Fibromyalgia Review

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Fibromyalgia Review

FDA-Approved Indications

Drug	Manufacturer	Fibromyalgia	Other indications
duloxetine (Cymbalta®)[1]	Lilly	X	Major depressive disorder, generalized anxiety disorder, diabetic peripheral neuropathic pain
milnacipran (Savella™)[2]	Forest	X	None
pregabalin (Lyrica®)[3]	Pfizer	X	Partial onset seizures as adjunctive therapy, neuropathic pain associated with diabetic peripheral neuropathy, post-herpetic neuralgia

Overview[4,5,6,7,8]

Fibromyalgia is a chronic disorder characterized by pain, fatigue, and sleep disturbances. It predominantly affects women and is difficult to treat. A multidisciplinary approach should be utilized. Diagnostic criteria for fibromyalgia are based on the American College of Rheumatology (ACR) criteria, characterized by widespread musculoskeletal pain and excess tenderness in at least 11 of 18 predefined anatomic sites, referred to as trigger points. Pain is considered widespread when all of the following are present: pain in the left and right side of the body, pain above and below the waist, and axial skeletal pain (cervical spine, anterior chest, thoracic spine, or low back). Digital palpation should be performed with an approximate force of four kg. For a tender point to be considered "positive," the subject must state that the palpation was painful. "Tender" is not to be considered "painful." For classification purposes, patients will be said to have fibromyalgia if both criteria are satisfied. Widespread pain must have been present for at least three months. The presence of a second clinical disorder does not exclude the diagnosis of fibromyalgia. Laboratory tests for thyroid stimulating hormone (TSH) and erythrocyte sedimentation rate (ESR) are recommended to rule out hypothyroidism and polymyalgia rheumatica, respectively, as they have similar symptomatology.

Tricyclic antidepressants (TCAs), an unapproved class of drugs for the treatment of fibromyalgia, have been found to be effective in a couple of trials of short duration.[9,10] These drugs are associated with a number of adverse effects including anticholinergic effects (e.g., dry mouth and urinary retention), orthostatic hypotension, and cardiac dysfunction. Gabapentin, also unapproved for the treatment of fibromyalgia, has low bioavailability and is not rapidly absorbed; therefore, it requires a dosage regimen of three to four times daily. Gabapentin, too, has data to support its effectiveness in the treatment of fibromyalgia.[11] The American Pain Society (APS) last produced guidelines for fibromyalgia pain treatment in 2005, prior to any product receiving FDA approval for treatment of this condition.[12] FDA-approved drugs for the treatment of fibromyalgia now include duloxetine (Cymbalta), milnacipran (Savella), and pregabalin (Lyrica). The APS guidelines recommend amitriptyline (and other TCAs) or cyclobenzaprine as the initial pharmacologic option, with selective serotonin reuptake inhibitors (SSRIs), tramadol, and opioids also listed as subsequent options. Amitriptyline and cyclobenzaprine received the highest ranking regarding strength and consistency of evidence at the time. There is no comparative evidence to support the superiority of any of these products in fibromyalgia.

Pharmacology[13,14,15]

The effects of duloxetine (Cymbalta) and milnacipran (Savella), serotonin-norepinephrine reuptake inhibitors (SNRI), are thought to be due to its potentiation of serotonergic and noradrenergic activity in the central nervous system (CNS).

Pregabalin (Lyrica) binds to presynaptic α_2-delta subunit of voltage sensitive calcium channels. It may modulate release of sensory neuropeptide substance P and calcitonin gene-related peptide.

Pharmacokinetics

Drug	Bioavailability (%)	Tmax (hrs)	Half-life (hrs)	Active metabolites	Excretion (%)
duloxetine (Cymbalta)[16]	N/A	6	12	None	Urine: 70 Feces: 20
milnacipran (Savella)[17]	85-90	2-4	6-8	None	Urine: 55
pregabalin (Lyrica)[18]	≥90	1.5	6	None	Urine: 90-98

N/A = not available

Contraindications/Warnings[19,20,21]

In a FDA analysis, patients receiving antiepileptic drugs, including pregabalin (Lyrica), had approximately twice the risk of suicidal behavior or ideation (0.43 percent) compared to patients receiving placebo (0.22 percent).[22] The increased risk of suicidal behavior and suicidal ideation was observed as early as one week after starting the antiepileptic drug and continued through 24 weeks. The relative risk for suicidality was higher in patients with epilepsy compared to patients who were given one of the drugs in the class for psychiatric or other conditions. Healthcare professionals should closely monitor all patients currently taking or starting any antiepileptic drug for notable changes in behavior that could indicate the emergence or worsening of suicidal thoughts, behavior, or depression.

Duloxetine (Cymbalta) and milnacipran (Savella) also have black box warnings regarding the risk of suicide. SNRIs and other antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder and other psychiatric disorders. Anyone considering the use of any antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need.

Pregabalin should be gradually withdrawn over at least a one-week period to minimize the potential of increased seizure frequency. A gradual reduction in the dose of SNRIs rather than abrupt cessation is also recommended whenever possible.

Orthostatic hypotension and syncope have been reported with therapeutic doses of duloxetine, especially during the first week of therapy or after dose increases. The risk of blood pressure decreases may be greater in patients taking concomitant medications that induce orthostatic hypotension or are potent CYP1A2 inhibitors and in patients taking duloxetine at doses above

60 mg daily. Consider discontinuation of duloxetine in patients with symptomatic orthostatic hypotension and/or syncope during duloxetine therapy. \

Peripheral edema is a concern with pregabalin. There have been postmarketing reports of angioedema in patients during initial and chronic treatment with pregabalin (Lyrica). Specific symptoms included swelling of the face, mouth (tongue, lips, and gums), and neck (throat and larynx). There were reports of life-threatening angioedema with respiratory compromise requiring emergency treatment.

SNRIs

Duloxetine and milnacipran are contraindicated in patients with uncontrolled narrow-angle glaucoma. Concomitant use of SNRIs with monoamine oxidase inhibitors (MAO-Is) is also contraindicated.

The development of a potentially life-threatening serotonin syndrome or neuroleptic malignant syndrome-like reaction may occur with SNRI treatment, particularly with concomitant use of serotonergic drugs, including triptans, and with drugs which impair metabolism of serotonin, including MAO-Is. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

SNRIs may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anticoagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding.

SNRI treatment relative to placebo has been associated with increases in blood pressure. Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment.

Duloxetine and milnacipran should not be prescribed for patients with substantial alcohol use or evidence of chronic liver disease. Elevated transaminases, bilirubin, and other liver function markers have occurred when SNRIs have been given to such patients. There have been reports of hepatic failure in patients treated with either duloxetine or milnacipran.

SNRIs have been known to affect urethral resistance. If symptoms of urinary hesitation develop, consideration should be given to the possibility that it might be drug-related.

Drug Interactions[23,24,25]

Duloxetine should not be used concomitantly within two weeks of stopping an MAO-I. Additionally, when converting from an MAO-I to duloxetine, there must be a washout period of seven to 14 days.

Duloxetine is a moderate inhibitor of CYP2D6, and is also affected by inhibitors of CYP2D6 and CYP1A2 (increased duloxetine levels). Duloxetine may impact the metabolism of other drugs metabolized by CYP2D6; due to of the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, duloxetine and thioridazine should not be co-administered. Drugs that raise the gastric pH may lead to early release of duloxetine when given concomitantly. Duloxetine is highly protein bound and administration with another highly protein bound drug may increase free concentrations of the other drug.

Adverse Effects

Drug	Weight change	Nausea	Somnolence	Dizziness	Dry mouth	Constipation	Edema
duloxetine (Cymbalta)[26]	2 (1)	29 (11)	11 (3)	11 (7)	18 (5)	15 (4)	nr
milnacipran (Savella)[27]	reported	35-39 (20)	reported	10-11 (6)	5 (2)	15-16 (4)	reported
pregabalin (Lyrica)[28]	8-14 (2)	nr	13-22 (4)	31-45 (9)	6-9 (2)	4-10 (2)	5-9 (2)

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses.
nr = not reported.

Special Populations[29,30,31]

Pediatrics

The use of pregabalin (Lyrica), milnacipran (Savella), and duloxetine (Cymbalta) have not been adequately studied in children.

Pregnancy

All three products are Pregnancy Category C. Neonates exposed to SNRIs or SSRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding.

Renal impairment

Duloxetine is not recommended for patients with end stage renal disease (ESRD) or severe renal impairment (estimated creatinine clearance < 30 mL/min).

Milnacipran dose adjustment is necessary in patients with severe renal impairment.

Pregabalin is excreted primarily by the renal route; therefore, dosage should be adjusted based on renal function as determined by creatinine clearance.

Hepatic impairment

SNRIs should not be administered to patients with severe hepatic insufficiency as it increases the risk of elevation of serum transaminase levels.

Dosages

Drug	Initial dose	Maximum dose	Availability
duloxetine (Cymbalta)[32]	30 mg once daily	60 mg once daily	20, 30, 60 mg capsules
milnacipran (Savella)[33]	12.5 mg daily, titrated up to 50 mg twice daily over the course of one week	100 mg twice daily	12.5, 25, 50, 100 mg tablets
pregabalin (Lyrica)[34]	150 mg/day in two divided doses	450 mg/day	25, 50, 75, 100, 150, 200, 225, 300 mg capsules;

Clinical Trials

Search Strategies

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials for fibromyalgia are considered the most relevant in this category. However, due to the absence of comparative data, placebo-controlled trials have been included. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

duloxetine (Cymbalta) and placebo

A 12-week, randomized, double-blind, placebo-controlled trial assessed the efficacy and safety of duloxetine in 354 female patients with fibromyalgia, with or without current major depressive disorder.[35] Patients received duloxetine 60 mg once daily or twice daily or placebo. The primary outcome was the Brief Pain Inventory (BPI) average pain severity score (defined as $\geq$30 percent reduction in this score). Compared with placebo, both duloxetine groups improved significantly more ($p<0.001$) on the BPI average pain severity score (60 mg daily [55 percent; $p<0.001$]; 60 mg twice daily [54 percent; $p=0.002$]; placebo [33 percent]). The treatment effect of duloxetine on pain reduction was independent of the effect on mood and the presence of major depressive disorder. Patients treated with duloxetine 60 mg daily or twice daily had significantly greater improvement in remaining BPI pain severity and interference scores, Fibromyalgia Impact Questionnaire, Clinical Global Impression of Severity, Patient Global Impressions of Improvement (PGI-I), and several quality-of-life measures. Both doses of duloxetine were well tolerated. Duloxetine doses over 60 mg daily are not FDA-approved for

treatment of fibromyalgia. In a similarly designed trial using only duloxetine 120 mg daily, similar results were found.[36]

Efficacy and safety of duloxetine in reducing pain severity in 520 fibromyalgia patients with or without current major depressive disorder were evaluated in a six-month, multicenter, randomized, double-blind, placebo-controlled study.[37] Patients were randomly assigned to duloxetine (20, 60, or 120 mg) or placebo, administered once daily. After three months, the duloxetine 20 mg group titrated to 60 mg daily. The co-primary outcome measures were the BPI average pain severity score and PGI-I score. Patients treated with duloxetine 120 mg daily improved significantly more on the co-primary outcome measures at three months (change in BPI score [-2.31 versus -1.39, p<0.001] and PGI-I [2.89 versus 3.39, p=0.004]) and at six months (change in BPI [-2.26 versus -1.43, p=0.003] and PGI-I [2.93 versus 3.37, p=0.012]) compared to placebo. Duloxetine 60 mg/day also significantly improved the co-primary measures at three months, but BPI improvement only at six months. Duloxetine was efficacious in patients both with and without major depressive disorder. There were no clinically significant differences among treatment groups in adverse events. Duloxetine doses over 60 mg daily are not FDA-approved for treatment of fibromyalgia.

milnacipran (Savella) and placebo

A multicenter, double-blind, placebo-controlled trial randomized 1,196 patients with fibromyalgia to receive milnacipran 100 mg daily, 200 mg daily, or placebo for 15 weeks.[38] The two primary endpoints were rates of fibromyalgia composite responders (based on pain diary scores, PGI-Change [PGI-C], and SF-36) and fibromyalgia pain composite responders (based on pain diary scores and PGI-C). Compared with placebo, significantly greater proportions of milnacipran-treated patients were fibromyalgia composite responders (100 mg: p=0.01; 200 mg: p=0.02) and fibromyalgia pain composite responders (100 mg: p=0.03; 200 mg: p=0.004). Milnacipran was associated with significant improvements in pain after one week of treatment (100 mg: p=0.004; 200 mg: p=0.04), global status (PGI-C: p<0.001 for both doses), physical function (SF-36: 100 mg: p<0.001; 200 mg: p=0.02), and fatigue (Multidimensional Fatigue Inventory: 100 mg: p=0.04). The most common adverse events with milnacipran were nausea, headache, and constipation.

Similarly, a 27-week, randomized, double-blind, multicenter study compared milnacipran 100 and 200 mg daily with placebo in the treatment of 888 patients with fibromyalgia and used the same primary endpoints as the above study.[39] After three-months of stable dose treatment, a significantly higher percentage of milnacipran-treated patients met criteria as fibromyalgia responders versus placebo (milnacipran 200 mg, p=0.017; milnacipran 100 mg, p=0.028). A significantly higher percentage of patients treated with milnacipran 200 mg also met criteria as fibromyalgia pain responders versus placebo (p=0.032). Significant pain reductions were observed after week one with both milnacipran doses. At 15 weeks, milnacipran 200 mg led to significant improvements over placebo in pain (p<0.05), PGI-C (p<0.001), and multiple SF-36 domains. Nausea and headache were the most common adverse events reported by milnacipran users.

pregabalin (Lyrica) and placebo

A multicenter, double-blind, eight-week, randomized clinical trial compared pregabalin 150, 300, and 450 mg daily with placebo in pain, sleep, fatigue, and health-related quality of life in 529 patients with fibromyalgia.[40] The primary outcome was the comparison of endpoint mean pain scores, derived from daily diary ratings of pain intensity. Pregabalin at 450 mg/day significantly reduced the average severity of pain in the primary analysis compared with placebo (-0.93 on a

0-10 scale, p≤0.001), and significantly more patients in this group had ≥50 percent improvement in pain at the endpoint (29 versus 13 percent in the placebo group; p=0.003). Dizziness and somnolence were the most frequent adverse events.

Meta-Analyses

The efficacy of antidepressants in the treatment of fibromyalgia was determined by performing a meta-analysis of randomized, placebo-controlled trials with TCAs, SSRIs, SNRIs, and MAOIs.[41] Eighteen randomized controlled trials (median duration, eight weeks; range, four to 28 weeks) involving 1,427 patients were included. Overall, there was strong evidence for an association of antidepressants with reduction in pain, fatigue, depressed mood, sleep disturbances, and improved health-related quality of life. Effect sizes for pain reduction were large for TCAs, medium for MAOIs, and small for SSRIs and SNRIs.

Summary

When prescribers choose to try pharmacologic therapy in the treatment of fibromyalgia, there are several options. However, with the lack of comparative data as well as placebo-controlled trials to judge by, selecting a drug to initiate cannot be done based on clinical effectiveness alone. Prescribers should make their choice based on other factors, including the adverse event profiles of the products that have shown effectiveness in fibromyalgia patients. Although duloxetine (Cymbalta), milnacipran (Savella), and pregabalin (Lyrica) have acquired the indication for fibromyalgia, the potential of other available drugs should not be ruled out.

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