



TITLE: Pregabalin Treatment for Patients with Fibromyalgia: Clinical Effectiveness

DATE: 30 July 2010

RESEARCH QUESTIONS:

1. What is the clinical effectiveness of pregabalin treatment for the management of symptoms of fibromyalgia?
2. What is the evidence regarding the use of pregabalin as a second-line therapy option for patients with fibromyalgia?
3. What are the adverse events and safety associated with pregabalin treatment for patients with fibromyalgia?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including PubMed, Ovid: EMBASE, the Cochrane Library (Issue 7, 2010) University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between January 1, 2005 and July 21, 2010. No filters were applied to limit the retrieval by study type. Internet links were provided, where available.

The summary of findings was prepared from the abstracts of the relevant information. Please note that data contained in abstracts may not always be an accurate reflection of the data contained within the full article.

RESULTS:

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials and non-randomized studies.

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One systematic review, three meta-analyses, and five randomized controlled trials were identified pertaining to the clinical effectiveness of and safety associated with pregabalin treatment for patients with fibromyalgia. No relevant health technology assessment reports or non-randomized trials were identified, and no information regarding the use of pregabalin as a second-line therapy option for patients with fibromyalgia was found. Additional information that may be of interest has been included in the appendix.

OVERALL SUMMARY OF FINDINGS:

Overall, evidence from meta-analyses and randomized controlled trials (RCTs) indicates that treatment with pregabalin at doses of 300 milligrams per day (mg/d) or more is effective in reducing pain^{1-5,7-9} and sleep disturbances,^{1,2,5,7,9} and improving health-related quality of life,^{3,9} Patient Global Impression of Change scores,^{5,7} and Fibromyalgia Impact Questionnaire scores.^{5,7} With respect to anxiety and depressed mood, two meta-analyses found no evidence for the effectiveness of pregabalin in treating depressed mood,^{1,3} one meta-analysis found pregabalin to be effective in decreasing anxiety,³ and one RCT found that pregabalin treatment effect on pain scores is not dependant on baseline depression or anxiety.⁸ Although most of the included studies concluded that pregabalin is a safe treatment option for patients with fibromyalgia,^{2,5-7,9} adverse events (e.g., somnolence,^{2,4,7} dizziness^{2,4,7}) were generally more common in patients taking pregabalin compared to placebo, and one trial reported a higher rate of discontinuation due to adverse events in the pregabalin group than in the placebo group.⁶ No relevant information regarding pregabalin as a second-line therapy was identified. Additional details regarding the included studies can be found in Table 1.

Table 1: Details of included studies			
Study Type, year	Interventions compared	Results	Notes
Meta-analysis, 2010 ¹	Duloxetine* (DLX) Milnacipran* (MLN) Pregabalin* (PGB) Placebo	PGB was superior to placebo for all outcomes except for depressed mood. PBG was superior to MLN for reduction in pain and sleep disturbance; superior to DLX for reducing fatigue. Risk of headache and nausea was lower for patients taking PGB than MLN and DLX; risk of diarrhea was lower for PGB than DLX. There is evidence for short term (six month) efficacy of PGB.	The drugs have different effects on the key symptoms of fibromyalgia.
Meta-analysis, 2010 ²	Pregabalin* Placebo	Pain and sleep scores were better in patients receiving PGB. Proportion of patients achieving at least 50% pain relief was higher in the PGB group.	All trial information was provided by Pfizer.

		No difference between placebo and PGB for serious adverse events, but more patients taking PGB had adverse effects (e.g., somnolence and dizziness).	
Meta-analysis, 2009 ³	Gabapentin* (GPT) Pregabalin*	Strong evidence for reduction of pain, improved health-related quality of life, and non-substantial reductions in fatigue and of anxiety, but no evidence for a reduction in depressed mood. Abstract does not specify which drug was superior.	External validity considered to be limited due to the exclusion of patients with severe somatic and mental disorders.
Systematic review and meta-analysis, 2009 ⁴	Pregabalin Placebo	PGB doses of 300 mg, 450 mg, and 600 mg are effective for pain reduction in patients with fibromyalgia. 600 mg PGB resulted in somnolence in 15% to 25% and dizziness in 27% to 46% of patients. Treatment discontinuation due to adverse events occurred in 19% to 28% of patients. Proportion of patients reporting an adverse event or a serious adverse event was not affected by dose. Serious adverse events were not more common in patients taking PGB.	Authors concluded that most patients who benefit from PGB will have moderate benefits and a minority will have substantial benefits.
RCT, 2008 ⁵	Pregabalin 300 mg/d, 450 mg/d, or 600 mg/d Placebo	Patient Global Impression of Change (PGIC) scores were more likely to improve for patients taking PGB. Significant improvements in Fibromyalgia Impact Questionnaire scores were seen in patients taking PGB 450 mg/d and 600 mg/d. All three doses were associated with an improvement in sleep. All three doses were considered efficacious and well tolerated for up to 14 weeks of treatment.	Authors concluded that PGB is an important treatment option for patients with fibromyalgia.
RCT, 2008 ⁶	Pregabalin	Loss of response was longer in PGB-	Randomized

	300 mg/d, 450 mg/d, or 600 mg/d Placebo	treated patients than in the placebo group. More PGB-treated patients withdrew due to treatment-related adverse events.	discontinuation trial.
RCT, 2008 ⁷	Pregabalin 300 mg/d, 450 mg/d, or 600 mg/d Placebo	All three doses of PGB were associated with significant improvement in PGIC scores, pain scores, and sleep assessments. Most frequent adverse events were dizziness and somnolence.	
RCT, 2007 ⁸	Pregabalin* Placebo	PGB treatment effect on pain scores is not dependant on baseline depression or anxiety.	Assessed impact of anxiety and depression on response to pregabalin.
RCT, 2005 ⁹	Pregabalin 150 mg/d, 300 mg/d, 450 mg/day Placebo	450 mg/d PGB was associated with reduced average severity of pain, greater number of patients with improved pain scores, and improvement in several domains of health-related quality of life. 450 mg/d and 300 mg/d PGB were associated with significant improvements in sleep quality, fatigue, and global measures of change. Discontinuation rates due to adverse events were similar in all medication and placebo groups.	Authors concluded that PGB 450 mg/d was efficacious.

d = day, DLX = duloxetine, mg = milligram, MLN = milnacipran, PGB = pregabalin, PGIC = Patient Global Impression of Change, RCT = randomized controlled trial

*dosages not provided in the abstract

REFERENCES SUMMARIZED:

Health technology assessments

No literature identified.

Systematic reviews and meta-analyses

1. Hauser W, Petzke F, Sommer C. Comparative efficacy and harms of duloxetine, milnacipran, and pregabalin in fibromyalgia syndrome. *J Pain*. 2010 Jun;11(6):505-21. [PubMed: PM20418173](#)
2. Straube S, Derry S, Moore RA, McQuay HJ. Pregabalin in fibromyalgia: meta-analysis of efficacy and safety from company clinical trial reports. *Rheumatology (Oxford)*. 2010 Apr;49(4):706-15. [PubMed: PM20056767](#)
3. Hauser W, Bernardy K, Uceyler N, Sommer C. Treatment of fibromyalgia syndrome with gabapentin and pregabalin--a meta-analysis of randomized controlled trials. *Pain*. 2009 Sep;145(1-2):69-81. [PubMed: PM19539427](#)
4. Moore RA, Straube S, Wiffen PJ, Derry S, McQuay HJ. Pregabalin for acute and chronic pain in adults. *Cochrane Database Syst Rev* [Internet]. 2009 [cited 2010 Jul 21];(3):CD007076. Available from: http://mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD007076/pdf_fs.html. Subscription required.

Randomized controlled trials

5. Arnold LM, Russell IJ, Diri EW, Duan WR, Young JP, Sharma U, et al. A 14-week, randomized, double-blinded, placebo-controlled monotherapy trial of pregabalin in patients with fibromyalgia. *J Pain*. 2008 Sep;9(9):792-805. [PubMed: PM18524684](#)
6. Crofford LJ, Mease PJ, Simpson SL, Young JP, Martin SA, Haig GM, et al. Fibromyalgia relapse evaluation and efficacy for durability of meaningful relief (FREEDOM): a 6-month, double-blind, placebo-controlled trial with pregabalin. *Pain*. 2008 Jun;136(3):419-31. [PubMed: PM18400400](#)
7. Mease PJ, Russell IJ, Arnold LM, Florian H, Young JP, Martin SA, et al. A randomized, double-blind, placebo-controlled, phase III trial of pregabalin in the treatment of patients with fibromyalgia. *J Rheumatol*. 2008 Mar;35(3):502-14. [PubMed: PM18278830](#)
8. Arnold LM, Crofford LJ, Martin SA, Young JP, Sharma U. The effect of anxiety and depression on improvements in pain in a randomized, controlled trial of pregabalin for treatment of fibromyalgia. *Pain Med*. 2007 Nov;8(8):633-8. [PubMed: PM18028041](#)
9. Crofford LJ, Rowbotham MC, Mease PJ, Russell IJ, Dworkin RH, Corbin AE, et al. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum*. 2005 Apr;52(4):1264-73. [PubMed:](#)

[PM15818684](#)

Non-randomized studies

No literature identified.

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APPENDIX – FURTHER INFORMATION:

Systematic reviews and meta-analyses

10. Garcia-Campayo J, Magdalena J, Magallón R, Fernández-García E, Salas M, Andrés E. A meta-analysis of the efficacy of fibromyalgia treatment according to level of care. *Arthritis Research & Therapy* [Internet]. 2008 Jul [cited 2010 Jul 21];10(4):1-15. Available from: <http://arthritis-research.com/content/pdf/ar2455.pdf>

Secondary analyses

11. Byon W, Ouellet D, Chew M, Ito K, Burger P, Pauer L, et al. Exposure-response analyses of the effects of pregabalin in patients with fibromyalgia using daily pain scores and patient global impression of change. *J Clin Pharmacol*. 2010 Jul;50(7):803-15. [PubMed: PM20357295](#)
12. Straube S, Derry S, Moore RA, Paine J, McQuay HJ. Pregabalin in fibromyalgia - responder analysis from individual patient data. *BMC Musculoskelet Disord*. 2010 Jul 5;11(1):150. [PubMed: PM20602781](#)
13. Russell IJ, Crofford LJ, Leon T, Cappelleri JC, Bushmakin AG, Whalen E, et al. The effects of pregabalin on sleep disturbance symptoms among individuals with fibromyalgia syndrome. *Sleep Med*. 2009 Jun;10(6):604-10. [PubMed: PM19410509](#)
14. Owen RT. Pregabalin: its efficacy, safety and tolerability profile in fibromyalgia syndrome. *Drugs Today (Barc)*. 2007 Dec;43(12):857-63. [PubMed: PM18174971](#)

Review articles

15. Arnold L, Mease P, Silverman S. Pregabalin: an alpha2-delta (alpha2-delta) ligand for the management of fibromyalgia. *Am J Manag Care* [Internet]. 2010 May [cited 2010 Jul 21];16(5 Suppl):S138-S143. Available from: http://www.ajmc.com/media/pdf/A291_10may_Arnold_S138to143.pdf [PubMed: PM20586522](#)
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19. Zareba G. New treatment options in the management of fibromyalgia: role of pregabalin. *Neuropsychiatr Dis Treat* [Internet]. 2008 Dec [cited 2010 Jul 21];4(6):1193-201. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2646648> [PubMed: PM19337459](#)

20. Yousefi P, Coffey J. For fibromyalgia, which treatments are the most effective? *J Fam Pract.* 2005;54(12):1094-5.

Additional references

21. Pregabalin (Lyrica): suicidal ideation and attempt. *Canadian Adverse Reaction Newsletter* [Internet]. 2010 Jul [cited 2010 Jul 21]; 20(3):1-2. Available from: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/medeff/bulletin/carn-bcei_v20n3-eng.pdf