomized patients	Primary outcome measure		% Responders-50% (*P*-value)	% Drop-outs due to AEs (*P*-value)	Mean final dose
				Definition/analysis	Results (95% CI) [*P*-value]			
Siddall[65]	DB 12-week Spinal cord injury	PGB 150→600 PBO	70 67	Mean pain score/ Difference from PBO (ANCOVA) ITT	1.53 (0.92, 2.15) [<0.001]	22 (0.05) 8	21 (NA) 13	483 –
Vranken[66]	DB 4-week Central neuropathic pain	PGB 150→600 PBO	20 20	Mean pain score/ Difference from PBO (Student's *t*-test) ITT	2.18 (0.57, 3.80) [0.01]	35 (NA) 5	15 (NA) 15	–
Kim[67]	DB 13-week Central post-stroke pain	PGB 150→600 PBO	110 109	Mean pain score/ Difference from PBO (ANCOVA) ITT	–0.2 (–0.7, 0.4) [0.578]	(NS)	8.2 (NA) 3.7	–

Abbreviations: DB, double-blind; NS, non-significant difference; NA, not available; PGB, pregabalin; PBO, placebo.

cord injury,[65] and the other enrolled patients with a variety of diagnoses, mainly spinal cord injury and post-stroke pain.[66] The response rates were 22%–35% with pregabalin and 5%–8% with placebo. Unfortunately, only one of these studies provided the mean final dose of pregabalin, which was 483 mg/day in the patients with spinal cord injury.[65]

In a recently published randomized, placebo-controlled trial of pregabalin (also flexibly dosed at from 150 to 600 mg/day) in patients with post-stroke pain, the drug was not significantly different from placebo for the primary outcome (the mean pain over the last week).[67] However, pregabalin was significantly superior to placebo for several secondary outcomes, including sleep, anxiety and the clinician's global impression of change.[67]

Given the high refractoriness of naturopathic pain associated with spinal cord injury,[68] the positive efficacy results found for pregabalin in the two trials involving patients with this condition are encouraging. In one of the trials, moreover, the number needed to treat was 3,[65] indicating a clinically relevant effect of pregabalin on this type of pain.

As it will be discussed below, an indirect comparison from a review of the literature suggests that the benefits obtained from pregabalin in patients with spinal cord injury are greater than those obtained from gabapentin.[69] Pregabalin is the only drug in Europe approved for the treatment of central neuropathic pain.

Other painful neuropathic conditions

Several randomized clinical trials have been performed for pregabalin in various other painful neuropathic conditions (Table 5). In a mixed population of patients with diabetic peripheral neuropathy or postherpetic neuralgia,[40] the results with pregabalin were similar to those reviewed above. In the same population, the combination of pregabalin and oxycodone was not superior to pregabalin alone,[71] and the combination of pregabalin and 5% lidocaine appeared to provide better results than either treatment alone.[70]

In other populations, pregabalin was superior to placebo in patients with traumatic peripheral neuropathic pain[73] or patients with severe burn injury pain,[76] there was a trend towards significantly higher response rates than placebo in patients with chronic pelvic pain

Table 5. Randomized clinical trials of pregabalin for the treatment of other neuropathic painful conditions.

Reference author	Design and study duration diagnosis	Study groups	No. randomized patients	Primary outcome measure
				Definition/analysis
Freynhagen[40]	DB 12-week Peripheral neuropathy pain (DPN, PHN)	PGB 150→600 PGB 600 PBO	141 132 65	Mean pain score/ Difference from PBO (ANCOVA) ITT
Baron[70]	OL 12-week[1] Peripheral neuropathy pain (DPN, PHN)	5% LDC[1] 5% LDC + PGB (150→600)[1] PGB (150→600)[1] PGB (150→600) + 5% LDC[1]	79 60 63 48	Mean change score during the combination phase[1]/ Per-protocol
Zin[71]	DB 4-week/ Peripheral neuropathy pain (DPN, PHN)	PGB 75→600 + OXC 10[5] PGB 75→600 + PBO[5]	24 29	Percentage of response[6]/ Chi-squared test
Pontari[72]	DB 6-week Chronic prostatitis/Chronic pelvic pain syndrome	PGB 150→600 PBO	218 106	Percentage of response[7]/ Comparison between groups (Mantel-Haenszel) ITT
Van Seventer[73]	DB 8-week Post-traumatic peripheral neuropathic pain	PGB 150→600 PBO	127 127	Mean pain score/ Difference from PBO (ANCOVA) ITT
Simpson[74]	DB 14-week HIV neuropathy	PGB 150→600 PBO	151 151	Mean pain score/ Difference from PBO (ANCOVA) ITT
Moon DE[75]	DB 10-week Peripheral neuropathic pain	PGB 150→600 PBO	162 78	Mean pain score/ Difference from PBO (ANCOVA) ITT
Gray[76]	DB 4-week Severe burn injury pain	PGB 150→600 PBO	46 44	Mean change in sharp and hot pain (NPS)/ *t*-test

Results	% Responders-50% (*P*-value)	% Drop-outs due to AEs (*P*-value)	Mean final dose
[*P*-value ≤ 0.01][2] [*P*-value ≤ 0.01][2]	48.2 (<0.001) 52.3 (<0.001) 24.2	17.0 (NA) 25.0 (NA) 7.7	372.2 481.5
–0.7 (SD 1.2) –2.5 (SD 1.6) –0.6 (SD 1.3) –1.7 (SD 1.8)	–	1.3 11.7 1.6 10.4	–
69 76 [*P*-value 0.581]	58 (0.551) 66	4.2 (NA) 3.4	–
47.2 35.8 [*P*-value 0.07]	–	–	–
–0.62 (–1.09, –0.15) [0.01]	39.7[3] (<0.05) 25.4[3]	20 (NA) 7	326
–0.25 [*P*-value 0.3914][4]	38.9 (0.5003) 42.8	6 (NA) 2.6	385.7
–0.50 (–1.00, 0.00) [0.049]	26.1 (0.041) 14.3	5 (NA) 7.7	480 513
PGB > PBO ("sharp pain" *P* = 0.04; "hot pain" *P* = 0.01)[8]	–	6.52 (NA) 6.82	520 574

Notes: [1]4-week comparative phase (5% LDC vs. PGB) followed by 8-week combination phase (patients with NRS ≤ 4 continued in monotherapy, whereas those with NRS > 4 initiated combination therapy with either PGB or LDC, whatever drug they were not in); [2]Results are presented in a figure. Only *P*-value is provided; [3]Percentage of responders with ≤30% reduction in pain from baseline to the end-point; [4]95% Confidence Interval is not provided; [5]Patients were randomized one week before to double-blinded oxycodone or placebo. After 1 week, open-label pregabalin was added in both groups for 4 weeks; [6]Response defined as at least a 2 cm reduction in the pain-intensity score and a pain-intensity score <4 cm measured by a visual analogic scale from baseline, following PGB dose escalation; [7]Response defined as a decrease in the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) score of at least 6 points from baseline to week 6; [8]When correcting for multiplicity (using $P < 0.025$) only "hot pain" is significantly improved in PGB group compared with PBO group.

Abbreviations: DB, double-blind; DPN, Diabetic polineuropathy; LDC, lidocaine; NS, non-significant difference; NA, not available; NPS, Neuropathic Pain Scale; OXC, oxycodone; PBO, placebo; PHN, Post-herpetic neuralgia; PGB, pregabalin.

syndrome secondary to a chronic prostatitis,[72] and there were no significant differences from placebo in patients with HIV neuropathy.[74]

Treatment of refractory neuropathic pain

Despite the availability of several effective drugs for the treatment of neuropathic pain, many patients are resistant or intolerant to treatment.[77] However, there are no reliable data on the prevalence of treatment-refractory neuropathic pain, probably because there is no standard definition for refractoriness, although some attempts have been recently made.[78] Several surveys performed in Europe and the USA among patients with neuropathic pain have reported that, despite the patients receiving several drugs for pain treatment, moderate to severe levels of pain are common and are associated with a significant burden from poor quality of life, loss of productivity and elevated use of health resources.[17,79,80] Suboptimal treatment of neuropathic pain is frequent[17,81] and may contribute to these poor treatment results.

Several studies have been published on the use or pregabalin in patients with treatment-refractory neuropathic pain.[82–87] However, none of these studies was a randomized clinical trial; therefore, the data we are presenting below should be interpreted with caution.

Freynhagen et al reported a 4-week, non-comparative, prospective trial of pregabalin in 55 patients with several painful neuropathic conditions refractory to their previous treatments.[82] In this study, there was a significant 25% reduction in the pain score, and a significant and rapid improvement was observed in the sleep interference score and quality of life.[82] Using a design which alternated periods of 3-month treatments with pregabalin and drug-holiday periods of 3 to 28 days, Stacey et al showed that pregabalin (150–600 mg/day) was associated with clinically meaningful and sustained improvement of pain in patients with postherpetic neuralgia or painful diabetic peripheral neuropathy that was refractory to other treatments.[83] In one of the two comparative studies, 197 patients with chronic neuropathic pain of several origins who had shown unsatisfactory responses to other treatments were assigned, according to a neurologist's decision, to either receive pregabalin (add-on or monotherapy) or change the dose and/or combinations that the patients were receiving previously.[84] After 4 weeks, the patients assigned to pregabalin showed a significantly greater pain reduction than the patients on the other regimens.[84] The second comparative study consisted of a secondary analysis of a prospective, naturalistic 12-week study in which 683 patients with refractory low-back pain, 83% of whom had received pregabalin, were analyzed.[86] The authors found a 62% response rate in the pregabalin-treated patients and a 37% rate in those patients under usual care ($P < 0.001$).[86] Similar results were observed in another secondary analysis of a naturalistic study in 312 patients with refractory neck pain.[87] In this latter analysis, patients who were added pregabalin to their current regimen exhibited a higher response rate than patients under usual care (55% vs. 38%, $P < 0.001$).[87] Interestingly, in 29 gabapentin non-responders with peripheral neuropathy who completed the 12-month follow-up period, switching to pregabalin was associated with a significant 24% reduction in pain and a significant improvement in the quality of life.[85]

Plested et al performed a systematic review of pregabalin, a lidocaine plaster and duloxetine in patients with refractory neuropathic pain.[88] It included four of the 5 studies with pregabalin mentioned above and 3 studies published only as abstracts. According to the authors, significant pain reduction was reported in all 7 of the studies involving pregabalin, while only one study using lidocaine reported a significant reduction; there was only one study with duloxetine.[88]

Pregabalin in combination therapy

In clinical practice, it is common for patients with neuropathic pain to require treatment with more than one drug to obtain adequate pain control.[14] In addition, drug treatment for psychological distress or for the side effects of the main treatment is sometimes needed and contributes to the frequent polypharmacy in these patients.[14]

Information from randomized clinical trials on the use of combination therapies in patients with neuropathic pain has only recently become available. Interestingly, most of these trials involve the use of gabapentin or pregabalin, probably because of their pharmacodynamic and pharmacokinetic advantages: a novel mechanism of action for pain relief and an

almost complete lack of drug-drug interactions. A brief review of those trials can be found elsewhere.[13]

Randomized trials of pregabalin in combination therapy have been discussed above. Overall, the available data suggest that some combinations involving pregabalin may be useful, including combinations with amitriptyline for the treatment of painful diabetic neuropathy,[51] with 5% lidocaine for the treatment of postherpetic neuralgia[54] and with celecoxib for the treatment of low-back pain.[60] By contrast, the combination of pregabalin with oxycodone was not useful in a randomized clinical trial in patients with peripheral neuropathic pain.[71] In a non-randomized trial, however, this combination showed improved pain relief at lower doses than either treatment alone.[89]

When using a combination strategy, principles of rational poplypharmacy should be bear in mind which include take the advantage of complementary mechanism of action (eg, using pregabalin or gabapentin with serotonin norepinephrine reuptake inhibitors [SNRIs], opiods or other drugs), avoid additive adverse events (eg, avoiding the use of a SNRI with another antidepressant or tramadol) or decrease the risk of drug-drug interactions, among others.[90]

Experience with pregabalin in the clinical practice setting

Besides to the previously commented naturalistic studies in patients with refractory pain, we have run a series of studies and analyses of pregabalin for the treatment of various neuropathic conditions in the clinical practice setting.[91–96] Two of these studies were run with a similar design: 12-week studies in patients with chronic pain treated in the primary care setting with a diagnosis of neuropathic pain[91,92] or painful radiculopathy.[93,94] In addition, we performed a specific analysis of patients with trigeminal neuralgia.[95,96]

In patients with chronic pain due to diabetic neuropathy, post-herpetic or trigeminal neuralgia we found that treatment with pregabalin, either as monotherapy or add-on therapy, was associated with large effect on pain and associated symptoms such as sleep disturbance and mood disorders, improving disability and quality of life.[91] This improvement in patients receiving pregabalin was associated to reductions in health resources and cost as compared with patients receiving a non-pregabalin treatment regimen.[92] We observed almost identical results in clinical and pharmacoeconomic outcomes in patients with painful lumbar or cervical radiculopathy.[93,94] Finally, in an analysis of patients with trigeminal neuralgia,

Table 6. Main differences between pregabalin and gabapentin.

Characteristic	Pregabalin	Gabapentin
Indications	– Peripheral neuropathy – Central neuropathy[a] – Adjunctive therapy for adult patients with partial onset seizures – Management of fibromialgia[b] – Generalized anxiety disorder[a]	– Peripheral neuropathy[c] – Adjunctive therapy in the treatment of partial seizures.
Absorption	Not saturable	Saturable
Linear pharmacokinetics	Yes	No
Bioavailability	>90%	Drops from 60% to 33% as the dosage increases
Tmax	1 hour	3–4 hours
Dosage frequency	Every 8–12 hours	Every 8 hours
Effective dose	150–600 mg/day	1.200–2.400 mg/day
Clinical result: number of positive (+) and negative (–) RCTs[d]:		
– PDN	6+	3+/1–
– PHN	4+	2+
– HIV neuropathy	1–	1+/1–
– Central neuropathic pain	2+/1–	1–

Notes: [a]Only in Europe; [b]Only in USA; [c]In USA only indicated for postherpetic neuralgia; [d]Data for gabapentin from reference 115.
Abbreviations: HIV, human immunodeficiency virus; PDN, painful diabetic neuropathy; PHN, postherpetic neuralgia; RCTs, randomized clinical trials.

Table 7. Most common (>5%) adverse reactions in premarketing clinical trials of pregabalin in the treatment of painful diabetic neuropathy and postherpetic neuralgia.

Body system-preferred term	Painful diabetic neuropathy					
	75 mg/day [N = 77] %	150 mg/day [N = 212] %	300 mg/day [N = 321] %	600 mg/day [N = 369] %	All PGB* [N = 979] %	Placebo [N = 459] %
Dizziness	8	9	23	29	21	5
Somnolence	4	6	13	16	12	3
Peripheral edema	4	6	9	12	9	2
Dry mouth	3	2	5	7	5	1
Infection	–	–	–	–	–	–
Headache	–	–	–	–	–	–
Asthenia	4	2	4	7	5	2
Constipation	0	2	4	6	4	2
Weight gain	0	4	4	6	4	0
Accidental injury	5	2	2	6	4	3
Edema	0	2	4	2	2	0
Neuropathy	9	2	2	5	4	3
Ataxia	6	1	2	4	3	1
Confusion	0	1	2	3	2	1
Thinking abnormal†	1	0	1	3	2	0
Abnormal gait	1	0	1	3	1	0

treatment with pregabalin was associated with a significant and clinically relevant reduction of pain, anxiety and depressive symptoms, sleep disturbance and an improvement in patient functioning and health related quality of life.[95] Again, this clinical effect was accompanied by a reduction in health resource utilization and an improvement in work productivity.[96]

Pregabalin or Gabapentin: Does It Make a Difference from the Clinical Perspective?

We have previously commented on the differences in the pharmacology of pregabalin and gabapentin. Briefly, a higher affinity for the α_2-δ_1 subunit, a greater rate of absorption and linear pharmacokinetics, among others, distinguish pregabalin from its parent compound. A summary of these differences is presented in Table 6. Do these pharmacological differences translate into any differences in clinical benefits? Although there are no head-to-head randomized clinical trials comparing pregabalin with gabapentin, the data from some observational studies and other designs suggest that pregabalin may be somewhat superior to gabapentin.

The only prospective, direct comparison of pregabalin and gabapentin is a post-hoc analysis of two multicenter, prospective, 12-week studies that were conducted to evaluate the costs associated with neuropathic pain secondary to diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia and radiculopathy.[97] From these two studies, we selected all the patients treated with gabapentin (n = 44) and a matched group of pregabalin-treated patients (n = 88). At the end of the study, we found a significantly greater reduction in the last-week mean pain score with pregabalin. The pain control was also significantly greater with pregabalin, which had a 61% response rate versus 41% for gabapentin; we consider this difference to be clinically relevant.[97] We also found that the patients who received pregabalin showed a greater reduction in the number of medical visits and in the consumption of other analgesics, particularly opiates, which supports the hypothesis of better pain control with pregabalin.[97] In a retrospective evaluation of the use of these two drugs in patients with postherpetic neuralgia, Gore et al found that opioid use increased after initiating treatment with gabapentin and decreased after initiating pregabalin, which supports our results.[98] The differences in the pharmacokinetics of pregabalin and gabapentin may also account for the differences in efficacy. In these two studies, a greater proportion of the patients treated with pregabalin reached the therapeutic dose

Postherpetic neuralgia					
75 mg/d [N = 84] %	150 mg/d [N = 302] %	300 mg/d [N = 312] %	600 mg/d [N = 154] %	All PGB* [N = 852] %	Placebo [N = 398] %
11	18	31	37	26	9
8	12	18	25	16	5
0	8	16	16	12	4
7	7	6	15	8	3
14	8	6	3	7	4
5	9	5	8	7	5
–	–	–	–	–	–
4	5	5	5	5	2
1	2	5	7	4	0
4	3	3	5	3	2
0	1	2	6	2	1
–	–	–	–	–	–
1	2	5	9	5	1
1	2	3	7	3	0
0	2	1	6	2	2
0	2	4	8	4	1

than those treated with gabapentin.[97,98] Due to its pharmacokinetic characteristics, gabapentin requires high doses to achieve therapeutic levels (ie, 1,800 to 3,600 mg/day) but should be started at a relatively low dose (ie, 300 mg/day),[99] while pregabalin can be started at 150 mg/day, which is the lower limit of the therapeutic dose range.[20] However, based in our experience, in order to minimize tolerability problems, we recommend starting pregabalin at a dose of 75 mg/day for 2–3 days and then increased the dose up to 150 mg/day.

Again, there are no data from randomized clinical trials that support the superiority of pregabalin over gabapentin. Using simulation models based on the results from clinical trials, however, it has been reported that treatment with pregabalin resulted in more days with no or mild pain and more days with 50% reduction in pain intensity than did treatment with gabapentin[100,101] In addition, in a systematic review of the literature on the efficacy of pregabalin and gabapentin for the treatment of neuropathic pain in spinal cord injury, Tzellos et al reported that results from randomized trials support the superior efficacy of pregabalin when compared to gabapentin using several important outcome variables, although pregabalin is associated with more side effects than gabapentin.[69]

Data from other therapeutic areas also support this potential superiority of pregabalin over gabapentin. In a meta-analysis of randomized-controlled trials of pregabalin and gabapentin in patients with partial epilepsy, Delahoy et al reported that pregabalin shows a significantly higher response rate at a dose of 300 mg and 600 mg versus gabapentin at 1200 mg and 1800 mg, respectively.[102] An analysis of a prescription database showed that, among psychiatric patients, benzodiazepine use was reduced by 48% in patients treated with pregabalin, compared to a 14% reduction in patients who received gabapentin.[103] In another analysis of a database of patients with fibromyalgia, patients who were newly prescribed pregabalin showed a significant decrease in the consumption of nonsteroidal anti-inflammatory drugs, anticonvulsants and combination therapies, while patients treated with gabapentin showed a significant increase in the use of opioids, SNRIs, anticonvulsants, benzodiazepines and combination therapies.[104]

Finally, switching from gabapentin to pregabalin was associated with a 25% reduction of pain for both gabapentin responders and non-responders in a cohort study.[85] Some authors believe that the efficacy of pregabalin in gabapentin non-responders suggests the presence of an additional analgesic mechanism that is

specific to pregabalin.[105] In the clinical practice, the development of tolerance to gabapentin is not uncommon and might also explain the response to pregabalin in patients unsuccessfully treated with gabapentin.

Tolerability and Safety

Pregabalin was generally well tolerated in premarketing clinical trials, with most of the adverse reactions being of mild to moderate severity, dose-dependent and self-limited. In clinical trials in patients with neuropathic pain associated with diabetic peripheral neuropathy or postherpetic neuralgia, 9%–14% of patients treated with pregabalin and 4%–7% of those treated placebo discontinued treatment prematurely due to adverse reactions.[20] In these populations, the most frequent adverse reactions were dizziness, somnolence and peripheral edema (Table 7). The most frequent adverse reactions leading to drug discontinuation were dizziness (3%–4%) and somnolence (2%–3%).

In controlled clinical trials, 0.5% of the pregabalin patients and 0.2% of the placebo patients withdrew due to peripheral edema. Importantly, there was no apparent association between peripheral edema and cardiovascular complications, such as hypertension or congestive heart failure. In addition, peripheral edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function.[20]

Pregabalin treatment may cause weight gain. In controlled clinical trials of pregabalin use for up to 14 weeks, a gain of 7% or more over the baseline weight was observed in 9% of the pregabalin-treated patients and 2% of the placebo-treated patients. Few of the patients treated with pregabalin (0.3%) withdrew from the controlled trials due to weight gain. The pregabalin-associated weight gain was related to dose and duration of exposure, but did not appear to be associated with baseline BMI, gender, or age. The weight gain was not limited to patients with edema. While the effects of pregabalin-associated weight gain on glycemic control have not been systematically assessed, in controlled and longer-term open-label clinical trials with diabetic patients, pregabalin treatment did not appear to be associated with loss of glycemic control (as measured by HbA_{1C}).[20]

Following the abrupt or rapid discontinuation of pregabalin, some patients have reported symptoms that include insomnia, nausea, headache, and diarrhea. As with other psychotropic medications (eg, most antidepressants), therefore, pregabalin should be tapered down gradually over a minimum of 1 week rather than discontinued abruptly.

The overall adverse event profile of pregabalin was similar between women and men[20] and between young adults and elderly patients.[106] Among elderly patients with diabetic peripheral neuropathy or postherpetic neuralgia, moreover, the proportion of patients with any of the most common adverse reactions (ie, dizziness, somnolence, peripheral edema, asthenia, dry mouth, weight gain) did not differ in patients aged 75 years or older and patients aged 65 to 74 years.[106]

The Place of Pregabalin in the Pharmacotherapy of Neuropathic Pain

With the exception of some randomized clinical trials comparing pregabalin with amitriptyline, oxycodone and lidocaine for a few neuropathic conditions, there are no head-to-head comparisons of pregabalin with other pharmacological treatments for neuropathic pain. Therefore, it is difficult to establish the relative place of pregabalin in particular, and of calcium channel α_2-δ_1 ligands in general, in the treatment of neuropathic pain conditions. However, recommendations and/or guidelines prepared by scientific societies do provide valuable information in this regard.

In Table 8, we provide a summary of the recommendations of several scientific associations or groups on the treatment of neuropathic pain in general[13,108–111] and on the treatment of specific conditions, such as painful diabetic neuropathy[107,112] or postherpetic neuralgia.[113] Together with tricyclic antidepressants, pregabalin (and in most guidelines gabapentin as well) is considered the first line pharmacological treatment for both peripheral and central neuropathic pain. Serotonin and noradrenaline reuptake inhibitors, especially duloxetine, are also considered a first-line option for the treatment of painful diabetic neuropathy. In addition, topical lidocaine is also considered a first-line treatment for postherpetic neuralgia. Finally, the standard first-line treatment for trigeminal neuralgia is carbamazepine or oxcarbazepine. As has been suggested for peripheral neuropathic pain,[114] calcium channel α_2-δ_1 ligands may be better options than tricyclic antidepressants, if we take tolerability into account. Again, comparative data for the various drugs in the

Table 8. Treatment recommendations for neuropathic pain according to recent guidelines.

Guideline reference		Peripheral neuropathic pain			Central neuropathic pain		
		PDN	PHN	Other	SCI	Stroke	Other
AAN-AANEM-AAPMR Bril[107]	1st	PGB[a]	–	–	–	–	–
	2nd	DLX, VEN, AMT, GBP, valproate, opiods, capsaicin[b]					
IASP Dworkin[108] Dworkin[13]	1st	TCA/SNRI/PGB-GBP	TCA/PGB-GBP/LDC	–	PGB-GBP/TRM	TCA/PGB-GBP	CNB [MS]
	2nd	TRM/Opiods			Any 1st line drug for peripheral neuropathic pain		
EFNS Attal[109]	1st	TCA/SNRI/PGB-GBP	TCA/PGB-GBP/LDC	CBM/OCB [TN]	TCA/PGB-GBP		
	2nd	TRM/Opiods	Capsaicin/opiods	Surgery [TN]	CNB [MS]/LMT/Opiods/TRM [SCI]		
NICE National Institute for Health and Clinical Excellence[110]	1st	DLX/AMT	AMT/PGB				
	2nd	If DLX: switch to AMT or PGB, or combine with PGB; if AMT: switch to or combine with PGB	Switch or combine each other				
CPS Moulin[111]	1st	TCA/PGB-GBP					
	2nd	SNRI/LDC					
ASPE American Society of Pain Educators[112]	1st	DLX/OXC/PGB/TCA	–	–	–	–	–
	2nd	CBM/GBP/LMT/TRM/VEN	–	–	–	–	–
AAN Dubinsky[113]	1st	–	PGB-GBP/TCA/ Opiods/LDC	–	–	–	–
	2nd						

Notes: [a]The guidelines recommend that pregabalin should be offered for the treatment of PDN (Level A of evidence); [b]The guidelines recommend that these drugs should be considered for the treatment of PDN (Level B of evidence).

Abbreviations: AAN, American Academy of Neurology; AANEM, American Association of Neuromuscular and Electrodiagnostic Medicine; AAPMR, American Academy of Physical Medicine and Rehabilitation; AMT, amitriptyline; ASPE, American Society of Pain Educators; CBM, carbamazepine; CNB, cannabinoids; CPS, Canadian Pain Society; DLX, duloxetine; EFNS, European Federation of Neurological Societies; GBP, gabapentin; IASP, International Association for the Study of Pain; LDC, lidocaine; LMT, lamotrigine; MS, multiple sclerosis; NICE, National Institute for Health and Clinical Excelence; OCB, oxcarbazepine; OXC, oxycodone; SCI, spinal cord injury; SNRI, serotonina noradrenaline reuptake inhibitors (duloxetine and venlafaxine); TCA, tricyclic antidepressants; TN, trigeminal neuralgia; TRM, tramadol; VEN, venlafaxine.

treatment of neuropathic pain are scarce; therefore, firm conclusions on this subject are not possible. There have been two comparisons between pregabalin and amitriptyline in the treatment of painful neuropathic conditions,[35,51] but only one provided sufficient tolerability information.[35] In that study, as has been previously mentioned, amitriptyline (at a mean dose of 16 mg/day) was associated with a significantly higher risk of withdrawal due to adverse reactions than was pregabalin.[35] In our view, the tolerability advantages of pregabalin over the tricyclic antidepressants are likely to exist in elderly patients, but they should be further evaluated in young adults. Overall, pregabalin accounts for the largest body of evidence for the treatment of neuropathic pain, regarding both the number of randomized clinical trials performed and the indications evaluated.

In addition to efficacy and overall tolerability issues, certain other factors should be considered when selecting a drug for the treatment of neuropathic pain. Elderly patients are particularly sensitive to the anticholinergic side effects of tricyclic antidepressants, such as tachycardia, urinary retention, constipation, dry mouth, blurred vision, and exacerbation of narrow-angle glaucoma. The central nervous system anticholinergic effects include cognitive impairment, psychomotor slowing, confusion, sedation, and delirium, and they may be associated with an increased risk for falls. Overall, tricyclic antidepressants patients should be started on low doses, and elderly patients should be observed closely during treatment; in many patients, they should be avoided. The main contraindications and precautions of the first-line drugs for the treatment of neuropathic pain are presented in Table 9.

Table 9. Main contraindication and precautions for first-line medications for the treatment of neuropathic pain.

Comorbidity/factor	Avoid	Use with caution
Glaucoma	TCA, duloxetine	Venlafaxine
Suicidality	Tramadol	Duloxetine, Gabapentin, Pregabalin, TCA, Venlafaxine
Abuse/dependence		Tramadol[1]
Hypertension		Duloxetine, Venlafaxine
Orthostatic Hypotension and Syncope		TCA, Duloxetine[2]
Cardiovascular disease (eg, heart failure, myocardial infarction)	TCA[3]	Venlafaxine, Pregabalin[4]
Cholesterol		Venlafaxine
Risk of bleeding (use of NSAIDs, aspirin or other drugs that alter coagulation)		Duloxetine, Venlafaxine
History of seizures		Tramadol[5], Duloxetine, Venlafaxine
Hyperthyroidism		Venlafaxine
Weight gain		Pregabalin
Renal impairment		Duloxetine[6], TCA, venlafaxine
Hepatic impairment	Duloxetine[7]	TCA, venlafaxina, Lidocaine[8]
Risk of respiratory depression		Tramadol
Patients receiving CNS depressants such as alcohol, opioids, anesthetic agents, narcotics, phenothiazines, tranquilizers or sedative hypnotics		Tramadol
Patients using opiods		Gabapentin[9]
History of angioedema		Pregabalin

Notes: [1]Proper assessment of the patient and periodic re-evaluation of therapy are appropriate measures that help to limit the potential abuse of this product; [2]The risk of blood pressure decreases may be greater in patients taking concomitant medications that induce orthostatic hypotension (such as antihypertensives) or are potent CYP1A2 inhibitors; [3]These drugs are not recommended for use during the acute recovery phase following myocardial infarction. Patients with any evidence of cardiovascular disease require cardiac surveillance at all dosage levels of the drug; [4]Because there are limited data on congestive heart failure patients with New York Heart Association (NYHA) Class III or IV cardiac status, exercise caution when using pregabalin in these patients; [5]Risk of convulsions may increase in patients with epilepsy, those with a history of seizures, in patients with a recognized risk for seizure (such as head trauma, metabolic disorders, alcohol and drug withdrawal, CNS infections) or in patients receiving antidepressants; [6]Duloxetine should ordinarily not be used in patients with end-stage renal disease or severe renal impairment (creatinine clearance $<$30 mL/min). Increased plasma concentration of duloxetine, and especially of its metabolites, occur in patients with end-stage renal disease (requiring dialysis); [7]Duloxetine should not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease; [8]Patients with severe hepatic disease are at greater risk of developing toxic blood concentrations of lidocaine, because of their inability to metabolize lidocaine normally; [9]Patients who require concomitant treatment with morphine may experience increases in gabapentin concentrations. Patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of Neurontin or morphine should be reduced appropriately.

Conclusions

Neuropathic pain is a difficult to treat chronic condition. Pregabalin, an α_2-δ ligand, has demonstrated to be effective in several peripheral neuropathic painful conditions such as diabetic peripheral neuropathy, post-herpetic neuralgia and trigeminal neuralgia, as well as central neuropathic pain. In fact, pregabalin is the only drug in Europe approved for the treatment of central neuropathic pain. An important advantage of pregabalin, shared with gabapentin, is the lack of hepatic metabolism and lack of interaction with cytochrome P450 that confers these two drugs a reduced risk for drug-drug interactions. This latter characteristic and the distinctive mechanism of action make pregabalin an attractive drug for use in combination for the treatment of neuropathic pain. Most common adverse reactions with pregabalin are dizziness, somnolence, weight gain and peripheral edema. Central nervous system adverse reactions (eg, dizziness and somnolence) can be minimized with a slower dose titration. Overall, these characteristics of pregabalin explain why it has been placed among first-line treatments for neuropathic pain in most evidence-based clinical guidelines.

Acknowledgements

Neither author has received any direct or indirect commercial financial incentive associated with publishing this article.

Competing Interests

In the past three years, Perez C has received research support, consulting, or speaking fees from Grünenthal, Lilly/Boehringer, Astellas, Pfizer Pharma, Mundipharma, Boston Cientifics, Prostakan, Ferrer, Eisai; Margarit C has received research support, consulting, or speaking fees from Grünenthal, Lilly/Boehringer, Mundipharma, Pfizer, Janssen-Cilag, Astellas, Ferrer and Galvez R has received consulting and speaking fees from Grünenthal, Janssen-Cilag, Lilly/Boehringer; Mundipharma, Medtronic, Pfizer, Astellas, Ferrer, Eisai.

Disclosures

Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

References

1. Treede RD, Jensen TS, Campbell JN, et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. *Neurology*. Apr 29, 2008;70(18):1630–5.
2. Torrance N, Smith BH, Bennett MI, Lee AJ. The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey. *J Pain*. Apr 2006;7(4):281–9.
3. Bouhassira D, Lantéri-Minet M, Attal N, Laurent B, Touboul C. Prevalence of chronic pain with neuropathic characteristics in the general population. *Pain*. Jun 2008;136(3):380–7.
4. Schmader KE. Epidemiology and impact on quality of life of postherpetic neuralgia and painful diabetic neuropathy. *Clin J Pain*. 2002;18(6):350–4.
5. Doth AH, Hansson PT, Jensen MP, Taylor RS. The burden of neuropathic pain: a systematic review and meta-analysis of health utilities. *Pain*. May 2010;149(2):338–44. Epub 2010 Mar 15.
6. Berger A, Dukes EM, Oster G. Clinical characteristics and economic costs of patients with painful neuropathic disorders. *J Pain*. 2004;5:143–9.
7. Rodríguez MJ, García AJ, for the Investigators of Collaborative Study REC. A registry of the aetiology and costs of neuropathic pain in pain clinics: Results of the registry of etiologies and costs (REC) in neuropathic pain disorders study. *Clin Drug Investig*. 2007;27:771–82.
8. Gore M, Brandenburg NA, Dukes E, Hoffman DL, Tai KS, Stacey B. Pain severity in diabetic peripheral neuropathy is associated with patient functioning, symptom levels of anxiety and depression, and sleep. *J Pain Symptom Manage*. 2005;30(4):374–85.
9. Argoff CE. The coexistence of neuropathic pain, sleep, and psychiatric disorders: a novel treatment approach. *Clin J Pain*. Jan 2007;23(1):15–22.
10. Cornwall A, Donderi DC. The effect of experimentally induced anxiety on the experience of pressure pain. *Pain*. 1988;35(1):105–13.
11. Smith MT, Haythornthwaite JA. How do sleep disturbance and chronic pain inter-relate? Insights from the longitudinal and cognitive-behavioral clinical trials literature. *Sleep Med Rev*. Apr 2004;8(2):119–32.
12. Wilson KG, Eriksson MY, D'Eon JL, Mikail SF, Emery PC. Major depression and insomnia in chronic pain. *Clin J Pain*. Mar–Apr 2002;18(2):77–83.
13. Dworkin RH, O'Connor AB, Audette J, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. *Mayo Clin Proc*. Mar 2010;85(3 Suppl):S3–14.
14. Harden N, Cohen M. Unmet needs in the management of neuropathic pain. *J Pain Symptom Manage*. 2003;25(5 Suppl):S12–7.
15. Pérez C, Saldaña MT, Navarro A, Vilardaga I, Rejas J. Prevalence and characterization of neuropathic pain in a primary-care setting in Spain: a cross-sectional, multicentre, observational study. *Clin Drug Investig*. 2009;29(7):441–50.
16. Tolle T, Xu X, Sadosky AB. Painful diabetic neuropathy: a cross-sectional survey of health state impairment and treatment patterns. *J Diabetes Complications*. 2006;20(1):26–33.
17. Tolle T, Dukes E, Sadosky A. Patient burden of trigeminal neuralgia: results from a cross-sectional survey of health state impairment and treatment patterns in six European countries. *Pain Pract*. 2006b;6(3):153–60.
18. van Seventer R, Sadosky A, Lucero M, Dukes E. A cross-sectional survey of health state impairment and treatment patterns in patients with postherpetic neuralgia. *Age Ageing*. 2006;35(2):132–7.

19. O'Connor AB, Dworkin RH. Treatment of neuropathic pain: an overview of recent guidelines. *Am J Med*. Oct 2009;122(10 Suppl):S22–32.
20. Lyrica Prescribing Information. Available at: http://www.lyrica.com/main_prescribing_info.aspx.
21. Perret D, Luo ZD. Targeting voltage-gated calcium channels for neuropathic pain management. *Neurotherapeutics*. Oct 2009;6(4):679–92.
22. Gajraj NM. Pregabalin: its pharmacology and use in pain management. *Anesth Analg*. Dec 2007;105(6):1805–15.
23. Jones DL, Sorkin LS. Systemic gabapentin and S(+)-3-isobutyl-gamma-aminobutyric acid block secondary hyperalgesia. *Brain Res*. Nov 9, 1998;810(1–2):93–9.
24. Bockbrader HN, Wesche D, Miller R, Chapel S, Janiczek N, Burger P. A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. *Clin Pharmacokinet*. Oct 1, 2010;49(10):661–9.
25. Bockbrader HN, Burger P, Knapp L. Pregabalin effect on steady-state pharmacokinetics of carbamazepine, lamotrigine, phenobarbital, phenytoin, topiramate, valproate, and tiagabine. *Epilepsia*. Feb 2011;52(2):405–9.
26. Tesfaye S, Stevens LK, Stephenson JM, et al. Prevalence of diabetic peripheral neuropathy and its relation to glycaemic control and potential risk factors: the EURODIAB IDDM Complications Study. *Diabetologia*. Nov 1996;39(11):1377–84.
27. Tesfaye S, Boulton AJ, Dyck PJ, et al. Toronto Diabetic Neuropathy Expert Group. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. *Diabetes Care*. Oct 2010;33(10):2285–93.
28. Galer BS, Gianas A, Jensen MP. Painful diabetic polyneuropathy: epidemiology, pain description, and quality of life. *Diabetes Res Clin Pract*. Feb 2000;47(2):123–8.
29. Chong MS, Hester J. Diabetic painful neuropathy: current and future treatment options. *Drugs*. 2007;67(4):569–85.
30. Lesser H, Sharma U, LaMoreaux L, Poole RM. Pregabalin relieves symptoms of painful diabetic neuropathy: a randomized controlled trial. *Neurology*. Dec 14 2004;63(11):2104–10.
31. Rosenstock J, Tuchman M, LaMoreaux L, Sharma U. Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. *Pain*. Aug 2004;110(3):628–38.
32. 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*. Apr 2005;6(4):253–60.
33. Tölle T, Freynhagen R, Versavel M, Trostmann U, Young JP Jr. Pregabalin for relief of neuropathic pain associated with diabetic neuropathy: a randomized, double-blind study. *Eur J Pain*. Feb 2008;12(2):203–13.
34. Arezzo JC, Rosenstock J, Lamoreaux L, Pauer L. Efficacy and safety of pregabalin 600 mg/d for treating painful diabetic peripheral neuropathy: a double-blind placebo-controlled trial. *BMC Neurol*. Sep 16 2008;8:33.
35. Bansal D, Bhansali A, Hota D, Chakrabarti A, Dutta P. Amitriptyline vs. pregabalin in painful diabetic neuropathy: a randomized double blind clinical trial. *Diabet Med*. Oct 2009;26(10):1019–26.
36. Satoh J, Yagihashi S, Baba M, et al. Efficacy and safety of pregabalin for treating neuropathic pain associated with diabetic peripheral neuropathy: a 14 week, randomized, double-blind, placebo-controlled trial. *Diabet Med*. Jan 2011;28(1):109–16. doi: 10.1111/j.1464-5491.2010.03152.x.
37. Freeman R, Durso-Decruz E, Emir B. Efficacy, safety, and tolerability of pregabalin treatment for painful diabetic peripheral neuropathy: findings from seven randomized, controlled trials across a range of doses. *Diabetes Care*. Jul 2008;31(7):1448–54.
38. Hurley RW, Lesley MR, Adams MC, Brummett CM, Wu CL. Pregabalin as a treatment for painful diabetic peripheral neuropathy: a meta-analysis. *Reg Anesth Pain Med*. Sep–Oct 2008;33(5):389–94.
39. Quilici S, Chancellor J, Löthgren M, et al. Meta-analysis of duloxetine vs. pregabalin and gabapentin in the treatment of diabetic peripheral neuropathic pain. *BMC Neurol*. Feb 10, 2009;9:6.
40. 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*. Jun 2005;115(3):254–63.
41. Sharma U, Griesing T, Emir B, Young JP Jr. Time to onset of neuropathic pain reduction: A retrospective analysis of data from nine controlled trials of pregabalin for painful diabetic peripheral neuropathy and postherpetic neuralgia. *Am J Ther*. Nov–Dec 2010;17(6):577–85.
42. Roth T, van Seventer R, Murphy TK. The effect of pregabalin on pain-related sleep interference in diabetic peripheral neuropathy or postherpetic neuralgia: a review of nine clinical trials. *Curr Med Res Opin*. Oct 2010;26(10):2411–9.
43. Russell IJ, Crofford LJ, Leon T, et al. The effects of pregabalin on sleep disturbance symptoms among individuals with fibromyalgia syndrome. *Sleep Med*. Jun 2009;10(6):604–10.
44. Bollu V, Bushmakin AG, Cappelleri JC, Chen C, Feltner D, Wittchen H. Pregabalin reduces sleep disturbance in patients with generalized anxiety disorder via both direct and indirect mechanisms. *Eur J Psychiat*. [online]. 2010;24:18–27.
45. Jiang W, Ladd S, Martsberger C, et al. Effects of pregabalin on heart rate variability in patients with painful diabetic neuropathy. *J Clin Psychopharmacol*. Apr 2011;31(2):207–13.
46. Sampathkumar P, Drage LA, Martin DP. Herpes zoster (shingles) and postherpetic neuralgia. *Mayo Clin Proc*. Mar 2009;84(3):274–80.
47. Dworkin RH, Corbin AE, Young JP Jr, et al. Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial. *Neurology*. April 22, 2003;60(8):1274–83.
48. Sabatowski R, Gálvez R, Cherry DA, et al. 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*. May 2004;109(1–2):26–35.
49. van Seventer R, Feister HA, Young JP Jr, 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*. Feb 2006;22(2):375–84.
50. Stacey BR, Barrett JA, Whalen E, Phillips KF, Rowbotham MC. Pregabalin for postherpetic neuralgia: placebo-controlled trial of fixed and flexible dosing regimens on allodynia and time to onset of pain relief. *J Pain*. Nov 2008;9(11):1006–17.
51. Achar A, Chatterjee G, Ray TG, Naskar B. Comparative study of clinical efficacy with amitriptyline, pregabalin, and amitriptyline plus pregabalin combination in postherpetic neuralgia. *Indian J Dermatol Venereol Leprol*. Jan–Feb 2010;76(1):63–5.
52. Barbarisi M, Pace MC, Passavanti MB, et al. Pregabalin and transcutaneous electrical nerve stimulation for postherpetic neuralgia treatment. *Clin J Pain*. Sep 2010;26(7):567–72.
53. Baron R, Mayoral V, Leijon G, Binder A, Steigerwald I, Serpell M. 5% lidocaine medicated plaster versus pregabalin in post-herpetic neuralgia and diabetic polyneuropathy: an open-label, non-inferiority two-stage RCT study. *Curr Med Res Opin*. Jul 2009;25(7):1663–76.
54. Rehm S, Binder A, Baron R. Post-herpetic neuralgia: 5% lidocaine medicated plaster, pregabalin, or a combination of both? A randomized, open, clinical effectiveness study. *Curr Med Res Opin*. Jul 2010;26(7):1607–19.
55. Moore RA, Straube S, Wiffen PJ, Derry S, McQuay HJ. Pregabalin for acute and chronic pain in adults. *Cochrane Database Syst Rev*. July 8, 2009;3:CD007076.
56. Verhaak PF, Kerssens JJ, Dekker J, Sorbi MJ, Bensing JM. Prevalence of chronic benign pain disorder among adults: a review of the literature. *Pain*. 1998;77(3):231–9.
57. Lawrence RC, Helmick CG, Arnett FC, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum*. 1998;41(5):778–99.
58. Elliott AM, Smith BH, Penny KI, Smith WC, Chambers WA. The epidemiology of chronic pain in the community. *Lancet*. 1999;354(9186):1248–52.
59. Freynhagen R, Baron R. The evaluation of neuropathic components in low back pain. *Curr Pain Headache Rep*. Jun 2009;13(3):185–90.
60. Romanò CL, Romanò D, Bonora C, Mineo G. Pregabalin, celecoxib, and their combination for treatment of chronic low-back pain. *J Orthop Traumatol*. Dec 2009;10(4):185–91.
61. Baron R, Freynhagen R, Tölle TR, et al. A0081007 Investigators. The efficacy and safety of pregabalin in the treatment of neuropathic pain associated with chronic lumbosacral radiculopathy. *Pain*. Sep 2010;150(3):420–7.

62. Morlion B. Pharmacotherapy of low back pain: targeting nociceptive and neuropathic pain components. *Curr Med Res Opin*. Jan 2011;27(1):11–33. Epub 2010 Nov 18.
63. Finnerup NB. A review of central neuropathic pain states. *Curr Opin Anaesthesiol*. Oct 2008;21(5):586–9.
64. Rintala DH, Loubser PG, Castro J, Hart KA, Fuhrer MJ. Chronic pain in a community-based sample of men with spinal cord injury: prevalence, severity, and relationship with impairment, disability, handicap, and subjective well-being. *Arch Phys Med Rehabil*. Jun 1998;79(6):604–14.
65. 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*. Nov 28, 2006;67(10):1792–800.
66. Vranken JH, Dijkgraaf MG, Kruis MR, et al. Pregabalin in patients with central neuropathic pain: a randomized, double-blind, placebo-controlled trial of a flexible-dose regimen. *Pain*. May 2008;136(1–2):150–7.
67. Kim JS, Bashford G, Murphy TK, Martin A, Dror V, Cheung R. Safety and efficacy of pregabalin in patients with central post-stroke pain. *Pain*. Feb 11, 2011. [Epub ahead of print.]
68. Turner JA, Cardenas DD, Warms CA, McClellan CB. Chronic pain associated with spinal cord injuries: a community survey. *Arch Phys Med Rehabil*. Apr 2001;82(4):501–9.
69. Tzellos TG, Papazisis G, Amaniti E, Kouvelas D. Efficacy of pregabalin and gabapentin for neuropathic pain in spinal-cord injury: an evidence-based evaluation of the literature. *Eur J Clin Pharmacol*. Sep 2008;64(9):851–8.
70. Baron R, Mayoral V, Leijon G, Binder A, Steigerwald I, Serpell M. Efficacy and safety of combination therapy with 5% lidocaine medicated plaster and pregabalin in post-herpetic neuralgia and diabetic polyneuropathy. *Curr Med Res Opin.* Jul 2009b;25(7):1677–87.
71. Zin CS, Nissen LM, O'Callaghan JP, Duffull SB, Smith MT, Moore BJ. A randomized, controlled trial of oxycodone versus placebo in patients with postherpetic neuralgia and painful diabetic neuropathy treated with pregabalin. *J Pain*. May 2010;11(5):462–71.
72. Pontari MA, Krieger JN, Litwin MS, et al. Chronic Prostatitis Collaborative Research Network-2. Pregabalin for the treatment of men with chronic prostatitis/chronic pelvic pain syndrome: a randomized controlled trial. *Arch Intern Med*. Sep 27, 2010;170(17):1586–93.
80. McDermott AM, Toelle TR, Rowbotham DJ, et al. The burden of neuropathic pain: Results from a cross-sectional survey. *Eur J Pain*. 2006;10:127–35.
81. Gore M, Dukes E, Rowbotham DJ, Tai KS, Leslie D. Clinical characteristics and pain management among patients with painful peripheral neuropathic disorders in general practice settings. *Eur J Pain*. Aug 2007;11(6):652–64.
82. Freynhagen R, Grond S, Schüpfer G, et al. Efficacy and safety of pregabalin in treatment refractory patients with various neuropathic pain entities in clinical routine. *Int J Clin Pract*. 2007;61:1989–96.
83. Stacey BR, Dworkin RH, Murphy K, Sharma U, Emir B, Griesing T. Pregabalin in the treatment of refractory neuropathic pain: results of a 15-month open-label trial. *Pain Med*. Nov 2008b;9(8):1202–8.
84. Lampl C, Schweiger C, Haider B, Lechner A. Pregabalin as mono- or add-on therapy for patients with refractory chronic neuropathic pain: a post-marketing prescription-event monitoring study. *J Neurol*. Aug 2010;257(8):1265–73.
85. Toth C. Substitution of gabapentin therapy with pregabalin therapy in neuropathic pain due to peripheral neuropathy. *Pain Med*. Mar 2010;11(3):456–65.
86. Morera-Domínguez C, Ceberio-Balda F, Flórez-García M, Masramón X, López-Gómez V. A cost-consequence analysis of pregabalin versus usual care in the symptomatic treatment of refractory low back pain: sub-analysis of observational trial data from orthopaedic surgery and rehabilitation clinics. *Clin Drug Investig*. 2010;30(8):517–31.
87. Flórez-García M, Ceberio-Balda F, Morera-Domínguez C, Masramón X, Pérez M. Effect of Pregabalin in the Treatment of Refractory Neck Pain: Cost and Clinical Evidence from Medical Practice in Orthopedic Surgery and Rehabilitation Clinics. *Pain Pract*. 2010 Dec 29. doi: 10.1111/j.1533-2500.2010.00430.x.
88. Plested M, Budhia S, Gabriel Z. Pregabalin, the lidocaine plaster and duloxetine in patients with refractory neuropathic pain: a systematic review. *BMC Neurol*. Nov 19, 2010;10:116.
89. Gatti A, Sabato AF, Occhioni R, Colini Baldeschi G, Reale C. Controlled-release oxycodone and pregabalin in the treatment of neuropathic pain: results of a multicenter Italian study. *Eur Neurol*. 2009;61(3):129–37.
90. Argoff CE, Backonja MM, Belgrade MJ, et al. Consensus guidelines: treatment planning and options. Diabetic peripheral neuropathic pain. *Mayo Clin Proc*. Apr 2006;81(4 Suppl):S12–25.
91. Navarro A, Saldaña MT, Pérez C, Torrades S, Rejas J. Patient-reported outcomes in subjects with neuropathic pain receiving pregabalin: evidence from medical practice in primary care settings. *Pain Med*. May 2010;11(5):719–31.
92. Navarro A, Saldaña MT, Pérez C, Torrades S, Rejas J. A cost-consequences analysis of the effect of pregabalin in the treatment of peripheral neuropathic pain in routine medical practice in primary care settings. *BMC Neurol*. Jan 20, 2011;11:7.
93. Saldaña MT, Navarro A, Pérez C, Masramón X, Rejas J. Patient-reported-outcomes in subjects with painful lumbar or cervical radiculopathy treated with pregabalin: evidence from medical practice in primary care settings. *Rheumatol Int*. Jun 2010;30(8):1005–15.
94. Saldaña MT, Navarro A, Pérez C, Masramón X, Rejas J. A cost-consequences analysis of the effect of pregabalin in the treatment of painful radiculopathy under medical practice conditions in primary care settings. *Pain Pract*. Jan–Feb 2010b;10(1):31–41.
95. Pérez C, Navarro A, Saldaña MT, Martínez S, Rejas J. Patient-reported outcomes in subjects with painful trigeminal neuralgia receiving pregabalin: evidence from medical practice in primary care settings. *Cephalalgia*. Jul 2009b;29(7):781–90.
96. Pérez C, Saldaña MT, Navarro A, Martínez S, Rejas J. Trigeminal neuralgia treated with pregabalin in family medicine settings: its effect on pain alleviation and cost reduction. *J Clin Pharmacol*. May 2009c;49(5):582–90.
97. Pérez C, Navarro A, Saldaña MT, Masramón X, Rejas J. Pregabalin and gabapentin in matched patients with peripheral neuropathic pain in routine medical practice in a primary care setting: Findings from a cost-consequences analysis in a nested case-control study. *Clin Ther*. Jul 2010;32(7):1357–70.
98. Gore M, Sadosky A, Tai KS, Stacey B. A retrospective evaluation of the use of gabapentin and pregabalin in patients with postherpetic neuralgia in usual-care settings. *Clin Ther*. Aug 2007b;29(8):1655–70.
99. Neurontin Prescribing Information. Available at: www.pfizer.com/files/products/uspi_neurontin.pdf.
100. Tarride JE, Gordon A, Vera-Llonch M, Dukes E, Rousseau C. Cost-effectiveness of pregabalin for the management of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia: a Canadian perspective. *Clin Ther*. Nov 2006;28(11):1922–34.
101. Rodríguez MJ, Díaz S, Vera-Llonch M, Dukes E, Rejas J. Cost-effectiveness analysis of pregabalin versus gabapentin in the management of neuropathic pain due to diabetic polyneuropathy or post-herpetic neuralgia. *Curr Med Res Opin*. Oct 2007b;23(10):2585–96.
102. Delahoy P, Thompson S, Marschner IC. Pregabalin versus gabapentin in partial epilepsy: a meta-analysis of dose-response relationships. *BMC Neurol*. Nov 1, 2010;10:104.
103. Bramness JG, Sandvik P, Engeland A, Skurtveit S. Does Pregabalin (Lyrica((R))) Help Patients Reduce their Use of Benzodiazepines? A Comparison with Gabapentin using the Norwegian Prescription Database. *Basic Clin Pharmacol Toxicol*. Apr 23 2010. [Epub ahead of print.]
104. Gore M, Sadosky AB, Zlateva G, Clauw DJ. Clinical characteristics, pharmacotherapy and healthcare resource use among patients with fibromyalgia newly prescribed gabapentin or pregabalin. *Pain Pract*. Sep–Oct 2009;9(5):363–74.
105. Chiechio S, Zammataro M, Caraci F, et al. Pregabalin in the treatment of chronic pain: an overview. *Clin Drug Investig*. 2009;29(3):203–13.
106. Semel D, Murphy TK, Zlateva G, Cheung R, Emir B. Evaluation of the safety and efficacy of pregabalin in older patients with neuropathic pain: results from a pooled analysis of 11 clinical studies. *BMC Fam Pract*. Nov 5, 2010;11:85.
107. Bril V, England J, Franklin GM, et al. Evidence-based guideline: Treatment of painful diabetic neuropathy: Report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology*. Apr 11 2011. [Epub ahead of print.]

108. Dworkin RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain*. Dec 5, 2007;132(3):237–51.
109. Attal N, Cruccu G, Baron R, et al. European Federation of Neurological Societies. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol*. Sep 2010;17(9):1113–e88.
110. National Institute for Health and Clinical Excellence (2010) Neuropathic pain: the pharmacological management of neuropathic pain in adults in non-specialist settings. London: National Institute for Health and Clinical Excellence. Available from: www.nice.org.uk/guidance/CG96.
111. Moulin DE, Clark AJ, Gilron I, et al. Canadian Pain Society. Pharmacological management of chronic neuropathic pain—consensus statement and guidelines from the Canadian Pain Society. *Pain Res Manag*. Spring 2007;12(1): 13–21.
112. American Society of Pain Educators. Diabetic peripheral neuropathic pain. Consensus guidelines for treatment. *J Fam Pract*. Jun 2006;Suppl:3–19.
113. Dubinsky RM, Kabbani H, El-Chami Z, Boutwell C, Ali H. Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. Sep 28, 2004;63(6):959–65.
114. Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Algorithm for neuropathic pain treatment: an evidence based proposal. *Pain*. Dec 5, 2005;118(3):289–305.
115. Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. *Pain*. 2010;150:573–81.