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REVIEW

New and emerging therapeutic agents for the treatment of fibromyalgia: an update

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Abstract: Fibromyalgia (FM) is a chronic widespread pain condition that is estimated to affect 5 million US adults. Several molecular pathophysiologies are thought to contribute to the symptoms of FM, complicating the development of effective clinical management techniques. It is now known that abnormalities in both nociceptive and central pain processing systems are necessary (but perhaps not sufficient) to condition the onset and maintenance of FM, producing associated neuropsychologic symptoms such as pronounced fatigue, sleep abnormalities, cognitive difficulties, stress sensitivity, anxiety, and depression. Current treatment strategies are focused primarily on correcting the pathophysiologic mechanisms underlying these nervous system abnormalities. Clinical studies demonstrate the safety and efficacy of three drugs recently approved for the treatment of FM: pregabalin (an alpha-2-delta ligand), and duloxetine and milnacipran (serotonin/norepinephrine reuptake inhibitors). This review describes these pharmaceuticals in detail and discusses their current roles in FM management.

Keywords: fibromyalgia, treatment, pharmacotherapy, pregabalin, duloxetine, milnacipran

Introduction

Fibromyalgia (FM) is a complex chronic pain condition that is defined by widespread pain for more than 3 months and the presence of at least 11 of 18 tender points.[1] Additional neuropsychologic symptoms are often present, including pronounced fatigue, sleep abnormalities, cognitive difficulties, stress sensitivity, anxiety, and depression.[2] These symptoms are often worsened by physical or emotional stress, cold and humid weather, poor sleep, hormonal fluctuations, and lack of exercise, suggesting a complex etiology.[3] The prevalence of FM is estimated to be 2% in the US and Canada,[4] affecting women (3.4%) more frequently than men (0.5%).[5] Although children can be diagnosed with FM, the median age of onset is 29–37 years,[6] with an age-associated increase in prevalence.[5] Over the past 20 years, FM has emerged as a leading cause of visits to rheumatologists, either alone or in conjunction with other rheumatic disorders.[7] The condition is estimated to affect 5 million US adults,[8] and some authors have suggested that its prevalence is on the rise.[9] However, whether this observation reflects an actual increase in prevalence or simply an increased awareness of FM among physicians and the general public remains to be investigated.

It is now known that systemic nociceptive and central pain processing abnormalities are necessary (although perhaps not sufficient) to condition the onset and maintenance of FM. Recent studies suggest that prolonged exposure to a high-stress environment combined with polymorphisms in genes involved in stress, anxiety, and pain response systems[10] may play a significant role in the development of chronic FM pain through

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physical and functional modifications of the central nervous system (CNS), often referred to as "central sensitization".[11] The following etiologies have also been proposed and, when taken collectively, can explain the variable symptomatology associated with the condition: autonomic nervous system dysfunction, hypothalamic-pituitary-adrenal (HPA) axis dysfunction, neurotransmitter abnormalities, an inability to sustain deep (Stage 4) sleep, and peripheral sensitization due to microcirculation abnormalities or the release of proinflammatory cytokines from glial cells.[3,12]

Depression, mood and anxiety disorders, and other psychiatric comorbidities are also considered possible etiologies of FM. These conditions are historically considered to be separate illnesses with high comorbidity, and the inability to distinguish pre-existing conditions from manifestations of chronic illness has complicated the identification of cause-effect relationships. Recent research suggests that these conditions are in fact differential symptom presentations of a single underlying condition, and that major depressive disorder (MDD) and FM (as well as neuropathic pain) are both associated with neuroplastic changes in the CNS.[13] However, in a recent review of the relationship between FM and MDD, Pae et al assert that currently available findings do not support the assumption that MDD and FM refer to the same underlying construct, nor can they be seen as subsidiaries of one disease concept.[14]

Regardless of the underlying pathophysiology, symptoms or disorders commonly observed in FM patients, such as fatigue, stiffness, cognitive impairment, sleep disturbances, depression, and mood or anxiety disorders, must be adequately addressed.[15] A wide variety of treatment options are currently available for FM, including pharmacologic agents, herbal and dietary supplements, cognitive-behavioral therapy, acupuncture, tender (trigger) point injections, and chiropractic spinal manipulation.[16] While new holistic and non-pharmacologic approaches are continuously being assessed for their efficacy in the treatment of FM, their detailed description and assessment are beyond the scope of this review (readers are referred to a recent article by Hassett and Gevirtz[17] for a review of non-pharmacologic treatments for FM). Instead, the focus of this article is on new pharmacologic approaches to FM treatment.

The number of randomized controlled trials for FM treatment modalities has risen steadily over the past decade,[4] with pharmaceutical studies focusing on compounds that target the nervous system abnormalities implicated in the condition. Such compounds include tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), muscle relaxants, and analgesic medications (eg, non-steroidal anti-inflammatory drugs [NSAIDs] and opioids). These drugs have a broad range of activities in the brain and spinal cord, including modulation of pain sensation and tolerance.[16] FM patients display a common intolerance to many classes of pharmaceuticals, however. This sensitivity is likely conditioned by the same central sensitivity that is presumed to underlie the heightened response to pain seen in these patients, limiting the use of therapeutic drugs in FM treatment.[18]

Despite the general intolerance of FM patients to pharmacotherapy, pharmaceuticals remain a cornerstone of FM management. Most of the currently employed agents are used off-label, with some (eg, TCAs, SSRIs, muscle relaxants) demonstrating greater efficacy than others (eg, NSAIDs, opioids).[2,16] Specifically, there is no evidence that NSAIDs are effective when used alone to treat FM. There is, however, limited evidence that suggests patients may experience enhanced analgesia when NSAIDs are administered with other agents.[19] There have been no randomized, clinical trials of opioids in FM, but anecdotal evidence suggests that they are not effective. Because their use remains controversial, it is suggested that the focus of treatment with these drugs should be return to function rather than complete elimination of pain.[2]

The complex, often overlapping, etiologies responsible for FM have produced a patient population with heterogeneous pathology and, to some extent, a heterogeneous clinical presentation. As a result, FM continues to remain inadequately treated despite the availability of numerous pharmacologic and non-pharmacologic treatment approaches. Recent advances in our understanding of the factors contributing to the development and maintenance of FM have identified new therapeutic targets, however. Originally developed as an anticonvulsant medication, pregabalin (Lyrica®) became the first FDA-approved drug for the treatment of FM in June 2007. This adjuvant analgesic exerts its therapeutic effects by binding to, and decreasing the activity of, the alpha-2-delta subunit of the voltage-gated calcium ion channel (VGCC).[20] VGCC activity is known to play an integral role in nociceptive transmission, particularly in the development and maintenance of nociceptive hypersensitivity, suggesting a mechanism of action for the drug's efficacy in FM.

Serotonin-norepinephrine reuptake inhibitors (SNRIs) are a class of antidepressants that have also proven particularly efficacious for FM treatment. Unlike SSRIs, which act more selectively on the neurotransmitter serotonin (5-HT), SNRIs

target and increase the levels of both 5-HT and norepinephrine (NE). The roles of these neurotransmitters in sleep, attention, cognition, anxiety, and, perhaps most importantly, descending pain inhibition, are thought to facilitate the improvement of FM symptoms with SNRI treatment.[21] The SNRIs duloxetine (Cymbalta®) and milnacipran (Savella®) were approved by the FDA for the treatment of FM in June 2008 and January 2009, respectively.

Table 1 provides a summary of standard, new, and emerging FM treatment options. At the time of writing, pregabalin, duloxetine, and milnacipran are the only drugs currently approved by the FDA for the clinical treatment of FM. This review describes these pharmaceuticals in detail and discusses their roles in FM management. While knowledge of standard and emerging therapies is critical for the optimization of individual treatment strategies, a discussion of these compounds is beyond the scope of this review.

Pharmacology and pharmacokinetics

Pregabalin

Pregabalin has exhibited anxiolytic, anticonvulsant, and antinociceptive properties in human and animal studies.[24] Despite its structural similarity to GABA (gamma-aminobutyric acid), pregabalin is devoid of effects on $GABA_A$, $GABA_B$, and benzodiazepine receptors. It also has no effect on GABA uptake, degradation, or cerebral concentrations.[25] It is currently thought that pregabalin's effects are instead mediated by its affinity for the alpha-2-delta-1 subunit protein of VGCCs. This presynaptic binding results in a decrease in excitatory neurotransmitter release of neurochemicals such as substance P, calcitonin gene-related peptide, and glutamate.[26] These biomolecules have been found at pathologically high levels in FM patients,[11,27] suggesting that pregabalin's affinity for the alpha-2-delta-1 subunit of VGCCs is responsible for its therapeutic effects in FM.

Pregabalin is well absorbed after oral administration, primarily in the proximal colon.[28] The rate of absorption is decreased when administered with a meal, resulting in an approximately 25%–30% decrease in peak serum concentration (C_{max}) and an increase in T_{max} (the amount of time that a drug is present at the maximum concentration in serum) to approximately 3 hours. However, there is no clinically relevant effect on total absorption. Peak plasma concentrations occur within 1.5 hours, with steady state achieved within 24–48 hours. Oral bioavailability exceeds 90% and is independent of dose. Because pregabalin does not bind to plasma proteins, it is able to cross the blood-brain barrier, possibly through the involvement of the system L transporter for transport of large amino acids.[28] Its apparent volume of distribution is approximately 0.5 L/kg.[29]

Pregabalin undergoes negligible metabolism, with approximately 90% of an administered dose recovered in the urine as unchanged pregabalin. The major urinary metabolite, the N-demethylated derivative, accounts for only 0.9% of the dose. Pregabalin is not metabolized in the liver; it is eliminated primarily by renal excretion and has a mean elimination half-life of 6.3 hours in subjects with normal renal function.[28] Mean renal clearance is nearly proportional to creatinine clearance and estimated at 67–80.9 mL/min in young healthy subjects. Pregabalin's pharmacokinetic profile does not appear to be modified by race or gender.[29]

Because pregabalin undergoes negligible metabolism in humans, does not bind to plasma proteins, and is predominantly excreted unchanged in the urine, its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions or protein binding displacement. Indeed, *in vitro* and *in vivo* studies have demonstrated that pregabalin is unlikely to be involved in significant pharmacokinetic drug interactions.[29]

Duloxetine and milnacipran

SNRIs are a class of antidepressants, whose mechanism of action is dual inhibition of serotonin and NE reuptake. The SNRIs duloxetine and milnacipran have been shown to inhibit 5-HT and NE uptake in a dose-dependent manner *in vitro* and *in vivo*.[30–36] SNRIs block 5-HT and NE transporters but, unlike TCAs, do not concomitantly block receptors for these neurotransmitters.[37] Data from clinical and preclinical studies indicate that both drugs exert a more profound effect on NE reuptake than on 5-HT reuptake; the average selectivity for milnacipran and duloxetine (5-HT:NE) is 1:1.3 and 1:9.6, respectively.[38] Duloxetine has also been shown to have a low affinity for the dopamine transporter, which may be clinically relevant at higher doses.[38]

Duloxetine

Duloxetine is well absorbed orally, with absorption beginning two hours after oral administration. Taking duloxetine with meals does not affect peak plasma concentration. It does, however, prolong the time to peak plasma concentration by 6–12 hours and decreases the area under the concentration-versus-time curve (AUC) by 10%. Evening versus morning administration of duloxetine results in

Table 1 Examples of standard, new, and emerging therapeutic options for the treatment of fibromyalgia

Pharmacologic treatment	Type	Class	Molecular mechanism(s)	APS 2005[22]	EULAR 2007[23]	Approval status
Standard treatments						
NSAIDs (eg, aspirin, naproxen, ibuprofen)	N/A	Selective or nonselective	COX[b]-1,2 inhibition; COX[b]-2 inhibition	NE	NE	Not approved
Opioids (eg, morphine, codeine, fentanyl, nalbuphine)	Scheduled or nonscheduled	Agonist, partial agonist, agonist-antagonist, or antagonist	Mu-, kappa-, delta-opioid receptor binding	NE	NE	Not approved
Tramadol	Nonscheduled opioid analgesic; adjuvant analgesic (antidepressant)	Agonist; SNRI	Mu-opioid receptor binding; norepinephrine/ serotonin reuptake inhibition	ME	SE	Not approved
Amitriptyline	Adjuvant analgesic (antidepressant)	TCA	Na^+ ion channel inhibition; NMDA receptor blockade (non-neuroprotective)	SE	SE	Not approved
Fluoxetine	Adjuvant analgesic (antidepressant)	SSRI	Serotonin reuptake inhibition	ME	SE	Not approved
Gabapentin	Adjuvant analgesic (anticonvulsant)	N/A	VGCC alpha-2-delta subunit binding	N/A	N/A	Not approved
S-adenosylmethionine	Adjuvant analgesic (antidepressant)	N/A	Nervous system methylation	WE	N/A	Not approved
Cyclobenzaprine	Skeletal muscle relaxant	N/A	5-HT2 receptor antagonist	SE	N/A	Not approved
Growth hormone	N/A	Hormone	Numerous	WE	N/A	Not approved
New treatments						
Pregabalin	Adjuvant analgesic (anticonvulsant)	N/A	VGCC alpha-2-delta subunit binding	ME	SE	FDA-approved (2007)
Duloxetine	Adjuvant analgesic (antidepressant)	SNRI	Serotonin/ norepinephrine reuptake inhibition	ME	SE	FDA-approved (2008)
Milnacipran	Adjuvant analgesic (antidepressant)	SNRI	Serotonin/ norepinephrine reuptake inhibition	ME	SE	FDA-approved (2009)
Emerging treatments						
Pramipexole	Adjuvant analgesic	Agonist	Selective non-ergoline D2, D3, and D4 dopamine receptor binding	N/A	SE	Not approved
Dextromethorphan	Adjuvant analgesic	Antagonist	NMDAR	N/A	N/A	Not approved
Ketamine	Adjuvant analgesic	Antagonist	NMDAR	N/A	N/A	Not approved
Sodium oxybate	Adjuvant analgesic	Central nervous system depressant	$GABA_B$ and GHB receptors (proposed)	N/A	N/A	Not approved
Low-dose naltrexone	Opiate analgesia enhancer	Opioid antagonist	Disruption of mu-opioid receptor Gs coupling via filamin A binding	N/A	N/A	Not approved
Delta-9-THC	Adjuvant analgesic	Psychoactive cannabinoid	Numerous	N/A	N/A	Not approved

Abbreviations: APS, American Pain Society; COX, cyclooxygenase; EULAR, European League Against Rheumatism; FDA, Food and Drug Administration; FM, fibromyalgia; ME, modest efficacy; NA, not applicable; NE, no evidence of efficacy; NMDAR, N-methyl D-aspartate receptor; NSAID, nonsteroidal anti-inflammatory drug; SE, strong efficacy; SNRI, serotonin/norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; VGCC, voltage-gated calcium ion channel; WE, weak efficacy.

a three-hour delay in absorption and an approximately 33% increase in clearance.[39] The plasma and elimination half-lives of duloxetine are approximately 12 hours.[40] However, because duloxetine is able to cross the blood–brain barrier, its plasma half-life in the central nervous system (CNS) may be longer than in the peripheral measures typically reported.

Duloxetine is metabolized rapidly upon absorption. Lantz et al[41] analyzed the effects of 20 mg duloxetine in healthy human subjects and found that the drug itself accounted for only 3% of the AUC and 9% of C_{max}. Although duloxetine is metabolized extensively in the liver by the hepatic cytochrome P450 (CYP) enzymes 1A2 and 2D6, none of its metabolites appear to be pharmacologically active.[42] These metabolites, of which at least 25 have been identified, account for 70% of the duloxetine dose and are primarily excreted into the urine in the conjugated form. Twenty percent of the original dose is excreted in the feces.[41] Duloxetine is highly protein bound (>90%), primarily to albumin or 1-acid-glycoprotein,[43] and its estimated volume of distribution is 1640 L.[39,44]

Because both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism, it is not surprising that drugs that inhibit these molecules have a profound effect on duloxetine metabolism and concentration. Concomitant use of duloxetine (40 mg once daily [QD]) with paroxetine (20 mg QD) increased the concentration of duloxetine AUC by about 60%, and greater degrees of inhibition are expected with higher doses of paroxetine. Similar effects would be expected with other potent CYP2D6 inhibitors (eg, fluoxetine, quinidine). In addition, concomitant administration of 40 mg duloxetine twice daily (BID) with 100 mg fluvoxamine, a potent CYP1A2 inhibitor, to CYP2D6 poor metabolizer subjects (n = 14) resulted in a 6-fold increase in duloxetine AUC and C_{max}. Co-administration of duloxetine with CYP1A2 and CYP2D6 inhibitors should, therefore, be avoided.[39]

Milnacipran

Unlike typical TCAs, milnacipran is devoid of action at a large array of receptors, including alpha-1-, alpha-2-, beta-adrenergic, serotonergic (5HT-1A, 5HT-2A), dopaminergic, muscarinic, histaminergic H-1, or benzodiazepine receptors. While it does not inhibit rat brain monoamine oxidase A or B, it does appear to be a noncompetitive N-methyl D-aspartate receptor (NMDAR) antagonist.[45] It is currently unclear which pharmacokinetic action(s) mediate milnacipran's therapeutic effects in FM, but a recent clinical study of female FM patients has provided insights as to the drug's possible site of action. Gracely et al[46] used functional magnetic resonance imaging (fMRI) to identify areas of the brain exhibiting increased activity following administration of 100 mg milnacipran BID. In response to milnacipran administration, patients' brains showed an increase in activity in the thalamus, caudate nucleus, cingulum, anterior insula, and amygdala, while patients who received placebo exhibited increased brain activity in only a parietal region and mid insula. The caudate nucleus, anterior insula, and amygdala are implicated in the descending pain modulation inhibitory network,[47] and increased posterior cingulum activity has been reported after treatment in chronic pain patients.[48] These brain regions also function in reward-processing and emotional evaluation which are cognitive functions known to be involved in the experience of chronic pain, including that associated with FM.[49–51] Taken together, these observations suggest a physiologic mechanism of action for milnacipran in FM patients involving both pain inhibitory networks and higher order cognitive functions (reward processing and emotional evaluation).

Absorption of milnacipran occurs rapidly after oral administration, with plasma concentrations peaking approximately two hours after an oral dose of 50 mg (C_{max} = 120 ng/mL). Administering milnacipran with food does not change its bioavailability of ~85%.[39] QD or BID administration of 50–200 mg milnacipran produces a linear increase in plasma concentrations; steady-state plasma levels are reached within several days.[42,52] Milnacipran is metabolized primarily by glucuronic acid conjugation, and its metabolites are not pharmacologically active at clinically relevant doses.[53] Milnacipran is not metabolized by CYP isoenzymes (P450 2D6, P450 2C19, P450 3A4, and P450 1A2), nor does it modify the activity of the CYP isoenzymes. This characteristic minimizes the risk of pharmacokinetic interaction when milnacipran is co-administered with other drugs.[54] The mean elimination half-life of milnacipran is approximately eight hours, with the majority of the original dose (90%) eliminated renally.[39] Milnacipran's plasma protein binding is low (13%) and nonsaturable and, like duloxetine, its metabolites are not pharmacologically active at clinical levels.[42]

The full pharmacokinetic profiles for pregabalin, duloxetine, and milnacipran are available in the US Prescribing Information for each drug.[29,39,55]

Efficacy

Pregabalin

Four randomized, double-blind, placebo-controlled trials have examined the efficacy of pregabalin monotherapy in the treatment of FM.[26,56–58] These studies have illustrated pregabalin's

ability to improve the pain, fatigue, and sleep difficulties associated with FM, as well as patient health-related quality of life.[7] Short-term trials ranged from 8–14 weeks,[26,56,58] and a long-term durability study assessed pregabalin's effects on FM over a 6-month period.[57] Pregabalin was well tolerated overall, with no new adverse events occurring in FM patients that had not been reported with its use in other indications.[24] All three studies enrolled male and female patients ≥18 years of age who fulfilled the American College of Rheumatology (ACR) 1990 criteria for FM.[59] Patients presented with a mean score of ≥4 on a 0–10 pain numeric rating scale and a score of ≥40 mm on the 100 mm visual analog scale (VAS) of the Short-Form McGill Pain Questionnaire (SF-MPQ).[24]

Several measures were used to assess pregabalin's effects in the short-term studies, including FM intensity, sleep quality diary, Medical Outcomes Study (MOS)-sleep measure, Multidimensional Assessment of Fatigue (MAF), SF-36, and Hospital Anxiety and Depression Scale (HADS). Patients enrolled in the 8-week study were also asked to respond to Patient Global Impression of Change (PGIC) and Clinical Global Impression of change (CGIC) measures. Change in mean pain score from baseline was the primary endpoint in all three short-term studies. PGIC and Fibromyalgia Impact Questionnaire (FIQ) were also assessed in the 14-week study if the primary endpoint was positive.

Pregabalin was administered 3 times per day (TID) during the 8-week study.[26] Patients received equal doses of pregabalin (150, 300, 450 mg/day), with all other medications discontinued 7 days prior to the study. Individuals previously found to be resistant to gabapentin treatment were excluded from this trial. Only the 450 mg/day pregabalin dose significantly reduced the pain score (–0.93 on a 0–10 scale; $P \leq 0.001$) and increased the responder-rate versus placebo (29%, versus 13% in the placebo group; $P = 0.003$). In a weekly analysis of pain scores, significant improvement was seen through weeks 1–7 but not at week 8. This result may be attributable to a combination of reduced statistical power, comparison with a group likely to contain many placebo responders, a lack of durability of analgesic effect, or symptom fluctuation.[24] Both the 300 and 450 mg/day doses of pregabalin significantly improved sleep quality, fatigue, and global measures of change. Lack of change in the HADS score throughout the study suggests that reductions in pain scores are independent of improvements in anxiety or depression.

The 13-week trial[58] examined the effect of pregabalin on FM pain and symptom management. During this study, 748 FM patients were randomly assigned to receive pregabalin (300, 450, 600 mg/day BID) or placebo for 13 weeks. The primary outcome variable for the symptomatic relief of pain associated with FM was comparison of endpoint mean pain scores between each pregabalin group and placebo. Endpoint mean scores, PGIC, and FIQ total score were used as secondary outcome variables to assess the management of FM. Patients in all pregabalin groups showed statistically significant improvement in endpoint mean pain score and in PGIC response compared with placebo ($P = 0.0449$: 300 mg/day, –0.43; $P = 0.0449$: 450 mg/day, –0.47; $P = 0.0070$: 600 mg/day, –0.66).

Pregabalin was administered BID in escalating doses of 300, 450, and 600 mg/day during the 14-week study.[56] There was a 1-week baseline/placebo run-in evaluation phase during which patients who demonstrated a ≥30% decrease on the VAS were discontinued. This evaluation period was followed by the primary 2-week dose-escalation phase. The primary outcome variable was comparison of endpoint mean pain scores between each of the pregabalin groups and the placebo group. All three doses produced a significant decrease in pain from weeks 1–14, with the exception of the 300 mg/day dose at week 11. Mean changes in pain scores at the end point in pregabalin treated patients were significantly greater than in the placebo group ($P < 0.001$: 300 mg/day, –0.71; 450 mg/day –0.98; 600 mg/day, –1.00). Doses of 450 and 600 mg/day produced a significant (~20%) improvement in FIQ total score compared with placebo. All three doses of pregabalin were associated with significant improvement in sleep.

Pregabalin was administered BID during the 6-month durability study.[57] The 6-month double-blind phase was preceded by a 1-week baseline phase, and followed by a 6-week open-label phase to determine optimal dosage (300, 450, 600 mg/day) and detect "responders" (those with ≥50% reduction in pain VAS score from open-label baseline and a rating of "much improved" on the PGIC). Primary outcome was time to loss of therapeutic response (LTR), defined as <30% reduction in pain (from open-label baseline) or worsening of FM in the opinion of the investigator. Secondary measures included the time to LTR for PGIC, CGIC, MOS (sleep), MAF, FIQ, and SF-36. The study enrolled a total of 1,051 patients, of which 663 completed the open-label study phase and 566 were subsequently randomized to the double-blind phase (287 to placebo, 279 to pregabalin). Pregabalin (300–600 mg/day) significantly delayed the time to LTR approximately 5-fold versus placebo (7 versus 34 days, $P < 0.0001$). All secondary measures were statistically superior to placebo as well, with substantial delays in time to LTR for sleep and fatigue. Thus, in those who respond,

pregabalin demonstrates durability of effect for relieving the pain and accompanying symptoms of FM.

While the studies described here have perhaps been the most influential in determining FDA guidelines for the use of pregabalin in FM patients, a number of smaller monotherapy or adjuvant therapy studies have also demonstrated the efficacy of pregabalin in FM treatment.[60,61] It has been suggested that the exclusion of gabapentin-resistant FM patients from the 8-week study increased the likelihood of a positive result.[24] Taken together, however, the clinical trials conducted to date have demonstrated the short- and long-term effectiveness of pregabalin for the treatment of FM pain. Pain reduction was most robust at doses of 300–600 mg/day, with onset of effect occurring within the first week of treatment. The recommended dose of pregabalin in FM is 300–450 mg/day BID.[29] Doses of 600 mg/day produce an increase in adverse events with little additional benefit for pain relief. Doses that provide no significant reduction in FM pain often improve accompanying symptoms of the condition (eg, fatigue, sleep difficulties). Although a clinical application of this finding has not yet been demonstrated, one could speculate on its utility in FM patients for which pain is not the primary concern.

Duloxetine

Five randomized, double-blind, placebo-controlled trials have assessed the efficacy of duloxetine in the treatment of FM to date.[62–66] The two short-term studies[62,63] assessed the efficacy and safety of duloxetine in FM patients over a 12-week period. The first trial[62] enrolled a total of 207 male and female subjects, 38% of whom had concurrent MDD. Patients were recruited from 5 academic centers and 13 "independent research centers" within the US. Subjects were randomly assigned to receive duloxetine (60 mg/day BID) or placebo after a 1-week single-blind placebo treatment. FIQ total score and FIQ pain score were the co-primary outcome measures. Compared with those who received placebo, patients who received duloxetine showed a significant improvement on the FIQ total score ($P = 0.027$), but not on the FIQ pain score ($P = 0.130$). Although duloxetine decreased the pain and symptom severity of FM in most patients, improvements were significant in females only. These findings were independent of baseline status of MDD.

The second 12-week study[63] examined the effect of duloxetine (60 mg/day QD or 60 mg/day BID) versus placebo in 354 female FM patients with or without concurrent MDD. The primary outcome was the Brief Pain Inventory (BPI) average pain severity score, with response to treatment defined as ≥30% reduction in this score. Patients in both duloxetine groups had significantly greater improvement in BPI pain severity and interference scores, FIQ, Clinical Global Impression of Severity (CGIS), Patient Global Impression of Improvement (PGII), and several quality of life measures compared with patients who received placebo. The treatment effect of duloxetine on pain reduction was independent of the effect on mood and the presence of MDD.

The remaining 3 trials[64–66] assessed the long-term efficacy and safety of duloxetine for FM. Chappell et al[65] conducted a Phase III, randomized, double-blind, placebo-controlled, parallel-group study of the effect of duloxetine (60 mg/day QD) on the pain and additional symptoms of FM versus placebo over a 6-month period. Patients randomly assigned to the 60 mg/day group were blindly escalated to 120 mg/day if they did not exhibit a ≥50% reduction in the BPI-Modified Short Form average pain score at week 13. Patients were allowed to increase their dose to 120 mg/day any time between weeks 13 and 23 if they exhibited <50% reduction in their BPI average pain score. Duloxetine 60/120 mg/day failed to demonstrate significant improvement over placebo on the co-primary outcome measures of BPI average pain severity from baseline to endpoint ($P = 0.053$) and the PGII at endpoint ($P = 0.073$). However, duloxetine did demonstrate significant improvement compared with placebo on several secondary outcome measures, including the FIQ pain item, Multidimensional Fatigue Inventory, CGIS, and Beck Depression Inventory-II total scores.

In the second 6-month trial,[64] 520 patients with or without concurrent MDD were assigned to duloxetine (20, 60, 120 mg/day QD) or placebo; the duloxetine 20 mg/day group was titrated to 60 mg/day after 3 months. The BPI average pain severity score and the PGII score served as co-primary outcome measures. Patients treated with duloxetine 60 mg/day or 120 mg/day improved significantly more on the co-primary outcome measures at 3 months compared with those treated with placebo. Patients treated with 120 mg/day also demonstrated significant improvement at 6 months (BPI score, $P = 0.003$; PGII score, $P = 0.012$). Duloxetine was efficacious at doses of 60 or 120 mg/day in FM patients both with and without concurrent MDD.

The most recent trial of duloxetine in FM patients reports results from the 6-month extension phases of the previously conducted studies (total treatment of 12 months).[64,65] Over half of the patients from the initial studies entered and completed this extension phase (Study 1,[65] 56%; Study 2,[64] 69%). Most treatment groups showed small mean change improvements in the BPI average pain

severity score at the end of the 12-month period, supporting a positive risk/benefit profile for duloxetine in the long-term treatment of FM.

The trials completed on the use of duloxetine for FM differ with respect to dosing regimens, treatment duration, and primary measures of pain. Not surprisingly, their results were inconsistent on measures of pain efficacy and functional outcomes. Arnold et al[67] conducted a pooled analysis of the first 4 of these studies (2 short-term[62,63] and 2 long-term[64,65]) to gain a better understanding of the efficacy of duloxetine after approximately 3 months' treatment in FM patients. A total of 1,411 patients were randomly assigned to treatment across the 4 studies. Seventy-nine patients were excluded from the pooled analysis because they had received a suboptimal dose (20 mg/day) of duloxetine during the original trial. The remaining 1,332 patients received 60–120 mg/day duloxetine (797) or placebo (535). The majority of the patients were middle-aged (mean = 50 years), female (95%), and white (88%), and 26% had a current diagnosis of MDD. Duloxetine produced a significant improvement in BPI 24-hour average pain severity compared with placebo (all assessments $P < 0.001$). These results were observed during the entire 3-month analysis period. Duloxetine-treated patients experienced a significantly greater reduction in the total impact of FM symptoms and improvement in mood, quality of life, and function than patients who received placebo. Improvement on each of the eight SF-36 health domains and both of the component summaries was significant in the duloxetine-treated group compared with the placebo-treated group. No significant treatment-by-subgroup interaction for mean changes in the BPI 24-hour average pain scores were found for the subgroup analyses of sex, race, and age. By combining the data from several studies, the investigators were able to gain statistical power by effectively analyzing data from a single large study. This statistical improvement facilitated a more accurate analysis of secondary functional results and efficacy outcomes in underrepresented patient subgroups.

The target and maximum duloxetine dose recommended for the treatment of FM is 60 mg/day QD, as this appears to provide the best long-term combination of clinical results and tolerability.[39,42] A starting dosage of 30 mg/day is recommended if patient tolerance is a concern. Because the clinical trials conducted to date have reported no significant treatment-by-subgroup interactions, specific dose recommendations based on sex, smoking status, age, and ethnicity are not warranted.[68]

Milnacipran

Two open-label studies have assessed the efficacy of milnacipran in FM to date. Nagaoka et al[69] conducted a 12-week, uncontrolled, open-label study of milnacipran administration in 20 Japanese patients with FM and concurrent depression. Doses of 30–100 mg/day were used, with a mean dosage of 59.7 mg/day and a modal dose of 50 mg/day (13/18 completers). Using the Zung-Self-rating Depression Scale (Zung-SDS) to assess depressive symptoms and a visual analog scale to measure pain (pVAS) and global condition (gVAS), the group found that milnacipran improved both pain and global condition at 8 weeks and depression at 4 weeks. Importantly, only patients who were not depressed (Zung-SDS scores ≤ 50) at the end of the study exhibited significant improvements in pVAS (at 4, 8, and 12 weeks) and gVAS (at 8 and 12 weeks).

The second open-label study was a case report of a 35-year-old female with FM and concomitant temporomandibular disorder (TMD).[70] The patient responded positively to milnacipran treatment and experienced a decrease in pVAS (100 to 40), Zung-SDS (70 to 32), and pain palpation score (32 to 17) over a 6-month period. Her only medications were ethyl loflazepate (2 mg/day) and milnacipran (doses escalated from 30 to 120 mg/day over the 6-month trial period). This finding may have considerable implications for FM treatment if replicated by larger studies, as FM and TMD often occur comorbidly.[71]

A Phase II, 12-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial of milnacipran in FM was conducted in the US in 2004.[72] The study assessed pain scores in FM patients (n = 125) assigned to target doses of milnacipran (200 mg/day QD or BID). Pain was measured by the 2-week average daily pain score collected from electronic diary (e-diary) reports. Although several methods of clinical pain assessment were employed, including the Short Form McGill Pain Questionnaire, the Gracely and Kwilosz scale, and VAS, the primary outcome was a comparison of the e-diary reports from the final 2 weeks of the trial with the 2-week baseline period. Comorbid depression was assessed by the Mini International Neuropsychiatric Interview.

The majority of patients in both the QD and BID milnacipran groups (81% and 92%, respectively) reached their target doses of 200 mg/day, compared with 95% in the placebo group. Reductions in reported pain reached statistical significance for 9 of the 13 pain measures collected in the BID milnacipran group, but the QD group showed no significant improvements. E-diary results from non-depressed

patients taking milnacipran versus placebo (37% versus 5%, $P < 0.012$) were significantly better than those from depressed patients taking milnacipran versus placebo (38% versus 33%). This observation seems to contradict the findings of Nagaoka et al[69] which suggest that milnacipran exhibits increased efficacy for reducing FM pain in depressed versus non-depressed patients. However, the observed difference in effect between depressed and non-depressed patients in this Phase II trial was attributed to a higher placebo response in depressed patients rather than a greater efficacy of milnacipran in non-depressed patients.

Four Phase III controlled studies have assessed the efficacy of milnacipran in FM to date. The first two, conducted in the US, were double-blind, parallel-group, placebo-controlled trials examining the effects of 100 or 200 mg/day of milnacipran in FM patients over a 3–6 month period.[73,74] In the first study,[73] 1,196 patients with FM were randomized to a 3-month trial of milnacipran 100 mg/day (n = 399), 200 mg/day (n = 396), or placebo (n = 401). The smaller study, published in 2009, randomized 888 FM patients to similar groups to examine the effect of milnacipran on FM and the pain of FM over a 6-month period. The primary efficacy measure in both studies was a composite responder analysis. Pain composite responders were defined as individuals who achieved a reduction in pain of 30% or more compared with baseline as measured by VAS and recorded daily in an e-diary, and who rated themselves as "very much improved" or "much improved" on the PGIC. FM composite responders also had to demonstrate at least a six-point improvement in their Short-Form 36 Health Survey (SF-36) physical component summary score. Significant improvements in pain were apparent from the first week in both studies. Statistically significant differences between milnacipran and placebo were also seen on the condition as a whole, with relatively little evidence of a dose-related effect.[52]

The third Phase III study was conducted in Europe as a multicenter, multinational, double-blind, randomized, placebo-controlled trial.[75] The 884 patients enrolled in the study were divided into two groups of approximately equal size and given either placebo or 200 mg/day milnacipran for 12 weeks. The composite responder analysis method was also used to assess the effects of milnacipran on the pain of FM in this study, and the FIQ total score change from baseline was used as a secondary endpoint. Significant improvements in pain, sleep, and fatigue were apparent from weeks 1, 2, and 3, respectively.[52] At the end of the 12-week 200 mg/day fixed dose period, milnacipran demonstrated a significantly greater improvement relative to placebo in both the primary and secondary criteria. FIQ results indicated a –3 difference in favor of milnacipran ($P = 0.015$). Several other measures, including the SF-36, FIQ physical function subscore, Multidimensional Fatigue Inventory total score, and Multiple Ability Self-Report Questionnaire cognition total score confirmed an overall improvement in the patient's condition and functioning.

The final Phase III study examined the durability of response to milnacipran in a multicenter, randomized, blinded extension study from a 6-month, lead-in trial.[76] The 449 FM patients enrolled in the study were either maintained on milnacipran 200 mg/day (n = 209) or re-randomized from placebo or 100 mg/day milnacipran at a 1:4 ratio to either milnacipran 100 mg/day (n = 48) or 200 mg/day (n = 192) for an additional 6 months of treatment. Patients initially assigned to placebo and re-randomized to milnacipran 200 mg/day experienced significant reductions in total pain, PGIC, stiffness, fatigue, and depressed mood. While the results from the 100 mg/day dose group showed a trend toward significance ($P = 0.056$), the number of patients in this group was likely too small to produce robust results.[52]

Clinical trials have demonstrated the efficacy of milnacipran for both the short- and long-term treatment of FM. Studies addressing the effect of milnacipran on the condition as a whole in addition to assessing changes in associated pain have revealed that many of the hallmark symptoms of FM (eg, fatigue, cognitive dysfunction, poor sleep) also improve with milnacipran treatment. The recommended dose of milnacipran for the treatment of FM is 100–200 mg/day BID.[55] Dosing should begin at 12.5 mg/day and gradually increase to 100 mg/day over a 1-week period. Up to 200 mg/day may be administered based on individual patient response.

Safety and tolerability

Pregabalin

Most FM patients (~84%) reported treatment-emergent adverse events during the pregabalin efficacy and safety studies. These events led to premature discontinuation from the studies in ~16% of pregabalin patients (150–600 mg/day) and ~9% of patients treated with placebo. These rates are similar to the adverse event discontinuation rates seen in the whole of the pre-marketing program for all indications (14% for pregabalin versus 7% for placebo).[29]

The majority of adverse events in the pregabalin FM studies were mild to moderate in nature. Dizziness and somnolence were the most common adverse events, although the long-term 6-month study demonstrated that both adverse event rates and adverse event discontinuations decline with

time. Pregabalin treatment produced no clinically significant findings in analyses of hematology, blood chemistry, urinalysis, visual function, physical or neurologic signs, urinalysis or electrocardiograms.[24] While results suggest that the occurrence of adverse events is dose-dependent, differences are not always statistically significant.[7]

In vitro and *in vivo* studies have shown that pregabalin is unlikely to be involved in significant pharmacokinetic drug interactions. Importantly, no pharmacokinetic interactions were seen during the coadministration of pregabalin with oxycodone, lorazepam, or ethanol. Additive effects on cognitive and gross motor functioning were observed, however, suggesting the need for dose reduction of either or both concomitant drugs. Because pregabalin is eliminated primarily by renal excretion, dose reduction is necessary in renal dysfunction with the need for creatinine clearance to be monitored.[29]

Duloxetine

SNRIs, such as duloxetine and milnacipran, appear to have greater efficacy, greater likelihood of producing remission, and greater improvement of painful physical symptoms than the SSRIs widely used in FM treatment. However, SNRIs are also associated with a greater incidence of side effects. Duloxetine's side effects are generally somewhat dose-related at the beginning of treatment, and most diminish after the first few days.[42] Clinical trials to date have demonstrated that duloxetine is safe and well tolerated in the dosage range of 20 to 120 mg/day for up to 1 year.[66] Nausea, dry mouth, hyperhidrosis, dizziness, headache, insomnia, constipation, and fatigue were reported most frequently, leading to a premature discontinuation rate of ~21%. The rates for nausea with duloxetine appear to be comparable with those found with other SSRIs and SNRIs. For those patients for whom tolerance is a concern, starting at a loser dosage (30 mg/day) lowers the likelihood and severity of nausea. Detke et al[77] found no significant blood pressure differences in patients taking duloxetine (60 mg/day) for major depression compared with patients who received placebo. However, a small but statistically significant increase in heart rate was observed. Longer term monitoring is recommended, particularly for patients with hypertension or cardiac anomalies. The rate of duloxetine-related insomnia in FM patients may be of concern (10.4% with duloxetine treatment versus 5.6% with placebo treatment),[64] as sleep dysfunction is a major associated symptom with FM. The occurrence of insomnia is likely to be lessened by taking the drug in the morning.[42] It is generally recommended that duloxetine be taken with food, as this prolongs the time to peak plasma concentration and can limit the development of side effects.[78]

The FDA recently determined that a "black box" warning would be required for all antidepressants. Although there are no data indicating that duloxetine is causally related to suicidality,[42] caution and close observation should be used in patients taking duloxetine, particularly during the initial weeks of treatment. Adequate treatment of underlying depression is essential for minimizing suicide risk.

Duloxetine is metabolized by CYP1A2 and CYP2D6 enzymes and moderately inhibits the latter. Thus, the clinician should consider decreasing the dosage of concomitant drugs that are metabolized by CYP2D6, such as TCAs (eg, nortriptyline, amitriptyline, imipramine); phenothiazines; and Type 1C antiarrhythmics (eg, propafenone, flecainide). Of clinical relevance, duloxetine does not inhibit or induce the CYP3A4 system, but administration of CYP1A2 inhibitors may result in elevated duloxetine concentrations.[42] The CYP1A2 inhibitor thioridazine should not be coadministered with duloxetine due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine.[39] Adverse effects on the fetus have been found in animal reproductive studies, rendering duloxetine a Category C agent for women who are pregnant.[42]

Because it is metabolized extensively by the liver, duloxetine should not ordinarily be prescribed to patients with substantial alcohol use or evidence of chronic liver disease, and clinicians should assess and monitor alcohol use and caution against concomitant excessive alcohol use. Smoking is suspected to result in a 30% reduction of duloxetine from expected serum concentrations through its effects on CYP1A2. However, it is unclear whether this alteration in drug metabolism is clinically significant enough to warrant a dose adjustment.[39] Because renal clearance approximates 70% for both the parent drug and its metabolites, duloxetine is not recommended in patients with severe renal disease or those requiring dialysis.[42]

Milnacipran

Milnacipran (100, 200 mg/day) has been shown to be well tolerated up to 1 year.[76] As an SNRI, milnacipran exhibited the anticipated adverse event profile of nausea, headache, tachycardia, and hypertension typical of this class. Sinusitis, constipation, hyperhidrosis, and dizziness were also reported in ≥5% of patients. Although these events led to a premature discontinuation rate of ~18%, most (≥90%) were mild to moderate in nature. The most

frequent adverse event, nausea, decreased with time, and milnacipran's effects on blood pressure and heart rate were rarely of clinical significance (0.2%–1.1%).[52] No clinically relevant changes were seen in hematology, urinalysis, or other clinical laboratory parameters, with the exception of one study[79] that reported mild elevations in alanine transferase in 7% of milnacipran patients (compared with 4% on placebo).

Milnacipran exhibits low and nonsaturable plasma protein binding.[42] The liver CYP system is not involved in its metabolism, making dosage adjustments for patients with liver impairment unnecessary.[80] The limited reciprocal pharmacokinetic interaction between milnacipran and CYP isoenzymes allows the drug to be coadministered with antidepressants.[81] However, both milnacipran and duloxetine should be considered to have potentially serious interactions if given concomitantly with monoamine oxidase inhibitors. Depending on the dosages, both could induce adverse serotonergic interactions if given over a prolonged period with SSRIs, and possibly even with herbals such as St. John's Wort.[42] No pharmacokinetic changes were seen with coadministration of milnacipran and lorazepam, lithium, carbamazepine, or levomepromazine. Milnacipran's pharmacokinetics are not altered by alcohol,[52] and milnacipran is not expected to cause clinically significant P450 inhibition or induction.[81] However, the pharmacokinetics of milnacipran are markedly affected by renal impairment. Puozzo et al[82] found the elimination half-life of severely impaired subjects to be approximately three times that of the control group.

Similar to TCAs, repeated administration of milnacipran decreases the responsiveness of serotonergic 5-HT-2A receptors, increases the responsiveness of the alpha-1-adrenergic system, and induces adaptive changes in the dopaminergic system, particularly by enhancing the functional responsiveness of dopamine D2 and D3 receptors.[54,83] These findings may be extrapolated to include other SNRIs, although their clinical significance has not yet been determined.

The side effects and adverse events associated with milnacipran and duloxetine may be explained in part by their inhibition of 5-HT and NE uptake.[42] The overall sensory sensitivity seen in FM may predispose patients to a higher incidence of adverse events compared with other patient populations. Peak drug levels have been suggested to be a significant factor in the generation of certain side effects.[52] BID administration (as opposed to QD) is thus recommended in order to increase milnacipran's tolerability in FM patients.[84]

Patients

Adherence to prescription medications is critical for their effectiveness, and such adherence has historically been problematic in the management of FM. Sewitch et al[85] found the rate of nonadherence in a cohort of 127 female FM patients to be 47.2%, although it is unknown whether this was due to lack of efficacy, side effects, cost, or psychosocial factors. Dobkin et al[86] reported that patient-physician agreement on the patient's well-being and a lower level of patient distress predicted greater adherence to general FM treatment. Better adherence to medication was also seen in patients experiencing greater pain and better emotional health. Clinicians should instruct patients about the brief time courses of many common drug-related side effects in order to diminish adverse event-related nonadherence.[42]

In contrast with earlier prescription medications used for the treatment of FM, pregabalin, duloxetine, and milnacipran may increase adherence because of their favorable efficacy, safety, and tolerability profiles. Many of the side effects and discontinuations seen in the clinical trials of these drugs can be avoided in clinical practice by employing flexible dosing regimens that consider the overall sensory sensitivity characteristic of FM patients. The relative success of such regimens in FM treatment has precipitated the adage "start low, go slow." Practitioners also often prescribe a higher proportion of the daily dose of pregabalin at bedtime rather than equally splitting BID doses. In some cases only a night time dose is given, similar to the dosing of tricyclics in chronic pain states.[87] In addition, the recommended BID administration of pregabalin may improve patient compliance compared with the TID dosing of gabapentin, a similar alpha-2-delta ligand widely used in the treatment of FM.[88] Physician assistants can prove particularly valuable to the large percentage of FM patients who need to adjust their medications several times before finding a suitable combination and dosing schedule, as these clinicians can often provide adequate time and education to patients at a reasonable cost.[89]

Even with the development of new, safer and more efficacious drugs, current pharmacologic treatment for FM remains largely empiric, creating enormous challenges for primary care physicians. Despite positive results from clinical trials, many FM patients find that even new prescription medications do not sufficiently control their symptoms and/or are difficult to tolerate in a clinical setting. As a result, the majority of FM patients obtain only modest relief from drug treatments and in general compliance is low.[90]

In 2005, an internet survey of 2,596 FM patients revealed that, as expected, newer medications such as duloxetine and pregabalin were being used by only a small percentage of respondents (<8%).[7] This percentage has undoubtedly increased over the last few years. While clinical trials suggest an increased propensity for patient preference, satisfaction, adherence, and compliance through more favorable efficacy, safety, and tolerability profiles, the actual long-term clinical favorability of pregabalin, duloxetine, and milnacipran for the treatment of FM remains to be determined.

Conclusions

FM is a complex, multidimensional, chronic pain condition of heterogeneous nature. The goals of FM treatment are to alleviate pain, increase restorative sleep, and improve physical function through a reduction in associated symptoms.[7] The identification and treatment of all pain sources that may be present in addition to FM, such as peripheral inflammatory or neuropathic pain generators (eg, comorbid osteoarthritis or neuropathic pathologies) or visceral pain (eg, comorbid irritable bowel syndrome) is central to the proper clinical management of FM.[15]

Overall, depression and anxiety are among the most common comorbidities with FM, with prevalence rates ranging in studies from 20%–80% and 13%–63.8%, respectively.[91] Unfortunately, clinical trials conducted to date report little or no improvement in FM-associated psychiatric symptoms after administration of pregabalin, duloxetine, or milnacipran. However, FM-associated pain scores often improved during trials of all three drugs, regardless of the presence of concurrent anxiety or depression. This suggests that the pain, anxiety, and depression that frequently occur comorbidly with FM do not share the same underlying mechanism. The apparent lack of efficacy of pregabalin and milnacipran for the treatment of FM-associated anxiety and depression may be explained by the methodologic design of the relevant clinical trials – all of the studies excluded patients with concurrent MDD, limiting the ability for improvement in depressive symptoms. It is interesting to note that all of the studies of duloxetine, a drug approved by the FDA for the treatment of MDD and generalized anxiety disorder, included patients with MDD and still did not achieve significant results. Further studies are warranted to adequately address the effects of these drugs on FM-associated depression and anxiety.

It is increasingly evident that adequate treatment of FM presents a significant clinical challenge. High prevalence, frequent comorbidities, a constellation of different and fluctuating symptoms, and frustration with current treatment modalities has resulted in the use of a variety of different pharmacotherapies, alone or in combination.[92] New pharmacologic approaches, including pregabalin, duloxetine, and milnacipran, have demonstrated improved safety and efficacy in clinical trials. A recent study by Vera-Llonch et al suggests that treatment of FM with pregabalin is likely to be associated with substantially reduced use of other pain-related medications and cost savings based on US drug costs (0.46–0.97 US$).[93] Similar reductions in medication use and healthcare costs are expected for duloxetine and milnacipran, given their performance in clinical trials to date.

The mechanisms of action of pregabalin, duloxetine, and milnacipran are thought to be related to proposed pathophysiologies of FM. However, these new therapeutic agents are still not effective for all FM patients. Recent work by Katz et al suggests that the diagnostic criteria for FM may be partially responsible, as there is currently no gold standard for FM diagnosis.[94] While the ACR criteria for FM are the *de facto* criteria used for research, they are not generally utilized by non-rheumatologists. Rheumatologists may also diagnose FM in patients who do not satisfy the ACR criteria. These findings raise the question of whether clinical trials of FM treatments based on ACR criteria (ie, all of the studies described in this article) actually represent the population of FM patients seen by rheumatologists in clinical practice.

Regardless of the cause, the overall clinical ineffectiveness of single-drug treatment approaches in FM suggests the need for combined pharmacologic approaches that target multiple biochemical abnormalities and are developed on a somewhat individual basis. Emerging therapies, including NMDAR antagonists, dopamine agonists, sodium oxybate, low-dose naltrexone, and delta-9-THC have proven effective in preliminary studies, and may play important roles in combination treatment approaches. However, a thorough discussion of these emerging therapies is beyond the scope of this review.

In summary, pregabalin, duloxetine, and milnacipran appear safe and effective for the treatment of FM, although additional trials are warranted for efficacy, remission, indications, safety, and tolerability. The clinical trials conducted to date employed a variety of assessment tools and primary outcome measures, making the results difficult to cross-compare. Pharmacologic fMRI is a robust and reliable method for detecting central effects of pain-relieving drugs that will likely play a fundamental role in assessing the efficacy of current and future FM therapies. This technique may also be used as a guide for optimizing the potentially diverse

therapeutic requirements of this patient group.[7] If future data support emerging patterns, it is likely that these drugs will provide valuable options for the treatment of FM.

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