



Therapeutic Class ReviewSM

Duloxetine (Cymbalta[®])

July 2005

New Product(s) for Review

duloxetine (Cymbalta) [Eli Lilly & Co]

Dossier Provided by Manufacturer: Yes

Quality of Dossier: 3

1-Low quality (dossier w/missing components)

2-Medium quality (all components, except pharmacoeconomic model)

3-High quality (all components, well done)

Executive Summary

Depression

- There is possibly useful evidence that duloxetine (Cymbalta[®]) has efficacy over placebo in achieving a clinically relevant response.
- Duloxetine (Cymbalta[®]) was inconsistent in achieving a remission.
- There is no evidence that duloxetine (Cymbalta[®]) provides clinical advantages over selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs).
- Claims that duloxetine (Cymbalta[®]) decreases painful physical symptoms associated with depression are unsubstantiated.

Diabetic Neuropathic Pain & Fibromyalgia

- The evidence is weak for the efficacy and safety of duloxetine (Cymbalta[®]) in diabetic neuropathic pain or fibromyalgia. These studies have:
 - Major design flaws.
 - Conclusions not supported by study results.
- There is no evidence that duloxetine (Cymbalta[®]) provides efficacy over other established treatment options.

Decision

Duloxetine (Cymbalta[®]) is non-preferred/non-formulary because this product provides no additional clinical value relative to other established medication options for depression, diabetic neuropathic pain, or fibromyalgia.

Products

Drug Products	FDA approval ^a	FDA approved indications	Usual Dose/Route	Potential Off-label Uses ^c
Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs)				
duloxetine (Cymbalta [®])	8/2004	Major depressive disorder, Pain associated with diabetic peripheral neuropathy	60mg po QD 60mg po QD/BID	Pain management Stress urinary incontinance Fibromyalgia
venlafaxine (Effexor [®]) (Effexor XR [®])	12/2003 10/1997	Major depressive disorder, Generalized Anxiety disorder, Social Anxiety disorder	150mg po daily	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 ⁴⁹
Selective Serotonin Reuptake Inhibitors (SSRIs)				
citalopram	7/1998	Depression	20mg po daily	Headache Panic disorder
escitalopram (Lexapro [®])	8/2002	Depression, Generalized anxiety disorders	10mg po daily	Anxiety with depression
fluoxetine Prozac Weekly [®]	12/1987 02/2001	Depression, Bulimia nervosa, Obsessive-compulsive disorder, Panic disorder, Premenstrual dysphoric disorder	20mg po daily 90mg po QWk	Body dysphoric disorder, fibromyalgia, post-traumatic stress disorder, Raynaud's phenomenon
fluvoxamine	12/1994	Obsessive-compulsive disorder	200mg po daily	Depression, Autism, Panic disorder, Social anxiety disorder
paroxetine	12/1992	Same as sertraline (Zoloft) and generalized anxiety disorder	20mg po daily	Pathological gambling
sertraline (Zoloft [®])	12/1991	Depression, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, premenstrual dysphoric disorder, social anxiety disorder	100mg po daily	dysthymia
Tricyclic Antidepressants (TCAs)				
amitriptyline	4/1961	Depression w/ anxiety	25mg po TID	polyneuropathy, diabetic neuropathic pain, fibromyalgia
desipramine	10/1964	Depression	150mg po daily	Attention deficit disorder, Diabetic neuropathic pain
imipramine	5/1984	Depression Enuresis (children)	100mg po daily	Panic disorder, diabetic neuropathic pain, urinary incontinence
Dopamine reuptake inhibitors				
bupropion bupropion SR Wellbutrin XL	12/1985 10/1996 8/2003	Depression, smoking cessation	100mg po TID 150mg po BID 300mg po QD	
Antiepileptics				
carbamazepine	3/1968	Bipolar disorder, epilepsy, trigeminal neuralgia,	200mg po BID	Antidiuretic (diabetes insipidus), psychotic disorders
gabapentin	10/1998	Epilepsy, post herpetic neuralgia	900mg/day – 3600mg/day (divided doses TID)	diabetic neuropathic pain, migraine prophylaxis, social phobia
phenytoin	8/1976	Generalized tonic-clonic/complex partial seizures, seizures s/p neurosurgery	100mg po TID	Antiarrhythmic, antineuralgic, seizures from eclampsia or preeclampsia , skeletal muscle relaxant
topiramate (Topamax [®])	12/1996	Epilepsy, migraine	200mg po BID	Diabetic neuropathic pain ³⁷⁻³⁸
Opioids				
tramadol	3/1995	Moderate-severe pain	50mg po Q6hrs	Diabetic neuropathic pain ⁴²⁻⁴³
oxycodone	10/1998	Moderate-severe pain	5mg po Q4-6 hrs	Diabetic neuropathic pain ⁴⁴⁻⁴⁵
Others				
levocarnitine	12/1985	Carnitine deficiency	330mg po	Diabetic neuropathic pain ⁴⁷⁻⁴⁸
capsaicin	OTC	Arthritis pain, diabetic peripheral neuropathy, postherpetic neuralgia,	Apply thin layer 3-5x/day	psoriasis
cyclobenzaprine	8/1977	Muscle spasms	10mg pot id	Fibromyalgia

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

References

1. Detke MJ, Lu Y, Goldstein DJ, Hayes JR, Demitrack MA. Duloxetine, 60 mg once daily, for major depressive disorder: a randomized double-blind placebo-controlled trial. *J Clin Psychiatry* 2002;63:308-15
2. Detke MJ, Lu Y, Goldstein DJ, McNamara RK, Demitrack MA. Duloxetine 60 mg once daily dosing versus placebo in the acute treatment of major depression. *J Psychiatr Research* 2002;36:383-90.
3. Goldstein DJ, Mallinckrodt C, Lu Y, Demitrack MA. Duloxetine in the treatment of major depressive disorder: a double blind clinical trial. *J Clin Psychiatry* 2002;63:225-31.
4. Goldstein DJ, Lu Y, Detke MJ, Wiltse C, Mallinckrodt C, Demitrack MA. Duloxetine in the treatment of depression: a double-blind placebo-controlled comparison with paroxetine. *Journal of Clinical Psychopharmacology* 2004;24: 389-99.
5. Detke MJ, Wiltse CG, Mallinckrodt CH, McNamara RK, Demitrack MA, Bitter I. Duloxetine in the acute and long-term treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. *Eur Neuropsychopharmacology* 2004;14:457-70.
6. Brannan SK, Mallinckrodt CH, Brown EB, Wohlreich MM, Watkin JG, Schatzberg AF. Duloxetine 60 mg once-daily in the treatment of painful physical symptoms in patients with major depressive disorder. *J Psychiatr Research* 2005;39:43-53.
7. Wernicke J, Lu Y, D'Souza D, Jones M, Waninger A, Tran P. Duloxetine at doses of 60 mg QD and 60 mg BID is effective treatment of diabetic neuropathic pain. *APA*. May 2004. New York City.
8. Wernicke JF, Rosen A, Lu Y, Lee TC, Iyenger S, Knopp K, Goldstein DJ. The safety of duloxetine in the long-term treatment of diabetic neuropathic pain. *AAPM March Duloxetine at doses of 60 mg QD and 60 mg BID is effective treatment of diabetic neuropathic pain. Program and abstracts of the 20th Annual Meeting of the American Academy of Pain Medicine (March 3-7, 2004), Orlando, FL.*
9. Goldstein DJ, Lu Y, Detke MJ, Lee TC, Iyengar S. Duloxetine vs. placebo in patients with painful diabetic neuropathy. *Pain* 2005;116:109-118.
10. Cymbalta prescribing information. Eli Lilly and Company. Indianapolis, Indiana, January 26, 2005.
11. Arnold LM, Lu Y, Crofford LJ, Wohlreich M, Detke MJ, Iyengar S, Goldstein DJ. A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. *Arthritis Rheum* 2004;59:2974-84.
12. Mallinckrodt CH, Raskin J, Wohlreich MM, Watkin JG, Detke MJ. The efficacy of duloxetine: A comprehensive summary of results from MMRM and LOCF_ANCOVA in eight clinical trials. *BMC Psychiatry* 2004;4(1):26 (doi:10.1186/1471-244X-4-26).
13. Eli Lilly and Co. website; <http://llymedia.client.shareholder.com/ReleaseDetail.cfm?ReleaseID=154081>. (accessed June 26, 2005).
14. Ghoniem GM, Van Leeuwen JS, Elser DM, Freeman RM, Zhao YD, Yalcin I, Bump. Duloxetine/Pelvic Floor Muscle Training Clinical Trial Group. A randomized controlled trial of duloxetine alone, pelvic floor muscle training alone, combined treatment and no active treatment in women with stress urinary incontinence. *J Urol*. 2005 May;173(5):1647-53.

15. Cardozo L, Drutz HP, Baygani SK, Bump RC. Pharmacological treatment of women awaiting surgery for stress urinary incontinence. *Obstet Gynecol.* 2004 Sep;104(3):511-9.
16. van Kerrebroeck P, Abrams P, Lange R, Slack M, Wyndaele JJ, Yalcin I, Bump RC. Duloxetine Urinary Incontinence Study Group. Duloxetine versus placebo in the treatment of European and Canadian women with stress urinary incontinence. *BJOG.* 2004 Mar;111(3):249-57.
17. Millard RJ, Moore K, Rencken R, Yalcin I, Bump RC; Duloxetine UI Study Group. Duloxetine vs placebo in the treatment of stress urinary incontinence: a four-continent randomized clinical trial. *BJU Int.* 2004 Feb;93(3):311-8.
18. Dmochowski RR, Miklos JR, Norton PA, Zinner NR, Yalcin I, Bump RC. Duloxetine Urinary Incontinence Study Group. Duloxetine versus placebo for the treatment of North American women with stress urinary incontinence. *J Urol.* 2003;170(4 Pt 1):1259-63. Erratum in: *J Urol.* 2004 Jan;171(1):360.
19. Bump RC, Norton PA, Zinner NR, Yalcin I; Duloxetine Urinary Incontinence Study Group. Mixed urinary incontinence symptoms: urodynamic findings, incontinence severity, and treatment response. *Obstet Gynecol.* 2003 Jul;102(1):76-83.
20. Norton PA, Zinner NR, Yalcin I, Bump RC; Duloxetine Urinary Incontinence Study Group. Duloxetine versus placebo in the treatment of stress urinary incontinence. *Am J Obstet Gynecol.* 2002 Jul;187(1):40-8.
21. Wu EQ, Birnbaum HG, Mareva MN. Cost-effectiveness of duloxetine versus routine treatment for painful diabetic neuropathy in a randomized trial from a societal perspective (poster abstract). Presented at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 9th Annual International Meeting; 16-19 May 2004; Arlington, VA.
22. National Institute of Mental Health. CGI: Clinical Global Impressions. In: Guy W, Bonato RR, eds. *Manual for the ECDEU Assessment Battery.* 2. Rev ed. Chevy Chase, MD: National Institute of Mental Health; 1970:12-1-12-6.
23. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23:56-63.
24. Montgomery SA, Asberg MA. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979;134:382-9.
25. Ware JJ, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). Conceptual framework and item selection. *Medical Care* 1992;30:473-83.
26. Duloxetine hydrochloride capsule (Cymbalta). AMCP formatted formulary submission document (dossier). Eli Lilly and Company, Indianapolis, IN. February 2005.
27. Farrar JT, Young JP Jr., LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001;94:149-58.
28. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore.* 1994; 23:129-38.
29. Twycross R, Harcourt J, Bergl S. A survey of pain in patients with advanced cancer. *J Pain Symptom Manage* 1996;12:273-82.
30. Hamilton M. The assessment of anxiety states by rating. *Brit J Med Psychology* 1959;32:50-55.

31. Wohlreich MM, Mallinckrodt CH, Watkin JG, Hay DP. Duloxetine for the long-term treatment of Major Depressive Disorder in patients aged 65 and older: an open-label study. *BMC Geriatrics* 2004;4:11 (doi:10.1186/1471-2318-4-11).
32. American Psychiatric Association: Practice guideline for the treatment of patients with major depressive disorder, 2nd edition. 2000; pp. 1-71. (accessed June 26, 2005).
http://www.psych.org/psych_pract/treatg/pg/Practice%20Guidelines8904/MajorDepressiveDisorder_2e.pdf
33. Wiffen P, Collins S, McQuay H, Carroll D, Jadad A, Moore A. Anticonvulsant drugs for acute and chronic pain. *The Cochrane Database of Systematic Reviews* 2000, Issue 3. Art. No.: CD001133. DOI: 10.1002/14651858.CD001133.
34. Duhmke RM, Cornblath DD, Hollingshead JRF. Tramadol for neuropathic pain (Cochrane Review). In: *The Cochrane Library*, Issue 2, 2004. Chichester, UK: John Wiley & Sons, Ltd.
35. Perahia D, Prichett YL, Walker D, Tran P, Raskin J, Russell J. Comparing duloxetine and venlafaxine in the treatment of major depressive disorder using a global benefit-risk approach. Poster presented at the New Clinical Drug Evaluation Unit (NCDEU), June 6-9, 2005, Boca Raton, Florida.
36. Goldenberg DL, Buckhardt C, Crofford L. Management of fibromyalgia syndrome. *JAMA* 2004;292:2388-95.
37. Raskin P, Donofrio PD, Rosenthal NR, Hewitt DJ, Jordan DM, Xiang J, Vinik AI; CAPSS-141 Study Group. Topiramate vs. placebo in painful diabetic neuropathy: analgesic and metabolic effects. *Neurology* 2004;63:865-73.
38. Thienel U, Neto W, Schwabe SK, Vijapurkar U; Topiramate Diabetic Neuropathic Pain Study Group. Topiramate in painful diabetic polyneuropathy: findings from three double-blind placebo-controlled trials. *Acta Neurol Scand* 2004;110:221-31.
39. Canadian Diabetes Association. 2003 Clinical Practice Guidelines for the Management of Diabetes. (accessed June 28, 2005). <http://www.diabetes.ca/cpg2003/download.aspx>.
40. Boulton AJM et al. Technical Review : Management of diabetic peripheral neuropathy. *Clinical Diabetes* 2005;23:9-15.
41. Rowbotham MC, Goli V, Kunz NR, Lei D. Venlafaxine extended release in the treatment of painful diabetic neuropathy: a double-blind, placebo-controlled study. *Pain* 2004;110:697-706.
42. Harati Y, Gooch C, Swenson M, Edelman S, et al. Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. *Neurology* 1998;50(6):1842-6.
43. Sindrup SH, Andersen G, Madsen C, et al. Tramadol relieves pain and allodynia in polyneuropathy: a randomised, double-blind, controlled trial. *Pain* 1999;83(1):85-90.
44. Watson CPN, Moulin D, Watt-Watson J, Gordon A, Eisenhoffer. Controlled-release oxycodone relieves neuropathic pain: a randomized controlled trial in painful diabetic neuropathy. *Pain* 2003;105:71-8.
45. Gimbel JS, Richards P, Portenoy RK. Controlled-release oxycodone for pain in diabetic neuropathy. A randomized controlled trial. *Neurology* 2003;60:927-34.
46. Burckhardt CS, Clark SR, Bennett RM. The fibromyalgia impact questionnaire: development and validation. *J Rheumatol* 1991;18:728-33.

47. Sima AA, Calvani M, Mehra M, Amato A for the Acetyl-L-Carnitine Study Group. Acetyl-L-carnitine improves pain, nerve regeneration, vibratory perception in patients with chronic diabetic neuropathy: an analysis of two randomized placebo-controlled trials. *Diabetes Care* 2005;28(1):89-94.
48. DeGrandis D, Minardi C. Acetyl-L-carnitine (levacecarnine) in the treatment of diabetic neuropathy. A long-term, randomized, double-blind, placebo-controlled study. *Drugs R D* 2002;3(4):223-31.
49. Sayar K, Aksu G, Ak I, Tosun M. Venlafaxine treatment in fibromyalgia. *Ann Pharmacother* 2003;37:1561-5.