



Therapeutic Class ReviewSM

Pain & Inflammation – Treatments for Fibromyalgia

December 2008

New Product for Review:

pregabalin (Lyrica^{®*}) [Pfizer]

duloxetine (Cymbalta^{®*}) [Lilly]

Dossier Provided by Manufacturer: No

Dossier Evaluation: N/A

1 - Dossier missing significant clinical trial(s).

2 - Mfg. provided all relevant trials; Missing pharmacoeconomic model.

3 - Mfg. provided all relevant trials and information.

Executive Summary

Disease Background

- The American College of Rheumatology 1990 criteria for the classification of fibromyalgia defines two criteria for the diagnosis of fibromyalgia, when present more than 3 months: ^[1]
 - History of widespread pain.
 - Pain in 11 of 18 tender point sites on digital palpation.
- Fibromyalgia pain is central in nature (disturbances in pain processing). It is often accompanied by a depressive component. ^[1]

Treatment of fibromyalgia

- Current national fibromyalgia treatment guidelines include the following recommendations: ^[2]
 - Non-drug therapies such as exercise and cognitive behavioral therapy are recommended as a foundation of treatment.
 - Tricyclic antidepressants (TCAs) (e.g., amitriptyline) or cyclobenzaprine are considered first-line medication options.
 - Serotonin reuptake inhibitors (e.g., fluoxetine) or tramadol (with or without acetaminophen) may also be used with or without TCAs or cyclobenzaprine.
- Tricyclic antidepressants and seizure medications such as gabapentin have been used to treat the symptoms of fibromyalgia for many years.
 - Although not specifically approved to treat fibromyalgia, these medications have all been studied in fibromyalgia and have been recognized as providing benefit in symptomatic improvement.
 - Gabapentin demonstrated similar treatment effects to pregabalin (Lyrica) and duloxetine (Cymbalta) in an NIH funded study of similar quality and design. ^[3]

- Duloxetine (Cymbalta), a medication initially approved by the FDA as an antidepressant, and pregabalin (Lyrica), a seizure medication which is chemically similar to gabapentin, are both approved by the FDA as treatments for fibromyalgia pain.
 - There is no proof that they are better than other medications that have been used for decades to treat fibromyalgia.
 - Because tricyclic antidepressants and gabapentin are available as low cost generic products, the companies that make them do not have any financial incentive to do additional studies or to seek FDA approval in additional diseases.
- The effects of all of these medications appear to decrease over time.

Tolerability

All of the medications used to treat fibromyalgia have significant safety risks. No one medication has been proven to be better tolerated than another.

Decision

Pregabalin (Lyrica) and duloxetine (Cymbalta) are non-preferred/non-formulary because there is no useful evidence that either medication is safer or more effective than preferred/formulary options for the treatment of fibromyalgia syndrome.

Products

Drug Products	FDA approval ^a	FDA approved indications	Usual Dose/Route	Potential Off-label Uses ^c
Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs)				
duloxetine (Cymbalta [®]) ^[8]	8/2004	Major depressive disorder, Pain associated with diabetic peripheral neuropathy, and Generalized anxiety disorder	60mg po QD to BID	Pain management Stress urinary incontinence Fibromyalgia
venlafaxine (Effexor [®]) ^[9] (Effexor XR [®]) ^[9]	12/2003 10/1997	Major depressive disorder, Generalized anxiety disorder, Social anxiety disorder, and Panic disorder	75mg po BID 150mg XR po QD	Atypical facial pain, Post-mastectomy pain syndrome, Colonic sensorimotor functions, Obsessive-compulsive disorder, Diabetic peripheral neuropathy, Painful polyneuropathy ¹ , Bipolar depression, Premenstrual dysphoric disorder, Management of hot flushes, diabetic neuropathic pain ⁴¹ , fibromyalgia, migraine HA
Tricyclic Antidepressants (TCAs)				
amitriptyline ^[9]	4/1961	Depression w/ anxiety	25mg po TID	polyneuropathy, diabetic neuropathic pain
desipramine ^[9]	10/1964	Depression	150mg po daily	Attention deficit disorder, Diabetic neuropathic pain
imipramine ^[9]	5/1984	Depression Enuresis (children)	100mg po daily	Panic disorder, diabetic neuropathic pain, urinary incontinence
Antiepileptics				
gabapentin ^[9]	10/1993	Epilepsy, post herpetic neuralgia	1200mg/day – 3600mg/day (divided doses TID)	diabetic neuropathic pain, migraine prophylaxis, social phobia
pregabalin (Lyrica [®]) ^[10]	12/2004	Adjunctive therapy for adult	150 - 600mg/day	Generalized anxiety

(Available strengths: 25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 225mg and 300mg)		patients with partial onset seizures, pain associated with diabetic peripheral neuropathy (PDN), postherpetic neuralgia (PHN) pain, Fibromyalgia	(divide 2-3 times/day) PDN: 100mg po TID PHN: 150-300mg/day (divide 2-3 times/day)	disorder, social anxiety disorder, fibromyalgia, other pain conditions
Opioids				
tramadol ^[9]	3/1995	Moderate-severe pain	50mg po Q6hrs	Diabetic neuropathic pain ⁴²⁻⁴³
oxycodone ^[9]	10/1998	Moderate-severe pain	5mg po Q4-6 hrs	Diabetic neuropathic pain ⁴⁴⁻⁴⁵

^a Date applies to approval date for the original brand name medication where there are now generics available.

^c As listed in © 1974 - 2008 Thomson MICROMEDEX database or as referenced.

References

1. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum.* 1990 Feb;33(2):160-72.
2. Buckhardt CS, Goldenberg D, Crofford L, Gerwin R, Gowens S, et al. Guideline for the management of fibromyalgia syndrome pain in adults and children. Glenview (IL): American Pain Society (APS); 2005. 109 p. (Clinical practice guideline; no. 4). Available at: http://www.guideline.gov/summary/summary.aspx?doc_id=7298&nbr=004342&string=fibromyalgia. Accessed on 10/23/2007.
3. Arnold LM, Goldenberg DL, Stanford SB, Lalonde JK, Sandun HS, et al. Gabapentin in the treatment of fibromyalgia: A randomized, double-blind, placebo-controlled, multicenter trial. *Arthritis Rheum.* 2007;56(4):1336-44.
4. Center for Drug Evaluation and Research. Medical Review for NDA #22-148, Cymbalta for the management of Fibromyalgia. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#app_hist. Accessed: September 11, 2008
5. Rappaport BA. Summary Review for Regulatory Action, Cymbalta for the management of Fibromyalgia. FDA Center For Drug Evaluation And Research, Division Of Anesthesia, Analgesia, And Rheumatology Products. June 13, 2008. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#app_hist. Accessed: September 11, 2008
6. Crofford S, Simpson SL, Young JP, Haig G, Barrett JA, et al. Fibromyalgia relapse evaluation and efficacy for durability of meaningful relief (FREEDOM) trial: A 6-month, double-blind, placebo-controlled trial of treatment with pregabalin [Abstract 694]. *Pain* 2007; 8(4):S24-24L.
7. Crofford LJ, Mease PJ, Simpson SL, Young JP Jr, Martin SA, 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;136(3):419-31.
8. Cymbalta[®] [package insert]. Indianapolis, IN: Eli Lilly and Company; August 2008.
9. Klasco RK (Ed): DRUGDEX[®] System (electronic version). Thomson Micromedex, Greenwood Village, Colorado, USA. Available at: <http://www.thomsonhc.com> (cited: 10/15/08).
10. Lyrica[®] [package insert]. New York, NY: Pfizer-Parke Davis; June 2007
11. Crofford LJ, Rowbotham MC, Mease PJ, et al. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum.* 2005;52(4):1264-73.
12. Arnold LM, Russell IJ, Duan WR, Diri E, Young JP, et al. A 14-week, randomized, double-blind, placebo-controlled, monotherapy trial of pregabalin (BID) in patients with fibromyalgia syndrome (FMS) [Poster]. Presented at 59th Annual Scientific meeting of the American Academy of Neurology; April 28 to May 5, 2007; Boston, MA.
13. Arnold LM, Russell IJ, Diri EW, Duan WR, Young JP Jr, et al. A 14-week, randomized, double-blinded, placebo-controlled monotherapy trial of pregabalin in patients with fibromyalgia. *J Pain.* 2008;9(9):792-805.
14. Mease PJ, Russell IJ, Arnold LM, 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.

15. Russell IJ, Mease PJ, Smith TR, et al. Efficacy and safety of duloxetine for treatment of fibromyalgia in patients with or without major depressive disorder: Results from a 6-month, randomized, double-blind, placebo-controlled, fixed-dose trial. *Pain*. 2008 Jun;136(3):432-44.
16. Arnold LM, Lu Y, Crofford LJ, et al. A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. *Arthritis Rheum*. 2004 Sep;50(9):2974-84.
17. Arnold LM, Rosen A, Pritchett YL, et al. A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder. *Pain*. 2005 Dec 15;119(1-3):5-15.
18. Uçeyler N, Häuser W, Sommer C. A systematic review on the effectiveness of treatment with antidepressants in fibromyalgia syndrome. *Arthritis Rheum*. 2008 Sep 15;59(9):1279-98.
19. Tofferi JK, Jackson JL, O'Malley PG. Treatment of fibromyalgia with cyclobenzaprine: A meta-analysis. *Arthritis Rheum*. 2004 Feb 15;51(1):9-13.
20. Goldberg DL, Burckhardt C, Crofford L. Management of fibromyalgia syndrome. *JAMA*. 2004;292(19):2388-95.