Emerging Drug List
Duloxetine for Major Depressive Disorder and Stress Urinary Incontinence

Canadian Coordinating Office for Health Technology Assessment

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Generic (Trade Name): Duloxetine hydrochloride (Cymbalta®)

Manufacturer: Eli Lilly

Indication: Duloxetine has been studied for the treatment of major depressive disorder (MDD) and stress urinary incontinence (SUI) in women.

Current Regulatory Status: The US Food and Drug Administration issued an "approvable" letter for duloxetine for the treatment of SUI in September 2003.[1] It was approved for the treatment of major depressive disorder in August 2004.[2] Final approval is contingent upon submission and review of additional information. Eli Lilly and Boehringer Ingelheim have agreed to develop and commercialize duloxetine in several countries.[1]

Health Canada is reviewing duloxetine for use in depression and for the treatment of SUI (Ms. Deanne Wong, Eli Lilly Canada, Toronto: personal communication, 2004 Mar 9).

Description: Duloxetine inhibits neuronal reuptake of serotonin (5-HT) and norepinephrine (NE),[3] two key neurotransmitters involved in the etiology of depression and in neural control of the lower urinary tract.[4] Venlafaxine, a marketed antidepressant, is considered a dual reuptake inhibitor but more selective for 5-HT reuptake. Duloxetine is considered to be a relatively non-selective inhibitor. Duloxetine (like venlafaxine) has a low affinity for muscarinic, dopamine-2, alpha-1 adrenergic, alpha-2 adrenergic, and histamine-1 and -2 receptors.[3]

Current Treatment:

Depression

Several classes of antidepressants are marketed for the treatment of depression including selective serotonin reuptake inhibitors, non-selective cyclic agents, novel agents and monoamine oxidase inhibitors.[5]

Clinical guidelines for the treatment of depressive disorders were published in 2001 by the Canadian Network for Mood and Anxiety Treatments (CANMAT) and the Canadian Pyschiatric Association.[6] Evidence-based recommendations were presented regarding the choice of antidepressant, the optimal use of antidepressant drugs, maintenance treatment and treatments such as electroconvulsive therapy and light therapy (Table 1).

Stress Urinary Incontinence

Stress urinary incontinence (SUI) is the sudden, involuntary loss of urine that occurs with coughing, sneezing or exercise.[4] Treatment includes pharmacologic and non-pharmacologic options, including pelvic floor muscle training such as Kegel exercises, biofeedback and electrical stimulation therapy.[7]

Table 1: Recommendations for treatment of MDD[6]

First-line treatments	• Selective serotonin reuptake inhibitors (SSRIs) and novel agents (level 1 evidence) • Venlafaxine may lead to higher remission rates than SSRIs (level 1 evidence)
Second-line treatments	• Amitriptyline and clomipramine have greater efficacy than SSRIs in hospitalized patients with depression (level 2 evidence); safety and tolerability issues need to be considered
Third-line treatments	• Other tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), because of safety and tolerability issues (level 2 evidence)

Level 1: systematic review of RCTs or individual RCTs; level 2: systematic review of cohort studies or individual cohort studies.

Pharmacologic options include estrogen products, imipramine and pseudoephedrine. Pseudoephedrine use is based on data supporting the role of phenylpropanolamine, a similar decongestant that has been withdrawn from the Canadian market. None of these agents are officially approved for treating SUI.[7]

Cost:

There is no information on the cost of duloxetine at this time, since it is not marketed in any country.

Evidence:

Depression

Two randomized, double-blind trials, conducted according to the same protocol, compared duloxetine 60 mg with placebo for nine weeks.[8,9] In both trials, duloxetine-treated patients had a significantly lower Hamilton Depression Rating Scale (HAMD17) total score compared with those given placebo. They demonstrated a significantly greater probability of response, but only one trial demonstrated a significantly greater probability of remission compared with placebo.[9] Several other secondary efficacy measures were recorded. Both trials demonstrated a significant difference in the Patient's Global Impression of Improvement (PGI-I) and Quality of Life Depression Scale (QLDS) compared with placebo. A significant improvement in the Clinical Global Impression of Severity (CGI-S) was also shown.[9] A reduction in pain was reported in both trials. Discontinuation due to adverse events was greater in the duloxetine group in both trials.

An eight-week randomized, double-blind trial comparing duloxetine (40 mg and 80 mg daily) with paroxetine 20 mg daily and placebo was reported in an abstract. The abstract reported lower HAMD-17 total scores and a greater proportion of patients who achieved remission after receiving duloxetine 80 mg compared with paroxetine 20 mg daily.[10]

A one-year open-label trial (n=1,279) reported significant improvements in CGI-S, HAMD-17, Beck depression score, Sheenan disability score and PGI-I compared with baseline ($p<0.001$).[11] The estimated probabilities of remission at six, 28 and 52 weeks were 50.8%, 75.6% and 81.8% respectively.

An earlier phase II trial randomized 173 patients to duloxetine 40 mg to 60 mg twice daily (n=70), placebo (n=70) and fluoxetine 20 mg daily (n=33). The differences in outcomes between fluoxetine and duloxetine were rarely reported. Duloxetine-treated patients, however, had a statistically significantly greater improvement on the HAM-17 anxiety subscale compared with those receiving fluoxetine. Duloxetine-treated patients also experienced greater reductions in HAMD-17, Montgomery-Asberg Depression Rating Scale and CGI-S compared with those given fluoxetine, but the statistical significance was not reported.[12]

Dunner *et al.* pooled the results from four trials (two comparing duloxetine 60 mg/day to placebo; one comparing duloxetine 120 mg/day, fluoxetine 20 mg/day and placebo; and one comparing duloxetine 40 mg/day, duloxetine 80 mg/day, paroxetine 20 mg/day and placebo).[13] Duloxetine was superior to placebo, paroxetine and fluoxetine for improving anxiety symptoms. Duloxetine was also associated with a significant improvement in pain symptoms as measured using the Visual Analog Scale and Somatic Symptom Inventory.[14]

Stress Urinary Incontinence (SUI)

Norton *et al.* conducted a double-blind, randomized, placebo-controlled study in 553 women with SUI.[15] Subjects received placebo (n=138), duloxetine 20 mg/day (n=138), 40 mg/day (n=137) or 80 mg/day (n=140) for 12 weeks. The median decrease in incontinence episode frequency (IEF) at 12 weeks was 41% with placebo compared to 54% with duloxetine 20 mg/day ($p=0.06$), 59% with duloxetine 40 mg/day ($p=0.002$) and 64% with duloxetine 80 mg/day ($p<0.001$). Increases in the Incontinence Quality of Life (I-QOL) questionnaire was reported in all groups; only the 80 mg/day group was significantly different from the placebo group.[4] The PGI-I was 27%, 31%, 37% and 44% with placebo, duloxetine 20 mg, 40 mg and 80 mg respectively ($p=0.09$ for 40 mg dose versus placebo and $p=0.005$ for 80 mg dose versus placebo).[4] Discontinuation rates were 5%, 9%, 12% and 15% for placebo, duloxetine 20 mg, 40 mg, and 80 mg respectively ($p=0.04$).[15] Nausea was identified as the most common cause of discontinuation. It has been suggested in a secondary analysis of 171 women with mixed urinary incontinence (MUI), that duloxetine is equally effective for women suffering from MUI or SUI.[16]

Two other studies (n=683 and n=458) compared duloxetine 40 mg with placebo once daily in 12-week randomized, double-blind, placebo-controlled trials.[17,18] Both showed significant decreases in IEF, improvements in the I-QOL and increases in voiding intervals. Discontinuations due to adverse events (mainly nausea) were greater in the duloxetine groups.

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Adverse Effects:

Withdrawal due to adverse events was significantly greater in duloxetine-treated patients compared with placebo in all trials. In two RCTs for MDD, the incidence of nausea, dry mouth, dizziness and constipation were significantly higher in duloxetine-treated patients compared with those given placebo.[8] Other adverse events included somnolence, diarrhea, insomnia and anorexia.[8]

In the trials for SUI, nausea was the most common adverse event causing withdrawal. Other adverse events were reported, but were not considered to be clinically severe.[15-18]

The long-term use of duloxetine was associated with a mean weight increase of 1.1 kg. The discontinuation of duloxetine has been associated with serotonin-like withdrawal symptoms, including anxiety, abnormal dreams, nausea, irritability, insomnia, dizziness and headache.[4]

Commentary:

Duloxetine is another choice in the growing list of marketed antidepressants. Trials comparing duloxetine with appropriate doses of comparators are lacking. Direct evidence of a long-term benefit from comparative trials is also lacking.

Duloxetine is a novel choice for the treatment of SUI, but comparative trials demonstrating its effectiveness relative to other agents are lacking. The high incidence of treatment withdrawal due to nausea may limit the use of duloxetine in practice.

References:

1. *FDA issues second approvable letter for Eli Lilly and Company's (LLY) Cymbalta for the treatment of depression [news release]*. 2004. Available: http://www.biospace.com/ccis/news_story.cfm?StoryID=13925820&full=1 (accessed 2004 Jul 15).
2. *Cymbalta (duloxetine hydrochloride)* [package insert]. Indianapolis: Eli Lilly and Company; 2004 Aug 3. Available: http://pi.lilly.com/us/cymbalta-pi.pdf (accessed 2004 Aug 11).
3. Lott RS, Baker DE. Duloxetine: a new antidepressant. *Advances in Pharmacy* 2003;1(3):228-41.
4. Kirwin JL, Goren JL. Duloxetine: an antidepressant that inhibits both norepinephrine and serotonin uptake. *Formulary* 2003;38:29-37.
5. Bezchlibnyk Butler KZ, Jeffries JJ, editors. *Clinical handbook of psychotropic drugs.* 13th rev. ed. Seattle: Hogrefe & Huber; 2003.
6. Kennedy SH, Lam RW, Cohen NL, Ravindran AV, CANMAT Depression Work Group. Clinical guidelines for the treatment of depressive disorders. IV. Medications and other biological treatments. *Can J Psychiatry* 2001;46 Suppl 1:38S-58S.
7. Grymonpre RE. Urinary incontinence in adults. In: Gray J, editor. *Therapeutic choices.* 4th ed. Ottawa: Canadian Pharmacists Association; 2003.
8. 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 Res* 2002;36(6):383-90.
9. 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(4):308-15.
10. Goldstein DJ, Lu Y, Detke M, Wiltse C, Demitrack MA. Duloxetine vs. paroxetine in the treatment of depression: a double-blind placebo-controlled comparison [abstract]. 42nd Annual NCDEU Meeting; 2002; Boca Raton (FL) (accessed 2004 Jun 29).

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11. Raskin J, Goldstein DJ, Mallinckrodt CH, Ferguson MB. Duloxetine in the long-term treatment of major depressive disorder. *J Clin Psychiatry* 2003;64(10):1237-44.
12. 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(3):225-31.
13. Dunner DL, Goldstein DJ, Mallinckrodt C, Lu Y, Detke MJ. Duloxetine in treatment of anxiety symptoms associated with depression. *Depress Anxiety* 2003;18(2):53-61.
14. Goldstein DJ, Lu Y, Detke MJ, Hudson J, Iyengar S, Demitrack MA. Effects of duloxetine on painful physical symptoms associated with depression. *Psychosomatics* 2004;45(1):17-28.
15. Norton PA, Zinner NR, Yalcin I, Bump RC. Duloxetine versus placebo in the treatment of stress urinary incontinence. *Am J Obstet Gynecol* 2002;187(1):40-8.
16. Bump RC, Norton PA, Zinner NR, Yalcin I. Mixed urinary incontinence symptoms: urodynamic findings, incontinence severity, and treatment response. *Obstet Gynecol* 2003;102(1):76-83.
17. Dmochowski RR, Miklos JR, Norton PA, Zinner NR, Yalcin I, Bump RC. Duloxetine versus placebo for the treatment of North American women with stress urinary incontinence. *J Urol* 2003;170(4 Pt 1):1259-63.
18. Millard RJ, Moore K, Rencken R, Yalcin I, Bump RC. Duloxetine vs placebo in the treatment of stress urinary incontinence: a four-continent randomized clinical trial. *BJU Int* 2004;93(3):311-8.

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