Issues in Emerging Health Technologies

Pregabalin for Peripheral Neuropathic Pain

Issue 67
March 2005

Summary

- ✓ **Pregabalin is an anticonvulsant drug that is under review for use in Canada. It was recently approved in the US and Europe for the treatment of adults with peripheral neuropathic pain (NeP).**
- ✓ **In most short-term randomized controlled trials (RCTs) of pregabalin in patients with diabetic peripheral neuropathy (DPN) and or post-herpetic neuralgia (PHN), there were early and significant decreases in mean pain scores. The number of subjects with ≥50% reduction in pain score was increased when pregabalin was compared to placebo.**
- ✓ **The most common adverse effects were dizziness and sleepiness. Withdrawal due to adverse events was also more frequent with pregabalin than with placebo.**
- ✓ **While pregabalin appears to be an effective treatment for NeP, there is no evidence that it offers advantages over treatments being used in Canada.**

The Technology

Pregabalin is an anticonvulsant drug that is similar to gabapentin in function but it has a faster onset of action and shorter titration period.[1] Its mechanism of action is unclear, but it is thought to relieve NeP by reducing calcium influx at nerve terminals and the subsequent release of excitatory neurotransmitters in the central nervous system.[1,2]

Regulatory Status

Pregabalin (Lyrica™) is under review for use in Canada.[3] The Food and Drug Administration (FDA) approved the use of pregabalin in the US for the management of NeP associated with DPN and PHN, in December 2004.[4] In July 2004, pregabalin was licensed for use in peripheral NeP and as an adjunctive therapy for epilepsy in the European Union (EU).[5]

Patient Group

NeP is a painful condition that results from nerve damage.[6] The two most common types of peripheral NeP are PHN, which may occur after shingles; and DPN, which affects 10% to 16% of patients with diabetes.[6,7] Patients generally present with burning, stabbing or tingling pain and numbness or increased sensitivity to touch. The pain can last indefinitely and may escalate. It can result in pain-related sleep interference, depression, anxiety and severe disability.[8]

Current Practice

There is no cure for NeP. Treatment is provided for the symptoms. Current guidelines using good quality data derived from RCTs indicate that anticonvulsants, lidocaine patch, opioid analgesics, capsaicin (topical cream) and tricyclic antidepressants (TCAs) are an evidence-based pharmacological approach to treatment.[9,10] None of these options are entirely satisfactory; and many patients respond poorly to all of them.[9,10]

The Evidence

Four good quality RCTs are published[11-14] and data from abstracts are available for other trials.[15-18] Additional data are available from the European Public Assessment Report.[5] Pregabalin's approval in the EU was based on the results of 12 RCTs, 10 of which are described in Table 1. The remaining two trials were

Table 1: Results of completed RCTs assessing pregabalin's short-term efficacy versus placebo in patients with peripheral neuropathic pain

Study	Duration (weeks)	Number of Patients*		Number of Patients with ≥50% Pain Reduction		Relative Benefit (95% CI)	NNT (95% CI)
		Placebo	Pregabalin†	Placebo	Pregabalin†		
Painful diabetic neuropathy							
DPN-014[15]	6	85	161	12	47	2.1 (1.2 to 3.7)	7 (4 to 20)
DPN-029[12]	5	97	164	17	77	2.7 (1.7 to 4.3)	3 (3 to 5)
DPN-040[5]	8	81	87	24	34	1.3 (0.9 to 2)	NE
DPN-131[13]	8	70	76	10	30	2.8 (1.5 to 5.2)	4 (3 to 9)
DPN-149[17]	12	97	299	28	110	1.3 (0.9 to 1.8)	NE
Post-herpetic neuralgia							
PHN-030[5]	5	88	84	15	18	1.3 (0.7 to 2.3)	NE
PHN-045[14]	8	81	157	8	42	2.7 (1.3 to 5.5)	6 (4 to 14)
PHN-127[11]	8	84	89	17	44	2.4 (1.5 to 3.9)	3 (2 to 6)
PHN-19[18]	13	94	276	7	83	4.0 (1.9 to 8.4)	4 (3 to 7)
Painful diabetic neuropathy and post-herpetic neuralgia							
Study-155[16]	12	65	132	15	67	2.2 (1.4 to 3.5)	4 (2 to 7)

*Intention-to-treat analysis defined as number of all randomized patients. †Some trials included >1 pregabalin-treated group. All data taken from scientific discussion document of European Public Assessment report[5] and compared with published results when available. Heterogeneity of studies prevented statistical pooling. CI=confidence interval, DPN=diabetic peripheral neuropathy, NE=not estimable with confidence, NNT=number needed to treat, PHN=post-herpetic neuralgia.

stopped prematurely for unknown reasons. The trials in Table 1 compared pregabalin in doses ranging from 150 mg/day to 600 mg/day with placebo. There were 2,367 patients treated for a period of five to 13 weeks.

In these trials, a change in pain severity was measured using an 11-point numerical rating scale (NRS), where zero was used to indicate no pain and 10 indicates the worst pain possible. The primary endpoint in all studies was the mean pain score, defined as the mean of the last seven available pain diary entries, while patients were taking the study medication. Response rates, defined as ≥50% reduction in pain score as compared with baseline, were also reported. A reduction ≥50% was equivalent on average to a reduction of three points on the NRS. This was considered to be a clinically important improvement.[19] Secondary outcomes, such as sleep interference and quality of life, were also measured. Pfizer sponsored all trials referenced in Table 1.

In most trials, there was a significant decrease in mean pain scores with pregabalin treatment compared with placebo.[11-16,18] The mean differences in pain score between placebo and pregabalin ranged from –0.18 to –1.57 points for the 300 mg daily dose[12-14,17,18] and –0.64 to –2.02 points for the 600 mg daily dose.[11,12,15-18] Results were not always significant with pregabalin 150 mg/day.[15,17] Only at the 600 mg/day dose did the pain reduction level become "much improved" or better on the patient global impression of change (PGIC) scale.[19] This was a change in pain score of –1.74 or greater, which was a clinically important improvement. The effect was rapid (as early as week 1) and sustained throughout the treatment period. Three (95% CI: 2 to 6) to seven (95% CI: 4 to 20) patients would need pregabalin treatment rather than placebo for one additional patient to have ≥50% reduction in pain from baseline (Table 1). Sleep interference also improved.[11-14]

The differences in effect size observed in the studies may be related to the dose and regimen (150 mg/day to 600 mg/day in two or three divided doses) and to the study population (DPN versus PHN).

Pregabalin also induced sleepiness, which may affect patients' perception of pain. When these patients were excluded and trial data re-analyzed, pregabalin still demonstrated a significant effect on pain reduction.[5]

Patients who failed to respond to previous treatment with gabapentin (dose ≥1,200 mg/day) were included in three out of the 10 trials.[16-18] This is the group in which Canadian clinicians would consider the use of pregabalin. It is unknown, however, how many gabapentin-refractory patients have been included in the three trials and how they responded.

Adverse Effects

The most common adverse effects observed with pregabalin versus placebo were dizziness [risk difference (RD): 19.9%, 95% CI: 18.1 to 21.7] and sleepiness (RD: 14%, 95% CI: 12.4 to 15.7).[5] Other common side effects included blurred vision (RD: 4.5%, 95% CI: 3.6 to 5.5), dry mouth (RD: 4.8%, 95% CI: 3.7 to 5.9), abnormal thinking (RD: 3.4%, 95% CI: 2.5 to 4.2), peripheral edema (RD: 5.3%, 95% CI: 4.3 to 6.2) and weight gain (RD: 5.2%, 95% CI: 4.4 to 6.0).[5]

The risk of an adverse effect occurring with pregabalin treatment was increased by 14.4% (95% CI: 12.1 to 16.7) when it was compared with placebo.[5] The RD for an event causing the subject to withdraw from a study was increased by 7.7% (95% CI: 6.2 to 9.1) with pregabalin versus placebo.[5] For one subject to have an adverse effect or to withdraw from a trial, seven patients (95% CI: 6 to 8) and 13 patients (95% CI: 11 to 16) respectively would have to receive treatment with pregabalin rather than placebo.

Administration and Cost

The price of pregabalin in Canada is not established. Pregabalin's approved dosage ranges from 150 mg/day to 600 mg/day in two to three divided doses. In the UK, a twice daily regimen is less expensive than a three times daily regimen.[20]

Concurrent Developments

In September 2004, the FDA approved the use of duloxetine (Cymbalta®) in the treatment of DPN. Duloxetine is a selective serotonin- and noradrenaline-reuptake inhibitor indicated in the treatment of major depressive disorder to be used to treat DPN.[21]

Ruboxistaurin is a protein kinase C inhibitor that is in phase III clinical trials for DPN and diabetic retinopathy.[22]

Sativex® is a cannabis-based pharmaceutical product being investigated for the management of NeP associated with multiple sclerosis.[23]

Rate of Technology Diffusion

Pregabalin's potential rate of diffusion may be based on its perceived effectiveness relative to gabapentin and its potential for off-label use.

The harm and benefit of using gabapentin in these patient groups is widely known; and it is available in a generic form.[24] Widespread use of pregabalin in NeP may require compelling evidence of an advantage from trials that directly compare pregabalin with gabapentin.

The off-label use of pregabalin could more greatly contribute to its diffusion. For example, pregabalin has been investigated in patients with generalized anxiety disorder.

Implementation Issues

The costs associated with pregabalin treatment may not compare favourably with that of generic gabapentin. However, gabapentin is not

approved for the treatment of NeP by Health Canada. While pregabalin appears to be an effective treatment for NeP, there is no evidence that it offers advantages compared with other treatments being used in Canada.

The long-term effects of treating NeP with pregabalin are largely unknown, because long-term RCTs are unavailable. Comparative cost and consequence data from head-to-head trials with recommended therapies are needed to define pregabalin's place in NeP therapy.[9,10]

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Cite as: Hadj Tahar, A. *Pregabalin for peripheral neuropathic pain* [Issues in emerging health technologies issue 67]. Ottawa: Canadian Coordinating Office for Health Technology Assessment; 2005.

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CCOHTA takes sole responsibility for this bulletin and appreciates comments from its reviewers.

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Dr. Saifee Rashiq has no financial interest in the drug or the company that makes it.

ISSN 1488-6324 (online)
ISSN 1488-6316 (print)
PUBLICATIONS MAIL AGREEMENT NO: 40026386
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CANADIAN COORDINATING OFFICE FOR
HEALTH TECHNOLOGY ASSESSMENT
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