ADIS DRUG PROFILE

Drugs 2004; 64 (22): 2567-2573
0012-6667/04/0022-2567/$34.00/0

Duloxetine

In Stress Urinary Incontinence

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Contents

Abstract

▲ Duloxetine is an orally administered, balanced, dual serotonin and norepinephrine (noradrenaline) reuptake inhibitor that increases neural input to the urethral sphincter, thereby relieving the symptoms of stress urinary incontinence (SUI).

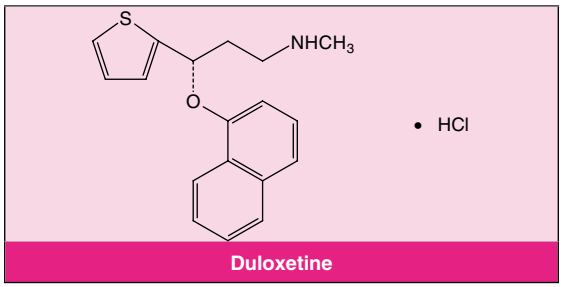
▲ Duloxetine 40mg twice daily for 12 weeks reduced the median incontinence episode frequency (IEF) to a significantly greater extent than placebo in women with predominant symptoms of SUI. In most studies, Incontinence Quality of Life (I-QOL) questionnaire total scores were significantly improved compared with placebo.

▲ In a dose-escalation study in women with severe SUI scheduled for continence surgery, duloxetine 80–120 mg/day for 8 weeks significantly reduced IEF and increased I-QOL total scores compared with placebo, and caused 20% of recipients to reconsider their willingness to undergo surgery.

▲ Duloxetine or duloxetine plus pelvic floor muscle training (PFMT) were more effective in reducing the median IEF than PFMT alone or no treatment in women with SUI. Mean I-QOL total scores suggested that combination therapy was more effective than either therapy alone.

▲ Nausea was the most frequent adverse event and was the main cause for discontinuing duloxetine therapy.

Features and properties of duloxetine (duloxetine hydrochloride; LY 248686; Yentreve™; Ariclaim®)	
Indication	
Stress urinary incontinence	
Mechanism of action	
Dual serotonin and norepinephrine reuptake inhibition leading to increased urethral sphincter activation	
Dosage and administration	
Dose	40mg
Route of administration	Oral
Frequency of administration	Twice daily
Pharmacokinetic profile (single 40mg dose)	
Peak plasma concentration (C_{max})	50 ng/mL
Time to C_{max}	6h
Area under the plasma concentration-time curve from time zero to infinity	699 ng • h/mL
Elimination half-life	12h
Adverse events	
Most frequent	Nausea
Common	Dry mouth, insomnia, fatigue, constipation, dizziness, somnolence, increased sweating and headache



Urinary incontinence is more prevalent in women than in men, and some estimates suggest that up to one-half of all mature women may suffer from symptoms of incontinence.[1,2] Stress urinary incontinence (SUI) is the most common form of urinary incontinence in women and involves the involuntary release of urine from the bladder caused by a sudden increase in intra-abdominal pressure, such as during coughing, sneezing, laughing or exercise.[1,3,4] Urge incontinence, involving involuntary urine loss preceded by a strong urge to void regardless of whether or not the bladder is full, is the other common primary form of incontinence.[5] However, many patients have mixed incontinence, probably the second most common form of urinary incontinence, in which the symptoms of stress and urge incontinence coexist.[1,6] One of the symptoms is often more troublesome to the patient than the other, and therefore becomes the focus of therapy.[6]

Treatment approaches to SUI include pelvic floor muscle training (PFMT) in association with the management of fluid intake and voiding, a range of surgical procedures, bulking agents and pharmacological therapy.[7,8] α-Adrenoceptor agonists, tricyclic antidepressants and estrogens have been widely used to treat SUI, but their efficacy has been only modest,[4,9] and none are approved therapies. Duloxetine is the first and only pharmacological agent to be approved for the treatment of SUI.

Duloxetine (duloxetine hydrochloride; LY 248686) is a new orally administered, balanced, dual serotonin and norepinephrine (noradrenaline) reuptake inhibitor that has been developed for the treatment of SUI (Yentreve™; Ariclaim®)[1], depression (Cymbalta®; Xeristar®)[10-12] and pain caused by diabetic peripheral neuropathy (Cymbalta®).[13]

This profile focuses on the use of duloxetine to treat SUI in adult or elderly women.

1. Pharmacodynamic Profile

- Duloxetine binds with high affinity to serotonin and norepinephrine transporters, but displays very low affinity for other monoamine receptors.[14,15]
- In SUI, duloxetine is thought to block the reuptake of serotonin and norepinephrine in Onuf's nucleus in the sacral spinal cord, thereby activating pudendal motor neurons that increase the urethral striated muscle (sphincter) tone and the force of sphincter contraction. This increased sphincter activation prevents involuntary urine loss.[16]
- *In vitro* binding studies using synaptosomal preparations isolated from rat cerebral cortex indicated that duloxetine was approximately 3-fold more potent at inhibiting serotonin uptake than norepinephrine uptake (K_i [dissociation constant for inhibitor binding] values of 4.6 vs 15.6 nmol/L).[14] However, *ex vivo* studies indicated equivalent inhibition by duloxetine of the uptake of serotonin and norepinephrine (50% effective doses of 31 and 38 μmol/kg).[14]
- While duloxetine had only weak effects on bladder function in female cats with non-irritated bladders, under conditions of bladder irritation induced by the infusion of acetic acid, the drug increased bladder capacity 5-fold and increased periurethral striated muscle (i.e. sphincter) activity 8-fold.[17]
- The effect of duloxetine on bladder capacity was reversed by a nonselective serotonin 5-HT receptor antagonist, while its effect on sphincter activity was reversed by 5-HT_2 receptor and α_1-adrenoceptor antagonists. Moreover, the effects of duloxetine appeared to be central effects, since duloxetine had no effect on bladder contractions evoked by direct electrical stimulation of efferent fibres in the pelvic nerve.[17]

1 The use of trade names is for product identification purposes only and does not imply endorsement.

• The effects of the dual reuptake inhibitor venlafaxine on bladder function and sphincter activity were an order of magnitude lower than those of duloxetine.[18] In contrast to the effects observed with the dual reuptake inhibitors duloxetine or venlafaxine, combined use of the selective serotonin reuptake inhibitor seproxetine (norfluoxetine) and the norepinephrine reuptake inhibitor thionisoxetine had no effect on bladder capacity or sphincter activity.[18]

2. Pharmacokinetic Profile

The pharmacokinetics of duloxetine have been examined in healthy adult volunteers (n = 78)[19-25] and in patients with stress or mixed urinary incontinence (n = 198).[19] Three of these studies are only available as abstracts.[21,23,24]

• In the dosage range of 40–80 mg/day administered to healthy adult volunteers, duloxetine displayed linear pharmacokinetics that were adequately described by a one-compartment model with first-order absorption and elimination rate constants.[22]

• The mean peak plasma concentrations (C_{max}) after single 20[20,23,25] or 40mg[19] oral doses of duloxetine were 13.0–23.5 and 49.8 ng/mL, respectively. The mean AUC values from time zero to infinity (AUC_∞) following single 20[20] or 40mg[19] oral doses of duloxetine were 257 and 699 ng • h/mL, respectively.

• Following single oral doses of duloxetine 20[20,23,25] or 40mg,[19] or after multiple dose administration with 20–160 mg/day for ≥7 days,[21,25] the time to reach C_{max} (t_{max}) was typically in the range of 4–6 hours (mean,[25] median[19,20] or not stated[21,23]) in healthy adult volunteers. The value for t_{max} stated in the European prescribing information is 6 hours.[26]

• Compared with overnight fasting, administering a single dose of duloxetine 40mg after a high-fat breakfast in 12 female volunteers significantly ($p < 0.05$) increased the t_{max} from 6 to 10 hours, without significantly affecting C_{max} or AUC.[24] Administering duloxetine at bedtime, as opposed to in the morning, also increased the t_{max} by 4 hours ($p < 0.05$) and significantly ($p < 0.05$) reduced the C_{max} by 29% and the AUC by 18%.[24]

• The pharmacokinetics of duloxetine did not differ significantly between healthy elderly and younger adult women, other than for an ≈30% lower ($p < 0.01$) mean elimination rate constant in elderly volunteers, which was not considered clinically significant.[19] Dosage adjustment of duloxetine on the basis of age is not regarded as necessary.

• Studies using ^{14}C-labelled duloxetine indicate that the drug is extensively metabolised, predominantly by cytochrome P450 (CYP) 2D6 and CYP1A2.[20] Unaltered drug accounted for only 9% of C_{max} and 3% of AUC values when ratios for duloxetine:total radioactivity in plasma were calculated.[20,23] Duloxetine was highly bound to plasma proteins (>95%), and 72–77% of the radioactivity was excreted in the urine and 15–19% in the faeces, with 8–10% of the radioactivity not being accounted for.[20,23]

• The apparent plasma clearance has been estimated at 70–119 L/h and the apparent volume of distribution at 962–1943L.[19,20,22] The mean terminal elimination half-life of duloxetine is 12 hours.[26]

3. Therapeutic Efficacy

The therapeutic efficacy of duloxetine has been assessed in six multicentre, randomised, double-blind[27-31] (or double/single-blind[32]), placebo-controlled trials which included patient selection criteria that increased the probability that the enrolled women had true SUI.[33] These trials consist of a dose-finding study,[30] three phase III placebo comparisons,[27-29] a dose-escalation placebo comparison in women with severe SUI awaiting surgery,[31] and an active treatment comparison between duloxetine and PFMT, alone and in combination.[32] The latter study is only published in abstract form.[32] The duration of all studies was 12 weeks,[27-30,32] except for one 8-week, dose-escalation study.[31]

Where stated, treatment was initiated after a 2-week, drug-free wash-out period, followed by a 2-week, single-blind, placebo run-in period,[27-30] or just following a 2-week, single-blind placebo run-in.[31] The dose-finding study,[30] the dose-escalation

study[31] and the active treatment comparison[32] used a single primary efficacy variable, the median percent change in the incontinence episode frequency (IEF). The three phase III studies also included the mean change in the validated, disease-specific, Incontinence Quality of Life (I-QOL) questionnaire total score (0–100 scale, worst–best) as a primary efficacy variable.[27-29] All studies performed intent-to-treat (ITT) primary analyses. The three phase III studies carried the last observation forward for patients who prematurely discontinued treatment.[27-29]

In the phase III studies, patients recorded incontinence episodes in diaries that they kept for the second week of the washout and run-in periods, and for the week prior to each monthly assessment visit.[27-29] In the dose-escalation placebo comparison, incontinence diaries were kept throughout the placebo run-in and the first 4-week treatment period, and for the final 2 weeks of the second 4-week treatment period.[31] IEF results reported herein derive from analyses performed using the last baseline and final treatment phase diaries for the dose-finding[30] and phase III studies,[27-29] and using pooled diary data for the dose-escalation placebo comparison[31] and the active treatment comparison.[32].

The Patient Global Impression of Improvement rating (PGI-I), consisting of a 7-point categorical self-rating (1 = very much better; 7 = very much worse), was included in most studies[27-31] as a secondary efficacy measure.

Dose-Finding Study

- Treatment with duloxetine 20 or 40mg twice daily significantly ($p < 0.05$) reduced the median IEF (59% and 58% decrease, respectively) compared with placebo (40% decrease) in a dose-finding study in 553 women with predominant symptoms of SUI.[30]
- The response was not dose-dependent in analyses using data from final baseline and last-visit patient diaries, but was dose-dependent in analyses using pooled data from the baseline and treatment phase diaries.[30]
- Duloxetine 20–80 mg/day increased the mean void interval by 16–18 minutes, which was significantly ($p \leq 0.05$) greater than the 5 minute increase observed with placebo.[30] I-QOL scores and PGI-I ratings increased with increasing dosage of duloxetine, but were only significantly ($p < 0.05$) greater than with placebo for the 80 mg/day dosage.[30]
- Subgroup analysis indicated that duloxetine was equally effective in patients with mixed urinary incontinence symptoms or pure SUI symptoms.[34]

Placebo Comparisons

- Duloxetine 40mg twice daily reduced the median IEF from baseline to a significantly greater extent than placebo (by 50.0–53.6% vs 27.5–40.0%; see figure 1) in three phase III studies of adult women with predominant symptoms of SUI (n = 458,[28] 494[27] and 683[29]).
- In two of the phase III studies,[28,29] duloxetine increased the mean total I-QOL scores to a significantly greater extent than placebo (figure 1). In the third study, the mean increase in I-QOL score at study end was not significantly different from that with placebo, but when analysed by visit, the differences were statistically significant ($p < 0.01$) for each monthly period (+5.6–8.6 vs +3.2–5.4 for placebo).[27]
- In all three phase III studies, duloxetine recipients experienced significantly greater increases in their average voiding interval than placebo recipients (15.0–20.4 vs 1.7–8.5 minutes; $p < 0.001$).[27-29] With respect to PGI-I ratings, significantly ($p < 0.05$) more duloxetine recipients than placebo recipients rated their condition as being improved in two studies,[28,29] but not in the third.[27]
- In women with predominantly severe SUI who were scheduled for continence surgery, duloxetine therapy reduced the median IEF to a significantly greater extent than placebo in both the ITT (59.8% vs 26.9% reduction; $p < 0.001$) [primary endpoint] and completers groups (60.4% vs 24.2%; $p = 0.01$).[31] Patients were randomised to receive double-blind therapy with duloxetine (40mg twice daily for 4 weeks followed by escalation of the dosage to 60mg twice daily for an additional 4 weeks) [n = 46 in the ITT population] or placebo (n = 52) for 8 weeks.[31]

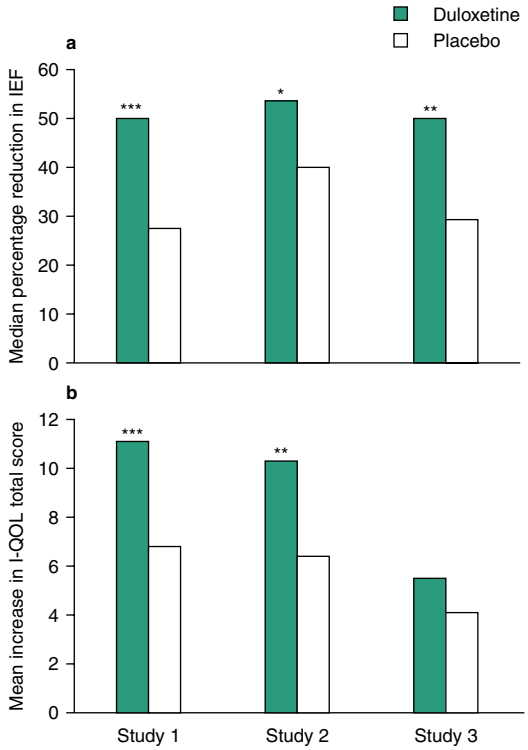


Fig. 1. Efficacy of duloxetine in women with predominant stress urinary incontinence symptoms. Effect of duloxetine 40mg twice daily for 12 weeks on incontinence episode frequency (IEF) and Incontinence Quality of Life (I-QOL) questionnaire total scores. Results from three multicentre, randomised, double-blind, placebo-controlled trials (n = 683 [study 1],[29] 458 [study 2][28] and 494 [study 3][27]). Treatment was initiated after a 2-week washout period, followed by a 2-week single-blind, placebo run-in period. IEF data were derived from patient diaries recorded the week prior to starting active treatment and the week prior to the last visit at 12 weeks. Analyses were intent-to-treat using the last observation carried forward for premature discontinuation. (**a**) Median percentage reduction in IEF. (**b**) Mean increase in I-QOL total score. * $p = 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs placebo.

- Mean I-QOL total score increases were significantly higher with duloxetine than with placebo (+10.6 vs +2.4; $p = 0.003$), continence pad use was reduced more with duloxetine than placebo (34.5% vs 4.8% reduction; $p = 0.008$) and more duloxetine than placebo recipients were classified as responders (63% vs 13.5% experiencing ≥50% decrease in IEF; $p < 0.001$).[31]
- All 28 patients who responded to duloxetine 80 mg/day had responded within 2 weeks, while three additional patients responded after the dosage increase to duloxetine 120 mg/day.[31] After therapy, ten patients (20.4%) in the duloxetine group, compared with none in the placebo group, indicated that they had reconsidered their willingness to undergo surgery.[31]

Active Treatment Comparison

- Both duloxetine alone (dosage not stated) and duloxetine in combination with PFMT significantly ($p < 0.05$) reduced the median IEF by 57%, compared with a 35% reduction with PFMT alone and a 29% reduction with no treatment.[32] This placebo-controlled study included 201 women, aged 18–75 years, with predominant symptoms of SUI. Duloxetine and placebo administration was double-blind, while PFMT and sham PFMT administration was single-blind.
- Secondary efficacy measures suggested that combination therapy was more effective than either treatment alone.[32] The mean total I-QOL score increased by 13.1 with combination therapy ($p < 0.05$ vs no treatment) compared with increases of 8.3 for duloxetine, 7.8 for PFMT and 4.8 for no treatment. The median decreases in pad use for the combination, duloxetine, PFMT and no treatment were 46%, 35%, 25% (all $p < 0.05$ vs no treatment) and 10%, respectively.[32]

4. Tolerability

- In the dose-finding study, the proportions of patients experiencing ≥1 adverse event with duloxetine 20, 40 and 80 mg/day were 62%, 68% and 73%, respectively, compared with 61% in the placebo group.[30] Significantly higher incidences with duloxetine versus placebo ($p < 0.05$) were only seen for the particular adverse events of nausea, insomnia and fatigue.[30]
- In the three phase III clinical trials, the incidences of adverse events with duloxetine 80 mg/day (74%,[29] 76%[28] and 81%[27] of patients, respectively) were significantly (all $p < 0.001$) higher than those with placebo (50%,[29] 59%[28] and 64%[27]).
- Nausea was consistently the most common adverse event associated with duloxetine therapy; oc-

curring with a significantly ($p < 0.05$) higher incidence in recipients of duloxetine 80 mg/day than in placebo recipients (13–28% vs 2–7%).[27-30] Nausea was generally of mild-to-moderate severity, usually occurred within the first 4 weeks of therapy and frequently resolved within 1–4 weeks.[27-29,31]

- Across the three phase III trials, other common adverse events occurring in significantly ($p < 0.05$) more duloxetine 80 mg/day than placebo recipients included dry mouth (12.2–19.4% vs 0.9–2.4%), insomnia (12.6–14.2% vs 1.2–2.6%), fatigue (10.1–14.8% vs 3.5–4.5%), constipation (9.6–14.2% vs 1.7–4.0%), dizziness (7.6–12.1% vs 2.4–3.2%), somnolence (4.0–8.7% vs 0–0.3%), increased sweating (5.7–8.5% vs 0.9–1.6%), vomiting (6.2–6.5% vs 1.7–2.0%), diarrhoea (6.1% vs 2.7%), anorexia (6.6% vs 0%) and tremor (4% vs 0%).[27-29] Headache occurred in significantly more duloxetine than placebo recipients in only one trial (7.3% vs 3.5%; $p = 0.04$).[29]
- Treatment discontinuation rates as a result of adverse events were significantly higher with duloxetine 80 mg/day than with placebo (15–24% vs 2–5%; $p < 0.05$).[27-30] Nausea was usually the most common cause of adverse event-related treatment discontinuation.[27-30]
- Most adverse events were of only mild-to-moderate severity. Serious adverse events with duloxetine were rare.[27-30] Although duloxetine 80 mg/day marginally elevated heart rate (<3 beats/minute), altered some ECG parameters and increased liver enzymes, these effects were not considered to be clinically important.[27-29]
- In the dose-escalation study, most adverse events started in the first 4 weeks of treatment with duloxetine 80 mg/day.[31] The incidence of new adverse events in the second 4-week period of treatment with duloxetine 120 mg/day did not differ between duloxetine and placebo recipients.[31]

5. Dosage and Administration

The recommended dosage of duloxetine in the EU for the treatment of moderate to severe SUI is 40mg orally twice daily without regard to meals.[26] If adverse events are troublesome beyond the first 4 weeks, the dosage may be reduced to 20mg twice daily.[26] It is also recommended that consideration be given to using PFMT concomitantly with duloxetine therapy.[26]

6. Duloxetine: Current Status

Duloxetine is approved throughout the EU for the treatment of moderate to severe SUI in women and is currently available in Germany, Denmark, Finland, Sweden and the UK, with further European launches to follow.[35,36] Regulatory approval of duloxetine for the treatment of SUI in women is pending in the US.[37]

Duloxetine has shown clinical efficacy superior to placebo in the treatment of SUI in several late-phase clinical trials. In women with predominant symptoms of SUI, duloxetine decreases IEF, increases voiding intervals and improves patients' QOL. Duloxetine may replace the need for surgery in some patients with severe SUI. Duloxetine is generally well tolerated, with nausea being the most common adverse event.

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