Class: Antidepressant, serotonin and norepinephrine re-uptake inhibitor (SNRI).

Indications: Depression, diabetic neuropathic pain, stress incontinence in women.

Contra-indications: Concurrent use with an MAOI or within 2 weeks of previous treatment with an MAOI (see Box 4H, p.115). Uncontrolled narrow-angle glaucoma. Hepatic impairment. End-stage renal failure requiring dialysis or creatinine clearance <30ml/min.

Pharmacology

Like **venlafaxine**, duloxetine inhibits the presynaptic neuronal re-uptake of both serotonin and norepinephrine, and of dopamine to a lesser extent.[1,2] Unlike **amitriptyline**, it has few post-synaptic antagonistic effects at muscarinic, α-adrenergic or H_1-receptors. It has little effect on cognitive or motor performance. Antidepressant effects of duloxetine 60mg q.d and **venlafaxine** 150mg SR q.d. were indistinguishable in a head-to-head comparative RCT.[3] In the treatment of depression, duloxetine 80–120mg q.d. is superior to **fluoxetine** 20mg q.d. and **paroxetine** 20mg q.d.[4,5]

As with other SNRIs, duloxetine is of benefit in neuropathic pain. In an RCT in >450 diabetic patients, duloxetine 60mg q.d and 60mg b.i.d. were significantly better than placebo, with about 50% of patients achieving ≥50% relief in terms of mean Average Pain Score.[6] Although the mean scores were consistently better in the patients who received 60mg b.i.d., the extra benefit was not significantly greater, and there was a general increase in undesirable effects. This suggests that doses >60mg are unlikely to be of greater benefit.

Duloxetine is also indicated in the management of stress incontinence in women.[7-9] Animal studies have demonstrated that serotonin and norepinephrine are involved in the central neural control of micturition.[7] Serotonin agonists generally suppress parasympathetic activity and enhance sympathetic and somatic activity in the lower urinary tract, enhancing the bladder's storage capacity. Duloxetine acts through the pudendal motor nucleus in the distal cord and thus stimulates the rhabdosphincter of the urethra. This is also the presumed mode of action on the urinary tract of peripheral α-adrenergic agents, including those with an indirect action, e.g. **imipramine**. The advantage of duloxetine is that it does not cause postural hypotension or cardiac conduction abnormalities.[8]

The incidence of initial nausea with duloxetine is comparable to that seen with **fluoxetine** and **paroxetine.**[10] Duloxetine has no significant effect on blood pressure.[11]

Bio-availability 90%.
Onset of action 2–3 weeks in depression.[12]
Time to peak plasma concentration 6h.
Plasma halflife 12h.
Duration of action >24h, situation dependent.

Cautions

Suicide risk: the possibility of a suicide attempt is inherent in major depression and persists until remission occurs.

Concurrent use of psychotropic drugs, and in patients with seizure disorders or in predisposing conditions such as brain damage or alcoholism. Antidepressants, including duloxetine, may precipitate a shift to mania or hypomania in patients with bipolar disorder. Duloxetine may exacerbate narrow-angle glaucoma and urinary hesitancy; may cause sexual dysfunction.

Undesirable effects
For full list, see manufacturer's PI.
Very common (>10%): sexual dysfunction (about 30%), nausea (20%), insomnia (20%), drowsiness (15%), dry mouth (15%), constipation (10%), sweating (10%).
Common (<10%, 1%): lightheadedness, dizziness, blurred vision, headache, altered taste, anorexia, diarrhea.[13]

Dose and use

The inclusion of duloxetine should not be interpreted as a recommendation for its use in depression or neuropathic pain in palliative care patients. It is featured because of its labeled indications, which include stress incontinence in women.

Depression
- 40mg/day; manufacturer recommends 20mg b.i.d. but pharmacokinetics suggest 40mg q.d. would be satisfactory
- if necessary, increase to 60mg/day after 2 weeks (either q.d. or 30mg b.i.d.)
- no extra benefit with higher doses.[11,14,15]

Diabetic peripheral neuropathy
- 60mg q.d.
- if associated renal impairment, start with 40mg q.d.

Management of stress incontinence in women
- 40mg b.i.d.

Supply
Cymbalta® (Eli Lilly and Co.)
Capsules (enclosing enteric pellets) 20mg, 30mg, 60mg, 28 days @ 60mg daily = $94.

---

1 Bymaster FP *et al.* (2001) Comparative affinity of duloxetine and venlafaxine for serotonin and norepinephrine transporters in vitro and in vivo, human serotonin receptor subtypes, and other neuronal receptors. *Neuropsychopharmacology.* **25**: 871–880.
2 Karpa KD *et al.* (2002) Duloxetine pharmacology: profile of a dual monoamine modulator. *CNS Drug Reviews.* **8**: 361–376.
3 Perahia D *et al.* (2005) *Comparing duloxetine and venlafaxine in the treatment of major depressive disorder using a global benefit-risk approach*. New Clinical Drug Evaluation Unit, Florida, USA.
4 Swindle R *et al.* (2004) Efficacy of duloxetine treatment: analysis of pooled data from six placebo-and SSRI-controlled clinical trials. Presented at: *ECNP*, October.

5 Hudson JI *et al.* (2005) Safety and tolerability of duloxetine in the treatment of major depressive disorder: analysis of pooled data from eight placebo-controlled clinical trials. *Human Psychopharmacology.* **20**: 327–341.
6 Goldstein DJ *et al.* (2005) Duloxetine vs. placebo in patients with painful diabetic neuropathy. *Pain.* **116**: 109–118.
7 Norton PA *et al.* (2002) Duloxetine versus placebo in the treatment of stress urinary incontinence. *American Journal of Obstetrics and Gynecology.* **187**: 40–48.
8 Dmochowski RR *et al.* (2003) Duloxetine versus placebo for the treatment of North American women with stress urinary incontinence. *Journal of Urology.* **170**: 1259–1263.
9 Millard RJ *et al.* (2004) Duloxetine vs placebo in the treatment of stress urinary incontinence: a four-continent randomized clinical trial. *BJU International.* **93**: 311–318.
10 Greist J *et al.* (2004) Incidence and duration of antidepressant-induced nausea: duloxetine compared with paroxetine and fluoxetine. *Clinical Therapeutics.* **26**: 1446–1455.
11 Detke MJ *et al.* (2004) Duloxetine in the acute and long-term treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. *European Neuropsychopharmacology.* **14**: 457–470.
12 Brannan SK *et al.* (2005) Onset of action for duloxetine 60 mg once daily: double-blind, placebo-controlled studies. *Journal of Psychiatric Research.* **39**: 161–172.
13 Goldstein DJ *et al.* (2004) Duloxetine in the treatment of depression: a double-blind placebo-controlled comparison with paroxetine. *Journal of Clinical Psychopharmacology.* **24**: 389–399.
14 Nemeroff CB *et al.* (2002) Duloxetine for the treatment of major depressive disorder. *Psychopharmacology Bulletin.* **36**: 106–132.
15 Mallinckrodt CH *et al.* (2003) Duloxetine: A New Treatment for the Emotional and Physical Symptoms of Depression. *Primary care companion to the Journal of clinical psychiatry.* **5**: 19–28.