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Duloxetine
In Patients with Fibromyalgia

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Contents

Abstract

▲ Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor available in delayed-release capsules for oral use.

▲ Duloxetine 60 mg/day, compared with placebo, was associated with a greater reduction from baseline in the Brief Pain Inventory (BPI) average pain severity score, a greater improvement in the patient-rated global impression of improvement (PGI-I) scale in patients with fibromyalgia, with or without major depressive disorder, in two 12- and 15-week phase III studies.

▲ In a 27-week, phase III trial, there was no significant difference between duloxetine (60 or 120 mg/day) and placebo for the least squares mean change from baseline to endpoint in BPI average pain scores and the PGI-I score.

▲ The significant improvements in efficacy that occurred in patients with fibromyalgia during 8 weeks of open-label treatment with duloxetine 60 mg/day were generally maintained during 52 weeks of subsequent blinded treatment at the same dosage in a phase III trial. Nonresponders during treatment with open-label duloxetine 60 mg/day, demonstrated no increased ability to respond if the duloxetine dosage was up-titrated to 120 mg/day than those who remained on the same dosage during the subsequent 52-week, double-blind phase.

▲ Duloxetine was generally well tolerated in studies of up to 1 year in duration, with nausea being the most frequent adverse event and main cause for discontinuing therapy.

Features and properties of duloxetine (Cymbalta®)	
Indication	
Fibromyalgia	
Mechanism of action	
Selective serotonin and norepinephrine reuptake inhibition	
Dosage and administration	
Dose	60 mg
Route of administration	Oral
Frequency of administration	Once daily
Pharmacokinetics of a single dose of duloxetine 60 mg in healthy Caucasian volunteers	
Peak plasma concentration (C_{max})	38.7 ng/mL
Time to C_{max}	6–10 h
Area under the plasma concentration-time curve from time zero to infinity	584 ng • h/mL
Elimination half-life	≈12 h
Most common adverse events (>10% of patients)	
Nausea, headache, dry mouth, insomnia, fatigue, constipation, diarrhoea, decreased appetite, dizziness, somnolence	

Fibromyalgia is an idiopathic, chronic, nonarticular pain syndrome that affects 2–4% of the general population in the US and is predominantly seen in women.[1,2] Although their use as a diagnostic tool in clinical practice has been questioned,[3,4] the 1990 American College of Rheumatology criteria[3] defined fibromyalgia as widespread aching pain for at least 3 months and hyperalgesia at a minimum of 11 of the 18 specified muscle-tendon sites. Possible accompanying symptoms included fatigue, sleep disturbances, morning stiffness, parathesias, headache and anxiety.[2]

Although the pathophysiology of fibromyalgia is unclear and no widely accepted model of the disorder currently exists, the syndrome appears to involve a dysfunction of neuroendocrine and autonomic nervous system function.[5] In particular, dysfunction of the serotonin and norepinephrine systems is a potential mechanism for the pain experienced by patients with fibromyalgia. Genetic and family influences, environmental triggers (e.g. co-morbid disease, infections or physical trauma) and psychological factors (e.g. somatization, anxiety, depression) may also contribute to the development of the syndrome.[2,5]

There is no known cure for fibromyalgia; however, nonpharmacological (e.g. exercise, cognitive behavioural therapy and patient education) and pharmacological therapies are recommended to help reduce pain and treat other symptoms.[6,7] The use of antidepressant medications has been associated with improvements in pain, depression, fatigue, sleep disturbances and health-related quality of life in patients with fibromyalgia.[8,9] Dual serotonin and norepinephrine reuptake inhibitors such as duloxetine (Cymbalta®), milnaciprin and venlafaxine that enhance serotonin and norepinephrine neurotransmission may reduce pain and improve mood-related symptoms in patients with fibromyalgia.

This article reviews the pharmacology, therapeutic efficacy and tolerability of duloxetine (available in delayed-release capsules for oral use) in patients with fibromyalgia. A discussion of the use of duloxetine in other indications approved in the US[10] or EU,[11] namely acute and maintenance treatment of major depressive disorder, acute treatment of generalized anxiety disorder, neuropathic pain associated with diabetic peripheral neuropathy and female stress urinary incontinence (in the EU only[11]) is beyond the scope of this article.

Medical literature on the use of duloxetine in patients with fibromyalgia was identified using Medline and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference lists of published articles.

1. Pharmacodynamic Profile

- The exact mechanisms of the central pain inhibitory action of duloxetine in patients with fibromyalgia are unknown, but are believed to be related to potentiation of serotonergic and noradrenergic activity in the CNS as a result of inhibition of neuronal reuptake of serotonin and norepinephrine.[10,12] Serotonin and norepinephrine have been implicated in the mediation of endogenous analgesic mechanisms via descending inhibitory pain pathways in the spinal cord and brain.[13] Imbalances in these inhibitory mechanisms may contribute to central sensitization and hyperexcitability of the spinal cord and supraspinal pain-transmitting pathways.[14] These imbalances may manifest as persistent pain.[15]
- Duloxetine has a high affinity for serotonin and norepinephrine reuptake transporters, and a lower affinity for dopamine reuptake transporters;[12,16] *in vitro* duloxetine inhibited binding to human serotonin, norepinephrine and dopamine transporters with inhibition constant values of 0.8, 7.5 and 240 nmol/L, respectively.[16]
- *In vitro*, duloxetine had no appreciable affinity for other receptors including dopaminergic, adrenergic, cholinergic, histaminergic, muscarinergic, glutamate, opioid and GABA.[16] Duloxetine did not appreciably inhibit monoamine oxidase activity.[16]
- Duloxetine 20–120 mg/day decreased levels of serotonin in whole blood (a surrogate marker for serotonin reuptake inhibition) in healthy volunteers ($n = 12$[17] and 27[18]) relative to baseline ($p < 0.0001$)[18] or placebo ($p = 0.01$)[17] in randomized, placebo-controlled studies.

• *In vivo* positron emission tomography studies demonstrated that serotonin transporter occupancy was >80% after a single dose of duloxetine 40 or 60 mg, and remained high after multiple 60 mg doses even when plasma duloxetine levels were decreasing.[19]
• Inhibition of norepinephrine reuptake was demonstrated in healthy volunteers, based on evidence from various physiological, biochemical and pharmacological markers including urinary excretion of norepinephrine and metabolites, cardiovascular effects of norepinephrine reuptake inhibition and the adverse events profile.[17,20,21] For example, duloxetine 80–240 mg/day was associated with a dose-dependent increase from baseline in urinary excretion of norepinephrine and its major metabolite in a study in 15 healthy volunteers.[20] Small changes in heart rate, systolic and/or diastolic BP, indicative of an increase in sympathetic tone resulting from norepinephrine reuptake inhibition, have been demonstrated in healthy volunteers administered duloxetine 60–240 mg/day.[17,18,20]
• Duloxetine was effective in preclinical models of persistent (formalin-induced, late-phase, paw-licking behaviour) and neuropathic pain.[22] Duloxetine was minimally effective in the tail-flick model of nociceptive pain, indicating a lack of a primary analgesic or anaesthetic effect.[22]
• Duloxetine did not affect ventricular repolarization in a randomized, positive- and placebo-controlled, multicentre study in 117 healthy volunteers.[23] After administration of duloxetine up to 200 mg twice daily, no prolongation of the corrected QT interval occurred.[23] A single dose of moxifloxacin 400 mg was used as a positive control and data were analysed using three QT interval correction methods.

2. Pharmacokinetic Profile

• Oral duloxetine exhibited linear pharmacokinetics in healthy volunteers when administered in the dosage range of 40–80 mg/day.[10,24,25] Following oral administration of duloxetine, there was a 2-hour lag period until absorption commenced.[10]
• In 24 healthy Caucasians in the fasted state who were administered a single dose of duloxetine 60 mg, mean values for peak plasma concentration (C_{max}) and area under the concentration-time curve (AUC) from time zero to infinity were 38.7 ng/mL and 584 ng • h/mL.[25] Mean values for C_{max} were reached after 6–10 hours.[10,24,25] Following multiple doses of duloxetine, steady-state plasma concentrations were typically reached by day 3.[10,24]
• The presence of food did not affect the C_{max} of duloxetine, but it increased the time to reach C_{max} from 6 to 10 hours and decreased AUC by 10%.[10] These changes are not considered to be clinically relevant and duloxetine can therefore be administered without regard to meals (section 5).[10,11] Evening, compared with morning, administration of duloxetine delayed its absorption by 3 hours and increased its apparent clearance by one-third.[10]
• Duloxetine has a large apparent volume of distribution (mean 1640 L) and is highly bound (>90%) to human plasma proteins, primarily albumin and α_1-acid glycoprotein.[10] Renal or hepatic impairment does not affect the extent of protein binding.[10]
• Duloxetine undergoes extensive hepatic metabolism via cytochrome P450 (CYP) 2D6 and CYP1A2 to form multiple oxidative and conjugated metabolites.[10,24,26] Metabolites found in plasma and urine include 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6-methoxy duloxetine sulphate; many additional metabolites were also found in the urine, including some representing only minor pathways of elimination. The major metabolites found in the plasma are inactive.
• Duloxetine is primarily excreted in the urine (≈72%), with ≈19% excreted in the faeces.[10,26] Only traces of unchanged duloxetine (<1%) have been detected in the urine.[26] Duloxetine is very weakly excreted into human milk, according to data from a study in six healthy lactating women who received duloxetine 40 mg twice daily for 3.5 days; the estimated amount of duloxetine received by an infant was 0.14% of that administered to the mother.[27]
• The mean elimination half-life ($t_{½\beta}$) of duloxetine was ≈12 hours (range 8 to 17 hours)[10,11,24] and

the mean apparent plasma clearance following an oral dose was ≈101 L/h (range 33 to 261 L/h).[11]

Special Populations

- Age,[10,11] sex,[10,11] race[25] and smoking status[10,11] had no clinically relevant effect on the pharmacokinetics of duloxetine.
- After administration of a dose of oral duloxetine 20 mg, the apparent clearance was 75% lower, AUC values were about 3-fold higher and the $t_{½β}$ of duloxetine was about three-fold longer (all $p < 0.05$) in patients with moderate liver cirrhosis (Child-Pugh class B) than in healthy healthy subjects.[28] The pharmacokinetics of duloxetine and its metabolites have not been studied in patients with mild or severe hepatic insufficiency.[10] The US manufacturer does not recommend the administration of duloxetine to patients with any hepatic insufficiency.[10]
- Pharmacokinetic data on duloxetine in patients with mild or moderate renal impairment (estimated creatinine clearance [CL_{CR}] 30–80 mL/min) are limited; however, population pharmacokinetic analyses suggest that this level of renal dysfunction will not significantly influence the apparent clearance of duloxetine.[10] The C_{max} and AUC of duloxetine were ≈2-fold higher in patients with end-stage renal disease requiring dialysis than in healthy volunteers after a single dose of duloxetine 60 mg; however, the duloxetine $t_{½β}$ was similar in both groups. Duloxetine is not recommended for use in patients with end-stage renal disease or severe renal impairment (estimated CL_{CR} <30 mL/min).[10]

Drug Interactions

- Because duloxetine is metabolized by CYP2D6 and CYP1A2,[10,29] concomitant administration of duloxetine with potent inhibitors of CYP2D6 and CYP1A2 activity results in elevated duloxetine concentrations. Coadministration of duloxetine 60 mg with fluvoxamine 100 mg (a potent CYP1A2 inhibitor) increased the duloxetine AUC ≈6-fold.[10] The US prescribing information recommends that coadministration of duloxetine and other CYP1A2 inhibitors (e.g. cimetidine, ciprofloxacin and enoxacin) should be avoided.[10] Coadministration of duloxetine 40 mg/day with paroxetine 20 mg/day (a potent CYP2D6 inhibitor) increased the duloxetine AUC by 1.6-fold.[10] Similar effects are expected with other potent CYP2D6 inhibitors such as fluoxetine or quinidine.[10]
- Duloxetine is a moderate inhibitor of CYP2D6 and so caution is advised when duloxetine is coadministered with drugs that are extensively metabolized by CYP2D6 and that have a narrow therapeutic index, including tricyclic antidepressants (e.g. nortriptyline, amitriptyline, imipramine and desipramine), phenothiazines (e.g. thioridazine) and type 1C antiarrhythmics (e.g. propafenone and flecainide).[10] The AUC of desipramine (a CYP2D6 substrate) was significantly ($p < 0.0001$) increased by 122%, when a single dose of desipramine 50 mg was coadministered with duloxetine 60 mg/day.[30] The US prescribing information does not recommend the concomitant use of duloxetine and thioridazine, because the increased concentrations of thioridazine may lead to serious arrhythmias and death.
- *In vitro*, duloxetine did not induce CYP1A2 activity. Therefore, an increase in the metabolism of CYP1A2 substrates (e.g. theophylline, caffeine) is not expected when these agents are coadministered with duloxetine; however, clinical studies involving these agents have not been conducted.[10] *In vitro*, duloxetine is an inhibitor of CYP1A2.[10] However, the pharmacokinetics of theophylline were unaltered when theophylline was coadministered with duloxetine 60 mg twice daily.[10] The US prescribing information notes that duloxetine is unlikely to have a clinically significant effect on the metabolism of CYP1A2 substrates.[10]
- Duloxetine does not affect CYP2C9, CYP2C19 or CYP3A activity *in vitro* and is not expected to modify the metabolism of substrates of these enzymes, although clinical drug-drug interaction studies have not yet been conducted.[10]
- Neither the pharmacokinetics of duloxetine, nor those of temazepam or lorazepam, were altered by coadministration under steady-state conditions.[10,31]
- Administration of duloxetine and alcohol several hours apart (so that the respective C_{max} would occur at the same time) did not exacerbate the impairment

of mental and motor skills produced by alcohol.[10] However, duloxetine should not normally be prescribed to patients with substantial alcohol use who are at risk of having severe liver injury.[10]

- Since duloxetine is highly protein bound in human plasma, it could displace other drugs (e.g. warfarin) that are also highly protein bound, increasing the free concentrations of the other drug.[10] Potentiation of the anticoagulant effect of warfarin by duloxetine causing severe elevation of the International Normalized Ratio (INR) has been reported.[32] However, the INR was not significantly altered after 30 patients who had a stable INR (1.5–2.0) while treated with warfarin 2–9 mg/day received concomitant duloxetine 60 or 120 mg/day.[33]

3. Therapeutic Efficacy

The efficacy of duloxetine has been investigated in adult patients with fibromyalgia, with or without major depressive disorder, in randomized, double-blind, multicentre trials.[10,34-38] This section focuses on efficacy data from phase III studies that administered the approved dosage of duloxetine (60 mg once daily).[10,34,36-38]

One study randomized 354 female patients to duloxetine 60 mg once daily, duloxetine 60 mg twice daily (initiated at 60 mg once daily and then uptitrated after 3 days) or placebo for 12 weeks of double-blind treatment; 216 patients completed this phase.[34]

In another study, after a 1-week screening phase, 520 patients (95% female) were initially randomized to duloxetine 20 mg once daily, 60 mg once daily or 120 mg once daily for 15 weeks of double-blind treatment; 325 patients completed this phase.[37] The dosage of duloxetine was then increased to 60 mg/day in recipients of duloxetine 20 mg/day, while recipients of duloxetine 60 or 120 mg/day maintained this dosage for a further 13 weeks of double-blind treatment; 278 patients completed this phase.[37]

In a third study,[36] after a 1-week screening phase, 330 patients (93% female) were randomized to double-blind treatment with duloxetine 60 mg once daily (initiated at 30 mg once daily and then uptitrated after 1 week) or placebo for 27 weeks; in patients assigned to duloxetine 60 mg once daily, the duloxetine dosage was increased to 120 mg/day after 8 weeks in patients with inadequate response (<50% reduction in the Brief Pain Inventory[39] [BPI] average pain severity score); 204 patients completed this phase. This study presented combined data from patients receiving duloxetine 60 or 120 mg/day.

Preliminary data from a 60-week, uncontrolled study involving 350 patients with fibromyalgia are available online,[38] with some of the study details being reported in the US manufacturer's prescribing information.[10] However, tolerability, not efficacy, was the primary focus of this study. Patients (96% female) were treated with duloxetine 30 mg once daily for 1 week, then duloxetine 60 mg once daily for 7 weeks in an open-label manner; subsequently, patients were randomized to double-blind treatment with duloxetine 60 mg once daily or 120 mg once daily for 52 weeks; 195 patients completed this phase.[10,38]

Patents included in these trials were aged ≥18 years and met the American College of Rheumatology criteria[3] for fibromyalgia. A score ≥4 on the BPI average pain severity score at baseline was also an entry criterion in two of the studies (mean 6.5).[10,34,37] Approximately 25% of participants had a co-morbid diagnosis of major depressive disorder.[10,34,36,37]

In the studies in which efficacy was the focus,[34,36,37] a primary/co-primary endpoint was the change in BPI average pain severity score (assessed during the past 24 hours using an 11-point scale ranging from 0 [no pain] to 10 [worse possible pain]) from baseline to the 12-week,[34] 15-week[37] or 27-week endpoint.[36] The Patient Global Impressions of Improvement (PGI-I)[40] score (assessed using a 7-point scale ranging from 1 [very much better] to 7 [very much worse]) at the 15-month[37] or 27-week endpoint[36] was a co-primary endpoint in two of the trials. Efficacy analyses were conducted on an intent-to-treat basis.

• Duloxetine 60 mg/day reduced pain severity compared with placebo, when assessed according to the change in BPI average pain severity score from baseline after ≈3 months, according to data from two studies.[34,37] The respective least squares mean changes in BPI average pain severity scores were −2.39 versus −1.16 ($p < 0.001$)[34] and −1.99 versus −1.39 ($p \leq 0.05$).[37] In the study that continued with double-blind treatment for a further 13 weeks, the respective least squares mean changes in BPI average pain severity scores continued to be significantly different between recipients of duloxetine 60 mg/day and placebo at endpoint (−1.98 vs −1.43; $p \leq 0.05$).[37]

• The reduction in BPI average pain severity score in duloxetine versus placebo recipients was observed in patients with and without comorbid major depressive disorder.[34,36,37] There was no significant difference in the reduction in BPI average pain severity score between duloxetine 60 and 120 mg/day in the two studies that compared these dosages.[10,34,37]

• Duloxetine 60 mg/day, compared with placebo, was associated with a significantly greater proportion of patients with a ≥30% reduction in the BPI average pain severity score after 15 weeks (50.7% vs 36.0%; $p = 0.016$) in one of the studies.[37] At least 30% pain reduction has been considered necessary to provide clinically meaningful relief.[41] The proportion of patients with a ≥50% reduction in the BPI average pain severity score was not significantly different between the two groups (34.0% vs 23.7%).[37]

• Duloxetine 60 mg/day resulted in patient-rated global improvements in patients with fibromyalgia.[34,37] The PGI-I score was significantly lower (indicating an improvement) with duloxetine 60 mg/day than placebo when assessed at 12 weeks (3.11 vs 3.71; $p < 0.01$) in one study,[34] and at 15 weeks (3.04 vs 3.39; $p \leq 0.05$; co-primary endpoint), but not 28 weeks (3.08 vs 3.37), in the other study.[37]

• Duloxetine 60 mg/day resulted in clinically-rated global improvements in patients with fibromyalgia, assessed according to the Clinical Global Impressions of Severity (CGI-S)[40] score.[34,37] The reduction in CGI-S score was significantly greater with duloxetine 60 mg/day than placebo when assessed at 12 weeks (−0.84 vs −0.44; $p < 0.01$) in one study,[34] and at 15 weeks (−1.06 vs −0.70; $p \leq 0.01$) and at 28 weeks (−1.07 vs −0.66; $p \leq 0.01$) in an other study.[37]

• Duloxetine 60 mg/day, compared with placebo, was associated with an improvement in aspects of health and functioning most affected by fibromyalgia, assessed according to the Fibromyalgia Impact Questionnaire (FIQ)[42] total score. In the 12-week study,[34] the between-group difference in the FIQ total score was significant from week 1 and continued until endpoint; the least squares mean change in FIQ from baseline to endpoint was −16.72 with duloxetine 60 mg/day and −8.35 with placebo ($p < 0.001$). In another study,[37] the least squares mean change in FIQ total score from baseline in duloxetine 60 mg/day versus placebo recipients was significantly different at 15 weeks (−15.41 vs −10.05; $p \leq 0.01$), but not 28 weeks.

• Patients treated with duloxetine 60 mg/day, compared with placebo, had significant improvements in various other secondary efficacy measures in two phase III studies after ≈3 months of treatment, including the BPI-interference scores,[34] Hamilton Depression 17-item Rating Scale[43] scores,[34] Short-Form-36 (SF-36)[44] mental component summary score[34,37] and the Multidimensional Fatigue Inventory (MFI)[45] mental fatigue dimension score.[37]

• In the 27-week study, the difference between duloxetine (60 or 120 mg/day) and placebo in the least squares mean change from baseline in BPI average pain scores (−1.62 vs −1.13; $p < 0.053$) and the PGI-I score (3.43 vs 3.73; $p = 0.073$) failed to reach significance at endpoint.[36] However, there were significant differences between the duloxetine (60 or 120 mg/day) and placebo groups at all visits through to week 8 (and some subsequent weeks) for both these parameters. Several secondary endpoints demonstrated significant improvements with duloxetine (60 or 120 mg/day) over placebo, including the FIQ pain score ($p = 0.03$), BPI least pain score ($p = 0.046$), the BPI average interference score

(p = 0.009), the CGI-S (p = 0.011), the MFI mental fatigue dimension (p = 0.023), the Beck Depression Inventory-II[46] total score (p = 0.017) and the SF-36 mental component summary score (p = 0.026) and mental health score (p = 0.005).

- In the 60-week study, significant improvements in efficacy and functional outcomes occurred during the 8-week, open-label treatment with duloxetine 60 mg/day, including improvements in BPI average pain score, FIQ total score, CGI-S score, and PGI-I. There was a mean increase in BPI average pain score of 1.26 from randomization to endpoint during the 52-week, double-blind study phase in patients treated with duloxetine 60 mg/day who were initial responders to this dosage during the open-label phase (≥50% reduction from baseline). The BPI average pain score was very low at the start of this 52-week phase (mean 1.75), with the average pain severity remaining mild at endpoint and below the BPI average pain score (mean 6.66) at study entry.[38]
- In patients who did not respond when treated with duloxetine 60 mg/day during the open-label phase of the 60-week study, there appeared to be no benefit associated with increasing the duloxetine dosage to 120 mg/day during the subsequent double-blind phase.[38] For patients with <50% reduction in pain score from baseline during the open-label phase, there was no significant difference in the BPI average pain score between those subsequently randomized to duloxetine 60 or 120 mg/day during the double-blind phase.[38]
- Overall discontinuation rates during the placebo-controlled trials were 37–39%, with significantly fewer duloxetine than placebo recipients withdrawing due to lack of efficacy in two of the trials (3–7% vs 15%; p < 0.05).[34,36] In the 60-week uncontrolled trial, 8% of patients treated with duloxetine withdrew due to lack of efficacy.[38] Withdrawal rates due to adverse events are discussed in section 4.

4. Tolerability

This section focuses on the tolerability of duloxetine in patients with fibromyalgia in the studies discussed in section 3. Data have been obtained from the placebo-controlled trials,[34,36,37] as well as pooled analyses of these studies (available as abstracts[47,48] or in the US manufacturer's prescribing information[10]). Long-term tolerability data are also available from a 6-month extension (n = 482 initially entered the extension phase)[49] of two of the placebo-controlled trials[36,37] and the 60-week, uncontrolled study (n = 350) in patients with fibromyalgia.[10,38] In these studies, patients generally received duloxetine 60 or 120 mg/day.

Data have also been obtained from pooled analyses of duloxetine-treated patients with a variety of approved indications, including a pooled analysis (reported in the US manufacturer's prescribing information[10]) of patients with major depressive disorder (n = 2327), generalized anxiety disorder (n = 668), diabetic peripheral neuropathic pain (n = 568) and fibromyalgia (n = 876) and a retrospective analysis of tolerability data from 23 983 patients with a variety of indications randomized to duloxetine 20–120 mg/day in 64 studies ranging from 3 weeks to 1 year in duration.[50]

- Duloxetine was generally well tolerated in patients with fibromyalgia, with adverse events generally being mild to moderate in severity. According to a pooled analysis[10] of the initial 3-month phase of two of the phase III studies[34,37] in patients with fibromyalgia, the most commonly occurring adverse events in duloxetine recipients were nausea, headache, dry mouth, insomnia, fatigue, constipation, diarrhoea, decreased appetite, dizziness, somnolence, hyperhidrosis and upper respiratory tract infection (figure 1). This duloxetine tolerability profile was similar to that obtained in pooled analyses of trials in patients with a variety of indications.[10,50]
- According the pooled analysis of patients with fibromyalgia enrolled in placebo-controlled studies, 19.5% (171/876) of the duloxetine recipients and 11.8% (63/535) of the placebo recipients discontinued treatment due to an adverse event.[10] Duloxetine-related discontinuations included those due to nausea (1.9%), somnolence (1.5%) and fatigue (1.3%).[10]
- The adverse event profile of duloxetine 60 and 120 mg/day reported in a 6-month extension[49] of

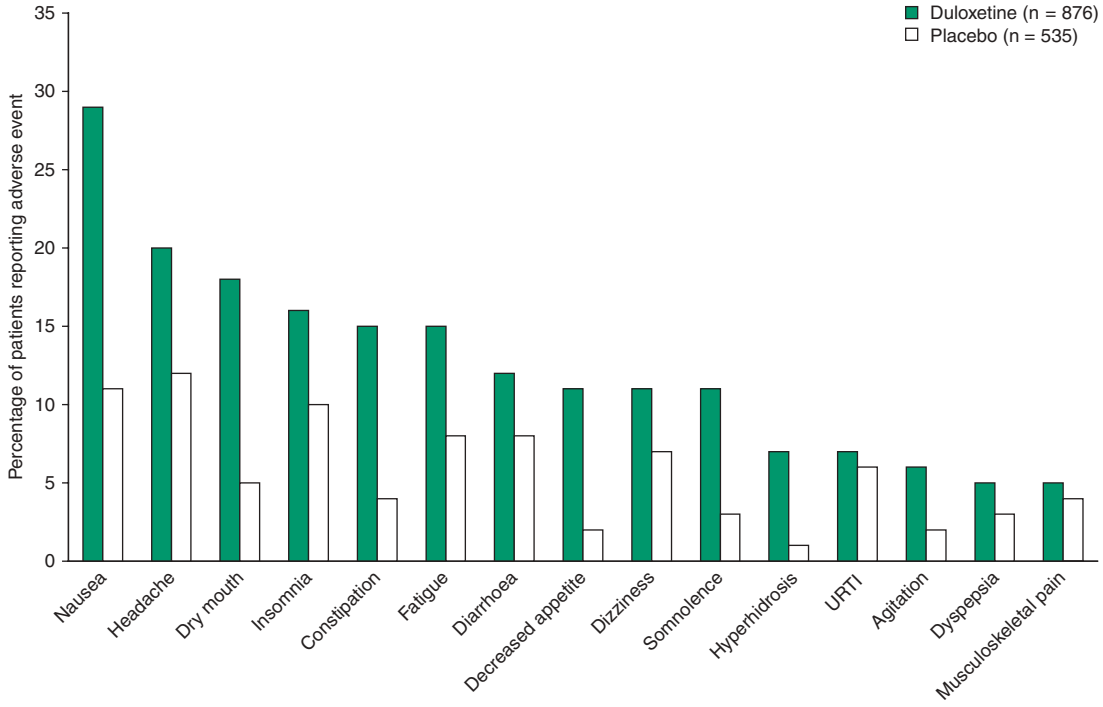

Fig. 1. Tolerability profile of duloxetine in patients with fibromyalgia. Incidence of treatment-emergent adverse events that occurred in ≥5% of patients treated with duloxetine 20–120 mg/day in a pooled analysis[10] of two randomized, double-blind, placebo-controlled, multicentre studies[34,37] with an initial treatment phase of ≈3 months (12[34] or 15[37] weeks). **URTI** = upper respiratory tract infection.

two 6-month phase III trials and in the 60-week study[10,38] was similar to that reported in placebo-controlled trials of a shorter duration (approximately 3- to 6-months).[34,36-38] Common treatment-emergent adverse events reported in these studies[49] included nausea, dry mouth, hyperhidrosis, dizziness, insomnia, headache and constipation. Serious adverse events were rare (≤1% of patients).[10,38]

- In the two phase III studies with an initial treatment phase of ≈3 months,[34,37] duloxetine 120 mg/day was associated with more adverse reactions and premature discontinuations of treatment than duloxetine 60 mg/day.[10]
- According to the pooled analysis of placebo-controlled studies in patients with fibromyalgia, duloxetine, compared with placebo, was associated with increases in systolic BP (+0.91 vs −1.58 mmHg; $p < 0.01$), increases in diastolic BP (+1.04 vs −1.17 mmHg; $p < 0.01$) and increases in heart rate (+1.22 vs −0.42 beats/min; $p < 0.01$).[47] In the longer 60-week study,[10,38] mean changes in supine systolic BP were −1.0 mmHg, in supine diastolic BP were −0.2 mmHg, in heart rate were +1.9 beats/min ($p < 0.001$ vs baseline).
- Duloxetine was not associated with clinically relevant changes in electrocardiogram parameters, according to a pooled analysis of placebo-controlled clinical trials.[10,51] Although duloxetine was associated with significant decreases from baseline to endpoint in the ECG intervals of PR, RR, QRS and QT (including QT interval corrected for heart rate using Fridericia's [QTcF] formula) compared with placebo in a pooled analysis of 42 placebo-controlled studies of up to 13 week in patients with a variety of indications, these changes were small and not considered to be clinically significant (also see section 1).
- Duloxetine has been associated with increases in liver enzymes (ALT, AST and alkaline phosphatase) in patients treated with duloxetine,

including those with fibromyalgia.[10,50] In a pooled analysis of clinical trials in patients with various indications, increases of ALT greater than three times the upper limit of normal (ULN) occurred in 1.1% (85/7632) of duloxetine recipients compared with 0.2% (13/5578) of placebo recipients.[10] In placebo-controlled studies, a dose-response relationship for ALT elevation of >3× ULN and AST elevation >5× ULN was evident in recipients of fixed dosages of duloxetine.[10] Although rare, hepatic failure (in some cases resulting in death) has been reported with duloxetine use.[10] The US prescribing information recommends discontinuing duloxetine in any patient who develops jaundice or other clinically significant liver dysfunction. It also cautions against the use of duloxetine in patients with any hepatic insufficiency.

- Duloxetine has also been associated with weight changes. Patients with fibromyalgia treated with duloxetine for up to 26 weeks had a mean weight reduction of 0.43 kg compared with a mean weight increase of approximately 0.28 kg in placebo recipients ($p < 0.01$), according to a pooled analysis.[10,47] A mean weight increase of 0.7 kg occurred in duloxetine recipients in the 60-week study in patients with fibromyalgia.[10,47]
- Sexual dysfunction was significantly more common in duloxetine 40–120 mg/day (n = 736) than placebo (n = 371) recipients, according to a pooled analysis of four placebo-controlled studies in patients with multiple depressive disorder.[52] Over the initial 8 weeks of treatment, sexual dysfunction was significantly more common in males treated with duloxetine than placebo, when assessed according to the change in Arizona Sexual Experience Scale (ASEX) total score and ASEX Item 4 (ease of orgasm). Mean changes in ASEX total score and individual ASEX items were not significantly different after duloxetine or placebo treatment in female patients.
- Serotonin release by platelets plays an important role in haemostasis; therefore, caution is advised when duloxetine is combined with oral anticoagulants or antiplatelet agents due to a potential increased risk of bleeding.[10]

5. Dosage and Administration

In patients with fibromyalgia,[10] the recommended dosage for duloxetine is 60 mg administered orally once daily. Initially, duloxetine should be administered at a dosage of 30 mg once daily for 1 week prior to increasing the dosage to 60 mg/day. Some patients may respond to the initial dosage.

The US prescribing information notes that there is no evidence that dosages of duloxetine greater than 60 mg/day confer additional efficacy, even in patients not responding to duloxetine 60 mg/day (section 3); the higher dosage is associated with a higher rate of adverse reactions.[10]

The efficacy of duloxetine has been demonstrated in placebo-controlled studies of up to 3 months in duration in patients with fibromyalgia (see section 3). It is recommended that continued treatment with duloxetine beyond the 3 months should be based on individual patient response. Duloxetine may be administered without regard to meals.

Concomitant administration of duloxetine and a monoamine oxidase inhibitor (MAOI) is contraindicated due to the risk of developing the potentially life-threatening serotonin syndrome or neuroleptic malignant syndrome-like reactions. Duloxetine should not be used for at least 5 days before, or within at least 14 days after, treatment with an MAOI.[10]

As with all antidepressants in the US, the manufacturer's prescribing information includes a black-box warning regarding the increased risk of suicidality among children and adolescents with multiple depressive disorders receiving antidepressants in short-term studies.[10]

Local prescribing information should be consulted for full details of contraindications, warnings and precautions regarding the use of duloxetine in the management of fibromyalgia.[10]

6. Duloxetine: Current Status

Duloxetine is approved in the US for use in patients with fibromyalgia.[10] Duloxetine 60 mg once daily has shown clinical efficacy superior to placebo in the treatment of fibromyalgia in two

phase III clinical trials, reducing the severity of pain (as measured by the BPI average pain scale) and resulting in an improvement in patient-rated global impression after 3 months of treatment. In a 27-week phase III trial, there was no significant difference between duloxetine (60 or 120 mg/day) and placebo for the least squares mean change from baseline to endpoint in BPI average pain scores and the PGI-I score. However, there were significant differences between duloxetine (60 or 120 mg/day) and placebo for several other endpoints (including the FIQ pain score, BPI least pain score, the BPI average interference score, the CGI-S, the MFI mental fatigue dimension, the Beck Depression Inventory-II total score and the SF-36 mental component summary score and mental health score).

Significant improvements in efficacy that occurred in patients during 8 weeks of open-label treatment with duloxetine 60 mg/day were generally maintained during 52 weeks of subsequent blinded treatment at the same dosage in a phase III trial. No further efficacy advantage was obtained for nonresponders to open-label duloxetine 60 mg/day by uptitrating the duloxetine dosage to 120 mg/day during the 52-weeks of blinded treatment. Duloxetine is generally well tolerated in studies of up to 1-year in duration, with nausea being the most common adverse event.

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