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Acute and Chronic Pain Management in Fibromyalgia: Updates on Pharmacotherapy

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Fibromyalgia (FM) is a mysterious pain syndrome with progressive and widespread pain, explicit areas of tender points, stiffness, sleep disturbance, fatigue, and psychological distress without any obvious disease. FM is commonly perceived as a condition of central pain and sensory augmentation. There are documented functional abnormalities in pain and sensory processing in FM. Central sensitization and lack of descending analgesic activity are the 2 leading mechanisms that have been demonstrated by advance in both basic and clinical research. The pathogenesis of FM may also be attributed to the genetic polymorphisms involving serotoninergic, dopaminergic, and catecholaminergic systems. Any psychiatric disorders and psychosocial influences in FM may also affect the severity of pain. The various external stimuli or trigger such as infection, trauma, and stress may all contribute to proceed to presentation of FM. The recent launches of 3 US Food and Drug Administration–approved pharmacotherapy for FM namely pregabalin, duloxetine, and milnacipran have certainly raised the profile of optimal chronic pain management. However, appropriate evaluation and efficacious management of acute pain has not been as well publicized as chronic pain in FM. Acute pain or flare up caused by any trauma or surgery certainly may present a real challenge for patients with FM and their health care providers. Pre-emptive analgesia and pro-active treatment may offer the momentum for acute pain control based on model of central sensitization and pain in FM. This review article on FM appraises the modern practice of multimodal therapy focus on both acute and chronic pain management. Meanwhile, the evolving nonpharmacological approach is summarized and stressed as an essential component of integrated care in FM.

Keywords: fibromyalgia, pain management, pharmacotherapy

Patients with fibromyalgia (FM) usually present with chief complaint of progressive and widespread pain and dysfunction. Patients with FM frequently describe constant pain and stiffness aggravated by any physical activity and environmental or emotional stress. The symptoms and signs of FM are quite different from the more localized trigger point with referral pain pattern in myofascial pain syndrome (MPS). Patients with FM present with multiple associated illness or comorbidities such as sleep disturbance, chronic fatigue syndrome, temporomandibular disorder (TMD), migraine headache, irritable bowel syndrome, endometriosis, and interstitial cystitis. Although there may be common involvement of many diverse psychological factors, FM should not be perceived only as part of the somatoform pain disorders.[1]

FM is a chronic pain syndrome noticeable by central augmentation of pain and sensory processes. More recent study on FM has identified neurobiological evidence sustaining many of the common symptoms and signs. Pioneer research in FM had the extraordinary scope within internal medicine community and subspecialty of rheumatology to apply the common theory and method as in chronic pain research. These insights facilitated rapid advances on FM research in favor of central augmentation. However, the more recent breakthrough in treatment of FM has been focus on genetics, patient assessment, latest therapeutic targets, and novel methods of drug delivery. This

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review article on FM will start with pharmacotherapy on chronic pain and then address the key points in acute pain.[2]

Prevalence and gender difference in FM

FM is a common diagnosis among the patients being referred to both medicine and rheumatology. The prevalence of FM is estimated to be 2%–3% in the general population.

Marcus[3] reported the new epidemiologic data supported important differences in severity of FM symptoms between genders and important role of comorbid psychological distress. FM is a common chronic pain and disabling condition that predominantly affects women. The diagnosis of FM is usually made at estimated rate of about 3-fold to 6-fold in women as compared with men. Symptoms of FM can be efficiently managed with pharmacological and nonpharmacological treatments. In general, treatment benefits in FM emerge mostly independent of any gender difference.

Diagnostic criteria

The American College of Rheumatology (ACR) established the diagnostic criteria on FM in 1990. It requires chronic widespread pain over 3 months duration, and physical examination must reveal pain induced by 4 kg of palpation pressure at no less than 11 of 18 anatomically defined tender points. These points are as follows[1,2]: Occiput: suboccipital muscle insertions.[3,4] Low cervical: anterior aspects of the C5-7 intertransverse spaces.[5,6] Trapezius: midpoint of upper borders.[7,8] Supraspinatus: origins, above the scapular spine, near medial border.[9,10] second rib: upper lateral surface of second costochondral junction.[11,12] Lateral epicondyles: 2 cm distal to the epicondyle.[13,14] Gluteal: upper outer buttock, anterior fold of muscle.[15,16] Greater trochanter: posterior to trochanteric prominence.[17,18] Knees: medial fat pad, just proximal to medial condyle. The sensitivity and specificity of the ACR criteria were estimated as more than 80%. In case of widespread pain yet failure to meet the ACR criteria for diagnosis of FM, the subject may still be evaluated for potential trigger points and patterns of referral pain as diagnosis in MPS.[4]

Laboratory test and clinical imaging study

There is no sensitive or specific laboratory test to help establishing the diagnosis of FM. No imaging study in clinical practice of FM contributed to the differential diagnosis. FM may be a diagnosis of exclusion being considered after extensive but negative work up for other systemic illness.

Pathophysiology of FM

FM is a chronic pain syndrome due to central pain and sensory augmentation. The primary pathophysiology in FM engages interactions between genetic and environmental factors. A surge of physiological, psychological, behavioral, and cognitive factors in FM interact to manifest in various symptoms and comorbidities. In addition to the left-shift in stimulus-response function, other pathophysiological progressions have lead to a better understanding of the biopsychosocial keystones of FM. The crucial mechanism in FM may include familial and genetic predisposition; environmental stressors as triggers; dysfunction of hypothalamus-pituitary-adrenocortical (HPA) axis and autonomic nervous system; functional abnormalities in pain and sensory processing; and various cognitive, behavioral, and psychological factors. Central sensitization and lack of descending analgesic activity have emerged as the leading mechanism for the augmented pain and sensory processing in FM.[2]

Current understanding of FM has made significant advances over the past decade. FM is now considered as the manifestation of central nervous system malfunction expressed in augmentation of pain perception, interpretation and modulation. The pathogenesis of FM has been attributed to documented genetic polymorphisms involve the serotoninergic, dopaminergic and catecholaminergic systems. The various external stimuli or triggers (infection, trauma, and stress) may contribute to the advance to presentation of FM.[5]

Peripheral and central mechanisms in the pathophysiology of FM

Peripheral mechanism

Although there has been no specific muscle pathology associated with FM, any peripheral pain generator causing persistent muscle pain may potentially perpetuate further central pain mechanisms and result in the widespread pain.

Central mechanism

There is emerging evidence that central sensitization may be relevant to the chronic pain in FM patients. The ''wind-up'' phenomenon, as described at the molecular level via activation of N-methyl-D-aspartate (NMDA) receptors, may also contribute to both initiation and maintenance of central sensitization in FM. The release of excitatory amino acids such as glutamate and their interaction with receptors are enhanced by neuropeptides such as substance P and nerve growth factor (NGF). This may be relevant to the abnormal sensory processing in FM. Elevated cerebrospinal fluid levels of

glutamate, substance P, and NGF in FM patients have also been reported.

FM might represent neurobiological amplification of sensory stimuli. The evidence from functional imaging studies speculated that the insula is the most consistently hyperactive neurocortical region of the pain matrix. Functional magnetic resonance imagery (fMRI) is a noninvasive brain imaging technique that depends on differences in the relative concentration of the oxygenated to deoxygenated hemoglobin within the brain in response to a stimulus such as evoked pain during scanning. FMRI has been used to study response to pain in FM patients. FMRI tracks local changes in blood flow has a higher spatial and temporal resolution than other techniques such as positron emission tomography or single-photon emission tomography. Although regions of activation were similar for the patients and controls, the groups differed with regard to the amount of stimuli needed to activate this pain matrix. For FM, this matrix was activated by only less than half of the stimulus needed for healthy controls. There was a documented left-shift in the stimulus response function, which is characteristic of centrally mediated hyperalgesia and reduced noxious threshold to sensory stimuli.[2]

Gracely et al[6] used fMRI to evaluate the pattern of cerebral activation during application of painful pressure and determine whether this pattern is augmented in patients with FM compared with controls. Gracely et al[6] reported that comparable subjectively painful conditions resulted in activation patterns that were similar in patients and controls, whereas similar pressures resulted in no common regions of activation and greater effects in patients. This study demonstrated that FM is characterized by cortical or subcortical augmentation of pain processing.

Cook et al[7] examined the function of the nociceptive system in patients with FM using fMRI. Specifically, in response to nonpainful warm stimuli, FM subjects had significantly greater activity than controls in prefrontal, supplemental motor, insular, and anterior cingulate cortices. In response to painful stimuli, FM subjects had greater activity in the contralateral insular cortex. Data from the practice session indicated brain activity in pain-relevant areas for the FM group but not for controls. This fMRI results provided further evidence for a physiological elucidation for FM pain.

FMRI and blood oxygenation level–dependent activation studies on FM patients have demonstrated augmented sensitivity to painful pressure and the association of this augmentation with variables such as depression and catastrophizing. It has also been used to evaluate the symptoms of cognitive dysfunction. Using a wide array of techniques, fMRIs have demonstrated the differences in opioid receptor binding, in the concentration of metabolites associated with neural processing in pain-related regions, in functional brain networks, and in regional brain volume and white matter tracks. All techniques had provided pertinent information to scrutinize the persistent widespread pain in FM.[8]

Maletic et al[9] synthesized recent data suggesting that the soaring rates of comorbidities observed between FM and major depression may be attributing to the multiple common biological and environmental foundations. These biologically complex conditions result from comparable genetic vulnerabilities interacting with environmental stress. There are mutual genetic determinants that may include poorly functional alleles regulating the monoaminergic, glutamatergic, neurotrophic, opioid, and inflammatory cytokine signaling. The leaders among various environmental risk factors are psychosocial stress and illness in vulnerable individuals, relative resistance to glucocorticoids, increased sympathetic and decreased parasympathetic activity, and augmented production and release of various proinflamnmatory mediators. The dysregulation of stress and inflammatory pathways promotes alterations in brain circuitry that modulates mood, pain, and the stress response. These functional changes possibly promote disruptions in neurotrophic support and disturbances of glia-neuronal communication over time. Maletic et al[9] proposed that both central sensitization in widespread pain disorders and kindling in depression may account for the progressive and self-perpetuating nature of FM when poorly treated.

The balance between descending controls, both excitatory and inhibitory, can be altered in various pain states. Bannister et al[10] explored the evidence for a prominent alpha 2-adrenoceptor–mediated inhibitory system and the 5-HT3 serotonin receptor–mediated excitatory controls originating from brainstem and midbrain regions. The ability of cortical controls to influence spinal function allows for top–down processing through these monoamines. The associations between pain and comorbidities of sleep problems, anxiety, and depression in FM may be due to the dual roles of norepinephrine (NE) and of 5-HT in these dysfunction and pain. Bannister et al[10] proposed an abnormal engagement of descending facilitations in FM with or without reduced inhibitions in widespread pain, fatigue, and mood changes. There may be an endogenous central malfunction of descending control with the distorted monoamine systems underlying the multiple symptoms in FM. There are a number of hopeful medications that can either interact with or modulate these descending systems thus reinforcing the importance in organization of pain and its control.

Pharmacotherapy

Clinical management of FM requires an integrated approach combining pharmacological and nonpharmacological modalities. It is a new era for development of more specific and efficacious medications thanks to recent US Food and Drug Administration (FDA) approval of the alpha2-delta ligand (pregabalin) and serotonin–norepinephrine reuptake inhibitors (SNRIs ie, duloxetine and milnacipran) for FM. As the understanding of biological basis and genetic underpinning of FM proceeds, health care providers may now achieve rational therapeutic modalities.[5]

FMRI studies in FM patients suggest that similar levels of subjective pain result in similar CNS activation in both FM patients and controls. For a similar stimulus, however, FM patients have a greater subjective sensation of pain. This increased sensitivity is often accompanied with a decreased activity in brain regions implicated in the descending pain inhibitory pathways. The hypothesis that increased sensitivity to pain is due to decreased activity of the descending inhibitory pathways was supported by results with milnacipran. FM patients treated with the SNRI, milnacipran, exhibited a reduction in pain sensitivity and a parallel increase in activity in brain regions that was implicated in the descending pain inhibitory pathways compared with placebo-treated patients.[11]

Perrot et al[12] summarized the present and emerging progress in the management of FM. Contemporary concepts of FM evolve in terms of clinical description and comparable advances in pathophysiology. A generally established paradigm assumes that FM is the clinical expression of a disorder in central sensitization and alteration over numerous neuronal systems. The European League against Rheumatism has also developed updated guidelines for the management of FM.

The efficacy of a variety of agents including alpha 2-delta ligands, SNRIs, and tricyclic antidepressants (TCAs) has been well documented in research. However, there is still common use of ineffective agents in treating the central nature of pain in FM. Clauw[13] has reviewed pharmacotherapy for FM including high level, moderate level, and little or no evidence for efficacy. The integrated nonpharmacological approach may include one or more of effective options such as education, aerobic exercise, and cognitive behavioral therapy.

Tricyclic antidepressants

Advances have occurred in the methodology and design of clinical trial in parallel with improved understanding of the underlying pathophysiology and mechanisms in FM. Several medications have been approved for the management of FM based on their clinically meaningful and durable effect on pain in monotherapy trials and their beneficial effect on patients' global impression of change, function, and other key symptom domains such as fatigue, sleep disturbance, and cognition. Adjunctive therapy with medicines targeted to specific symptom domains and common comorbid conditions should be considered for reducing the patient's overall symptom burden in FM.[14]

TCAs may increase synaptic concentrations of serotonin, NE, and other neurotransmitters in the CNS and may help to reduce pain, sleep, and fatigue associated with FM. Amitriptyline is the TCA most commonly used in FM. The short-term studies indicate benefit in up to one third of patients; if effective, benefit is frequently noticeable within the first 2 weeks of therapy. Long-term studies have not shown any extended beneficial effect. Amitriptyline may start at 10 mg and titrate up to 25–50 mg to minimize anticholinergic side effects at higher doses. Nortriptyline has a better side-effect profile than amitriptyline and may be considered as an alternative in management of FM.

Arnold et al[15] reviewed 9 randomized controlled trials (RCTs) suitable for meta-analysis of TCAs. The largest improvement was associated with measures of the sleep quality; the most modest improvement was found in measures of stiffness and tenderness.

Heymann et al[16] studied the efficacy and tolerability of amitriptyline and nortriptyline 25 mg at bedtime in a Brazilian population of 118 FM patients and evaluated instruments used to measure the efficacy of treatment. Only the patient's subjective global assessment of improvement differed between the amitriptyline treatment and the placebo group. The different measures of therapeutic effect were not better than the patient's self assessment in this study on FM.

Nishishinya et al[17] conducted a study to assess the efficacy and safety of amitriptyline as a treatment of FM. Amitriptyline 25 mg/day in 6 RCTs of FM demonstrated a therapeutic response compared with placebo in the domains of pain, sleep, fatigue, and overall patient and investigator impression. The study reported short-term efficacy of amitriptyline 25 mg/day in FM but no evidence to support either higher doses than 25 mg or for treatment over 8 weeks.

Joshi et al[18] conducted a 6-month follow-up to assess the benefit of amitriptyline and physiotherapy for disability reduction in 175 patients with FM in a rural tertiary care hospital in Central India. High FM impact questionnaire (FIQ) score at baseline and low socioeconomic status scores were found to be significant predictors of benefit. Either amitriptyline or physiotherapy was equally effective in improving outcome of FM over a period of 6 months.

Muscle relaxants in FM

Cyclobenzaprine (Flexeril) shares its tricyclic structure with both amitriptyline and nortriptyline but does not function as an antidepressant. Cyclobenzaprine may cause skeletal muscle relaxation at the level of brain stem. Short-term (12 weeks) studies reveal that 10–40 mg per day of cyclobenzaprine minimizes patients' pain and sleep disturbance in FM. However, long-term studies have not shown any benefit of cyclobenzaprine over placebo in FM.

Tofferi et al[19] reviewed the effectiveness of cyclobenzaprine in the treatment of FM based on RCTs of cyclobenzaprine. There was improvement in pain early on but not in fatigue or tender points at any time. Those patients in cyclobenzaprine treatment group were 3 times as likely to report overall improvement and moderate reductions in individual symptoms particularly sleep.

Tizanidine (tizanidine) is a centrally acting alpha-2 adrenergic agonist that was approved by FDA for the treatment of muscle spasticity associated with multiple sclerosis and stroke. Russell et al[20] reported significant improvements in several parameters in FM, including sleep, pain, and measures of quality of life. A reduction in substance P levels within the cerebrospinal fluid was found in patients with FM under the treatment of tizanidine.

Muscle relaxants have been widely used in treating musculoskeletal conditions such as FM. Systematic reviews and meta-analyses supported using skeletal muscle relaxants for short-term relief of acute low back pain when nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen are not effective or tolerable. Comparison studies have not shown 1 skeletal muscle relaxant to be superior to another. Cyclobenzaprine is the most heavily studied and has been shown to be effective for various musculoskeletal conditions. The sedative properties of tizanidine and cyclobenzaprine may benefit patients with insomnia caused by severe muscle spasms. Methocarbamol and metaxalone are less sedating, although effectiveness evidence is limited. Adverse effects such as dizziness and drowsiness are consistently reported with all skeletal muscle relaxants. The potential adverse effects should be communicated clearly to the patient. Because of limited comparable effectiveness data, choice of muscle relaxant should be based on side effect profile, patient preference, abuse potential, and possible drug–drug interactions.[21]

Newer anti-depressants

Selective serotonin reuptake inhibitors (SSRIs) also might be beneficial because of their ability to enhance serotonin availability at the neuronal synapse. SSRIs were developed for the treatment of depression. SSRIs are commonly prescribed in FM due to a better side-effect profile than TCAs. There were several reports on improvement of pain, sleep, and fatigue based on previous randomized controlled trials of SSRIs, for example, fluoxetine, citalopram, and paroxetine. In general, the results of clinical studies on SSRIs in FM have matched the preceding knowledge in management of other pain conditions. The newer or more selective SSRIs (eg, citalopram) seem to be less effective in FM than those less selective SSRIs that may provide noradrenergic action at higher doses.

In a 12-week, flexible dose and placebo-controlled trial, Arnold et al[22] reported that the higher dosages of SSRI fluoxetine (80 mg/day) was effective on most outcome measures and commonly well tolerated in women with FM. It was not clear whether the higher dosage of fluoxetine still function only as specific SSRI.

Dual receptor re-uptake inhibitors such as the serotonin–NE or NE–serotonin reuptake inhibitors (NSRIs) may offer edge over SSRIs in FM. These agents are pharmacologically similar to some TCAs in their ability to inhibit the reuptake of both serotonin and NE but differ from TCAs in being generally devoid of significant activity at other receptor systems. This selectivity may diminish side effects and enhance tolerability. The first available SNRI, venlafaxine, was first shown to be effective in the management of neuropathic pain and prophylaxis of migraine and tension headache. The higher dose of venlafaxine also revealed some efficacy in clinical trial of FM. Sayar et al[23] reported that venlafaxine was quite promising in FM by alleviating the levels of pain and disability in a 12-week study. The therapeutic effects of venlafaxine in FM seemed to be independent of its anxiolytic and antidepressant properties.

SNRIs may have edge over SSRIs in the management of FM. Both duloxetine (cymbalta) and milnacipran (savella) have recently been approved by US FDA for management of FM.

Duloxetine (cymbalta)

Duloxetine is available as delayed-release capsules (20, 30, 60 mg) for oral use by Eli Lilly and Company, Indianapolis, IN. Preclinical studies have shown that duloxetine is a potent inhibitor of serotonin and norepinephrine reuptake (SNRI) in the CNS that may attribute to the clinical efficacy. Duloxetine has no significant affinity for dopaminergic, adrenergic, cholinergic, histaminergic, opioid, glutamate, and gamma-aminobutyric acid (GABA) receptors. Duloxetine does not inhibit monoamine oxidase.

Indications

Duloxetine is indicated for FM in addition to major depressive disorder, generalized anxiety disorder, and

diabetic peripheral neuropathy. Duloxetine is contraindicated in patients take monoamine oxidase inhibitor (MAOI) and have uncontrolled narrow-angle glaucoma. Initial Treatment in FM may start with 30 mg once daily for 1 week and allow patients to adjust to duloxetine before consider increasing to 60 mg daily or higher dose. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. At least 14 days should pass between discontinuation of an MAOI and initiation of therapy with duloxetine. In addition, at least five days after stopping the duloxetine should be allowed before switching to MAOI.

Clinical efficacy

The efficacy of duloxetine in FM was demonstrated in placebo-controlled trials up to 12 weeks. Efficacy up to 6 months has also been documented in placebo-controlled studies after initial U.S. FDA approval.

Efficacy of duloxetine in FM was well established in two randomized, double-blind, placebo-controlled, fixed-dose studies. These adult patients all met the ACR criteria for FM (a history of widespread pain for 3 months, and pain is present at 11 or more of the 18 specific tender point sites). Both studies compared duloxetine 60 mg once daily or 120 mg daily (given in divided doses in study 1 and as a single daily dose in study 2) with the placebo. The treatments using duloxetine 60 mg once or twice daily resulted in statistically significant improvements of endpoint mean pain scores from baseline. In addition, those nonresponders with less than 30% pain reduction after 8 weeks of duloxetine were no more likely to meet response criteria at the end of 60 weeks of treatment even if blindly titrated to 120 mg as compared with those continued on 60 mg.[24]

Arnold et al[25] conducted a 12-week RCT (with a 1-week placebo lead-in phase) and enrolled 207 FM subjects (89% female, 87% white, mean age 49 years, 38% with current major depressive disorder). Duloxetine (60 mg twice a day) was an effective and safe treatment for improving symptoms and pain severity in FM regardless of baseline status of major depressive disorder. Duloxetine-treated female subjects demonstrated significantly greater improvement on most efficacy measures compared with placebo. However, the duloxetine-treated male subjects did not improve significantly on any efficacy measure. The treatment effect on significant pain reduction in female subjects was independent of the effect on mood or anxiety.

There was a 12-week RCT in 354 female patients with FM (90% white; mean age, 49.6 years; 26% with current major depressive disorder) to assess the efficacy and safety of duloxetine. The primary outcome was the Brief Pain Inventory (BPI) average pain severity score. Response to treatment was defined as ≥30% reduction in this score. Both duloxetine-treated groups improved significantly more on the BPI average pain severity score compared with placebo. The treatment effect of duloxetine on pain reduction was independent of the effect on mood and the presence of major depressive disorder. Arnold et al[26] demonstrated that duloxetine 60 mg every day and 60 mg twice a day were effective and safe in the treatment of FM in female patients with or without major depressive disorder.

Russell et al[27] reported that duloxetine was efficacious in 520 FM patients both with and without major depressive disorder in a 6-month RCT. The coprimary outcome measures were the BPI average pain severity score and Patient Global Impressions of Improvement (PGI-I) score. Safety was assessed via treatment-emergent adverse events, and changes in vital sign, laboratory, and electrocardiogram measures. Compared with placebo, treatment with duloxetine 120 mg/day improved significantly more on the coprimary outcome measures at 3 months and at 6 months; treatment with duloxetine 60 mg/day also significantly improved the coprimary measures at 3 months and BPI at 6 months. There were no clinically significant differences between treatment groups in changes in vital signs, laboratory measures, or electrocardiogram measures. This study results demonstrated that duloxetine at doses of 60 mg and 120 mg/day seemed to be safe and efficacious in patients with FM.

Choy et al[28] summarized the data on short-term and long-term safety from clinical studies in FM patients treated with duloxetine and continued postmarketing surveillance for adverse events. The profile of adverse events in patients enrolled at least 6 months, and for patients in the 1-year study, was similar to that found in the short-term treatment studies, with no new adverse events emerging at a notable rate. About 20% of patients in clinical trials discontinued due to adverse events in the short-term treatment studies and in the 1-year study. The mean changes in vital signs and weight were small.

Mease et al reported a positive risk and benefit profile for duloxetine (60–120 mg/day) in the long-term treatment (6 months) of FM.[29]

Pharmacokinetics

Duloxetine has an elimination half-life of about 12 hours, and its pharmacokinetics is dose proportional over the therapeutic range. Patients may reach steady-state plasma concentrations after dosing for 3 days. Elimination of duloxetine is mainly through the hepatic metabolism involving 2 P450 isozymes, CYP1A2, and CYP2D6. Oral duloxetine is well absorbed with

maximal plasma concentrations in 6 hours. Food delays the time to reach peak concentration from 6 to 10 hours and decreases 10% of absorption. There iscfa 3-hour delay in absorption and a one-third increase in apparent clearance of duloxetine after an evening dose as compared with a morning dose.

Duloxetine may be taken without regard to meals or fasting. Duloxetine should only be swallowed as whole and not to be chewed or crushed that may affect enteric coating. Duloxetine undergoes extensive metabolism to numerous inactive metabolites. Most of the duloxetine dose (about 70%) seems in the urine as metabolites of duloxetine and about 20% is excreted in the feces.

Duloxetine depends on P450 CYP1A2 and CYP2D6 for hepatic metabolism, thus may involve significant drug–drug interactions. Simultaneous use with inhibitors of CYP 1A2 and 2D6 resulted in higher level of duloxetine. Duloxetine is an inhibitor of the CYP1A2 and CYP2D6. Desipramine (a CYP2D6 substrate) level was increased by 3-fold when administered together with duloxetine 120 mg/day. Drugs that raise the gastrointestinal pH may lead to an earlier release of the duloxetine. Duloxetine is highly bound (>90%) to proteins in human plasma, binding primarily to albumin and alpha-1 acidglycoprotein. Co-administration of duloxetine with another highly protein bound drug may cause higher free levels of drugs and potential adverse reactions.[24]

Adverse reactions

The most commonly observed adverse reactions associated with duloxetine were nausea, decreased appetite, constipation, dry mouth, hyperhidrosis, somnolence, and headache. The concomitant use of duloxetine with other SSRIs, SNRIs, or tryptophan is not usually recommended due to the concern of serotonin syndrome.

Although duloxetine has not been systematically studied in humans for abuse potential, there was no suggestion of any drug-seeking behavior in the clinical trials. Clinicians should carefully evaluate and follow up any patients with previous history of drug abuse while being started on duloxetine.

In postmarketing experience, fatal outcomes have been reported for acute overdoses, primarily with mixed drugs overdoses but also with duloxetine only at doses as low as 1000 mg. Signs and symptoms of overdose on duloxetine included vomiting, somnolence, coma, seizures, serotonin syndrome, syncope, tachycardia, hypotension, and hypertension.[24]

Milnacipran (savella)

Milnacipran (Savella) is indicated for the management of FM. The exact mechanism of central pain inhibitory action of milnacipran and its ability to improve the symptoms of FM in humans are unknown. Preclinical studies have shown that milnacipran is a potent inhibitor of neuronal NE and serotonin reuptake. Milnacipran inhibits NE uptake with approximately 3-fold higher potency in vitro than serotonin without directly affecting the uptake of dopamine or any other neurotransmitters. Milnacipran has no significant affinity for serotonergic, α- and β-adrenergic, muscarinic, histamine, dopamine, opiate, benzodiazepine, and GABA receptors. Milnacipran has no significant affinity for Ca, K, Na, and Cl channels and does not inhibit the activity of human monoamine oxidase or acetyl cholinesterase.[30]

Clinical efficacy

Milnacipran, a SNRI that is more selective for NE reuptake inhibition, has been approved by FDA in FM. Vitton et al[31] enrolled 125 patients in a RCT and reported 37% of twice daily milnacipran-treated patients reported at least 50% reduction in pain intensity, compared with 14% of placebo-treated patients. Eighty-four percent of all milnacipran treated patients tolerated the highest dose (200 mg/day). Milnacipran 100 mg twice daily was more effective than at 200 mg once a day in published studies. Most adverse events were mild to moderate in intensity and transient in duration. Vitton suggested that milnacipran may have the potential to relieve not only pain but several of the other common symptoms associated with FM.

Clauw et al conducted a multicenter RCT to evaluate the efficacy and tolerability of milnacipran treatment in the multiple domains of FM. Compared with placebo, significantly greater proportions of milnacipran-treated patients were FM composite responders and FM pain composite responders. Milnacipran was associated with significant improvements in pain after 1 week of treatment, as well as significant improvements in multiple secondary efficacy end points, including global status, physical function, and fatigue. The most commonly reported adverse events with milnacipran were nausea, headache, and constipation. Clauw et al[32] demonstrated both doses of milnacipran (100 and 200 mg/day) for 15 weeks may provide significant improvements in pain and other symptoms for those adult patients with FM.

Milnacipran are available as 4 film-coated immediate release tablets of 12.5, 25, 50, and 100 mg. The recommended dose of milnacipran is 100 mg/day (50 mg twice daily) and may increase to 200 mg/day (100 mg twice daily). The most common adverse reactions (incidence ≥5% and twice placebo) in FM patients treated with milnacipran were nausea, vomiting, constipation, dry mouth, hyperhidrosis, hot flush, palpitations, and hypertension. In placebo-controlled clinical trials in FM, milnacipran-treated patients

experienced a mean weight loss of 0.8 kg in both the milnacipran 100 mg and 200 mg/day groups up to 3 months, compared with a mean weight loss of approximately 0.2 kg in placebo-treated patients.

Milnacipran may be given orally with or without food. However, taking milnacipran with food may improve the tolerability. Milnacipran is well absorbed after oral route with an absolute bioavailability of approximately 85%–90%. Milnacipran has a low binding to plasma proteins (13%) vs. duloxetine (>90%). The exposure to milnacipran increased proportionally within the therapeutic dose range. Milnacipran undergoes minimal CYP450 related metabolism (vs. duloxetine depends on P450 CYP1A2 and CYP2D6 for metabolism). Milnacipran is excreted predominantly unchanged in urine (55%) and has a terminal elimination half-life of about 6 to 8 hours. Steady-state levels are reached within 36–48 hours and can be predicted from single-dose data. Milnacipran has a low potential of interactions with drugs metabolized by these CYP 450 enzymes. Milnacipran is unlikely to be involved in clinically significant pharmacokinetic drug interactions based on in vitro and in vivo studies.[30]

Milnacipran has unique pharmacokinetic and pharmacodynamic characteristics that distinguish it from the other marketed SNRIs, for example, venlafaxine, desvenlafaxine, and duloxetine as the equipotent SNRIs. Milnacipran has a linear dose concentration trend at therapeutic doses. Milnacipran does not inhibit the cytochrome P450 system hence representing a minimal tendency for drug–drug interactions. Pae et al concluded that milnacipran was effective and tolerable in the treatment of FM and effective for fatigue and anxiety symptoms.[33]

Mease et al reported that milnacipran (100–200 mg/day) was safe and effective and well tolerated by the majority of 888 FM patients during 27 weeks of treatment.[34]

Adverse reactions with milnacipran

In the 3-month placebo-controlled clinical trials on FM, milnacipran treatment was associated with mean increases of up to 3.1 mm Hg in systolic blood pressure (SBP) and diastolic blood pressure (DBP). In clinical trials, milnacipran treatment was associated with mean increases in pulse rate of approximately 7–8 beats per minute relative to placebo. In the placebo-controlled FM trials, increases in the number of patients treated with milnacipran with mild elevations of alanine aminotransferase or aspartate aminotransferase (1–3 times the upper limit of normal) were observed. Increases in alanine aminotransferase were more frequently observed in the patients treated with milnacipran 100 mg/day (6%) and 200 mg/day (7%), compared with the patients treated with placebo (3%).

Hyponatremia may occur as a result of treatment with any SSRIs and SNRIs including milnacipran. It may be due to the syndrome of inappropriate antidiuretic hormone secretion with serum sodium lower than 110 mmol/L reported. SSRIs and SNRIs including milnacipran may increase the risk of bleeding events. The concomitant use of aspirin, NSAIDs, warfarin, and other anticoagulants may add to risk of bleeding.

Serotonin syndrome may occur when lithium is coadministered with milnacipran and other drugs that impair metabolism of serotonin. Serotonin syndrome may include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, tachycardia, labile blood pressure, hypertension), neuromuscular aberrations (eg, hyperreflexia, incoordination) and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea).

Physical dependence may occur as evidenced by severe withdrawal symptoms after the discontinuation of milnacipran similar to other SNRIs and SSRIs. Milnacipran should be tapered gradually in stead of abrupt discontinuation afer extended use.[30]

Alpha2-delta ligands in FM

Clinical studies on gabapentin and pregabalin

Gabapentin (Neurontin) has FDA-approved labels as both an anticonvulsant and for postherpetic neuralgia (PHN). However, gabapentin is frequently prescribed as off label use for neuropathic pain, for example, diabetic neuropathy and various chronic pain conditions. Although structurally related to GABA, gabapentin does not bind to GABA receptors, but instead emerges to modulate central voltage-gated calcium channels (VGCCs) similar to pregabalin.

In a 12-week RCT, gabapentin was statistically more effective than placebo in BPI scores (51% vs. 31%, clinically significant improvement defined as >30% improvement in pain level), sleep quality, FIQ and Patient Global Impression of Improvement in 150 FM patients. The dose range was between 1200 and 2400/day with an average of 1800 mg. No serious adverse events were noted in the gabapentin-treated groups. The most common side effects were dizziness, somnolence, and lightheadedness.[35]

Pregabalin (Lyrica) binds with high affinity to the alpha2-delta site (an auxiliary subunit of VGCCs) in central nervous system tissues. Although the exact mechanism of action of pregabalin is unknown, results with genetically modified mice and with compounds structurally related to pregabalin (such as gabapentin) suggest that binding to the $alpha_2$-delta subunit may be involved in antinociceptive and antiseizure effects of pregabalin in animal models. Pregabalin reduces the

calcium-dependent release of several neurotransmitters (glutamate, substance P) in vivo via modulation of calcium channel function.

Pregabalin (Lyrica) is described chemically as (S)-3-(aminomethyl)-5-methylhexanoic acid. The molecular formula is $C_8H_{17}NO_2$ and the molecular weight is 159.23. Pregabalin capsules are administered orally as imprinted hard-shell capsules containing 25, 50, 75, 100, 150, 200, 225, and 300 mg.

Pregabalin was initially FDA-approved for painful diabetic neuropathy and PHN. Pregabalin was then approved for the treatment of FM in June 2007. An 8-week RCT studied 3 set doses of pregabalin (150 mg, 300 mg, and 450 mg/day) in 529 patients with FM. The highest dose of pregabalin (450 mg/day) was significantly more effective than placebo at 8 weeks. Pregabalin treatment also resulted in the improvement of sleep quality, fatigue, global measures of change, and health-related quality of life. Common side effects included dizziness (49.2%) and somnolence (28%).[36]

Arnold et al[37] published a RCT of 300, 450, and 600 mg/day of pregabalin monotherapy and demonstrated that all 3 doses were well tolerated and efficacious in Patient Global Impression of Change and the FIQ total score for 14-week treatment of 750 FM patients. All 3 doses of pregabalin treatment resulted in significant improvement of sleep compared with placebo. The most common pregabalin-related adverse events were dose-related dizziness and somnolence.[37]

Mease et al published a RCT of pregabalin monotherapy with 300, 450, and 600 mg/day (dosed twice daily) and reported that all 3 doses were efficacious and safe for 13-week treatment of pain in 748 patients with FM. All pregabalin treatment groups showed statistically significant improvement in the assessments of sleep and in Patient Global Impression of Change. Pregabalin monotherapy provided clinically meaningful benefit to patients with FM. Dizziness and somnolences were the most frequently reported adverse events.[38]

Crofford et al published a multicenter RCT that included a 6-week open-label (OL) period of pregabalin treatment (300, 450, 600 mg/day) followed by 26-week double-blind treatment with placebo or pregabalin. Time to loss of therapeutic response (LTR) was longer in pregabalin treatment vs. placebo. Kaplan-Meier estimates of time-to-event showed half of the placebo group had LTR by Day 19 but half the pregabalin group still had not lost response even by 6 weeks. Pregabalin was well tolerated, though 17% discontinued during 6-week OL due to treatment-related adverse events (AE), and more pregabalin than placebo patients discontinued for AEs during double-blind. In those who respond, pregabalin demonstrated the durability of therapeutic effect for pain relief in FM.[39]

Sleep disturbances are common in patients with FM. Russell et al[40] conducted analyses based on 2 randomized, double-blind, placebo-controlled trials of pregabalin (300 mg, 450 mg, and 600 mg daily) in adult FM patients. A total of 748 and 745 patients were randomized in the respective studies. Patients were predominantly white females, average age 48–50 years, on average had FM for 9–10 years, and experienced moderate to severe baseline pain. Russell demonstrated improvement in FM-related sleep dysfunction with pregabalin therapy. The majority of benefit was a direct effect of pregabalin on the patients' insomnia, whereas the remainder occurred through the drug's analgesic activity.

Häuser et al[41] assessed the efficacy of gabapentin and pregabalin in the treatment of FM. Six of 127 RCTs studying 2422 subjects on treatment with gabapentin (1 study) or pregabalin (5 studies) and 1056 subjects on placebo with a median treatment duration of 11 weeks were included into the systematic review. There was strong evidence for a reduction of pain, improved sleep, and improved health-related quality of life but not for depressed mood. There was strong evidence for a nonsubstantial reduction of fatigue and of anxiety. The external validity of the studies was limited because patients with severe somatic and mental disorders were excluded.

Gore et al[42] conducted a study to characterize comorbidities, pain pharmacotherapy, and health care resource use among patients with FM newly prescribed pregabalin or gabapentin in clinical practice. There were significant decreases in the use of NSAIDs, anticonvulsants, and combination therapies in the pregabalin cohort. There were significant increases in use of short-acting opioids, any opioids, SNRIs, anticonvulsants, benzodiazepines, topical agents, and combination therapies in the gabapentin cohort. Although there were no changes in units of health care resources used, there were increases in the postindex period in hospitalization, medications, and total costs for pregabalin, and office visits and medication costs for gabapentin. Gore et al[42] demonstrated a high comorbidity and medication use burden in FM patients in this study and proposed further evaluation to clarify differences in resource utilization and costs observed with gabapentin and pregabalin treatment.

Pregabalin is indicated for the management of FM in addition to neuropathic pain associated with diabetic peripheral neuropathy and PHN. The recommended dose of pregabalin for FM is 300–450 mg/day. It is prudent to start pregabalin at a low dosage and then increase weekly to minimize side effect. Dosing should begin at 75 mg 2 times a day (150 mg/day) and may be increased to 150 mg 2 times a day (300 mg/day) within

1 week based on efficacy and tolerability. Patients who do not experience sufficient benefit with 300 mg/day may be further increased to 225 mg 2 times a day to dosage of 450 mg/day.

The alternative is to start with 75–100 mg at bedtime only and then increase the bedtime dosage weekly up to 300 mg before adding a smaller morning dosage to achieve 450 mg/day. Although pregabalin was also studied at 600 mg/day, higher dose provided no additional benefit and was less well tolerated than lower dose. In view of the dose-dependent adverse reactions, treatment with pregabalin at doses above 450 mg/day is not recommended in FM.

Pharmacokinetics

Pregabalin is well absorbed after oral administration and eliminated largely by the renal excretion. Pregabalin has an elimination half-life of about 6 hours. Following oral administration of prebabalin capsules under fasting conditions, the peak plasma concentrations occur within 1.5 hours. Pregabalin oral bioavailability is $\geq$ 90% and is independent of dose. Following single- (25 to 300 mg) and multiple- dose (75 to 900 mg/day) administration, maximum plasma concentrations (Cmax) and area under the plasma concentration-time curve (AUC) values increase linearly. Following repeated administration of pregabalin, the steady state is achieved within 24 to 48 hours. Multiple-dose pharmacokinetics of pregabalin can be predicted from single-dose data. The rate of pregabalin absorption is decreased when given with food, resulting in a decrease in Cmax of approximately 25%–30% and an increase in Tmax up to 3 hours. However, the administration of pregabalin with food has no clinically relevant effect on the total absorption of pregabalin. Therefore, pregabalin can be taken with or without food.[43]

Pregabalin does not bind to plasma proteins and is predominantly excreted unchanged in the urine with negligible metabolism in humans (<2% of a dose recovered in urine as metabolites). Pregabalin clearance is nearly proportional to creatinine clearance. Dosage reduction in patients with renal dysfunction is necessary. Pregabalin is effectively removed from plasma by hemodialysis. After a 4-hour hemodialysis treatment, plasma pregabalin concentrations are reduced by approximately 50%.

The pharmacokinetics of pregabalin are unlikely to be affected by other agents through metabolic interactions or protein binding displacement. Pregabalin is unlikely to be involved in significant pharmacokinetic drug interactions acoording to in vitro and in vivio studies. Any significant pharmacokinetic interactions would not be expected to occur between pregabalin and other commonly used antiepileptics such as carbamazepine, valproic acid, lamotrigine, phenytoin, phenobarbital, and topiramate.

The pharmacokinetic interactions of pregabalin and gabapentin were investigated in 12 healthy subjects after concomitant single-dose administration of 100-mg pregabalin and 300-mg gabapentin and also in 18 healthy subjects after concomitant multiple-dose administration of 200-mg pregabalin every 8 hours and 400-mg gabapentin every 8 hours. Gabapentin pharmacokinetics after single-dose and multiple-dose administration were unaltered by coadministration of pregabalin. The extent of pregabalin absorption was unaffected by gabapentin coadministration despite a small reduction in rate of absorption.[43]

Adverse reactions

In clinical trials of patients with FM, 19% of patients treated with pregabalin (150–600 mg/day) and 10% of patients treated with placebo discontinued prematurely due to adverse reactions. In the pregabalin treatment group in FM, the most common reasons for discontinuation due to adverse reactions were dizziness (6%) and somnolence (3%). In premarketing controlled trials of all patient populations combined, dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, and difficulty with concentration and attention were more commonly reported by subjects treated with pregabalin than by subjects treated with placebo.

There have been postmarketing reports of angioedema in patients during initial and chronic treatment with pregabalin. 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. Pregabalin should be discontinued immediately in patients with these symptoms.

As with all Antiepileptic drugs (AEDs), pregabalin should be withdrawn gradually to minimize the potential of increased seizure frequency in patients with seizure disorders. If pregabalin is to be discontinued, it should be done gradually over a minimum of 1 week.

AEDs including pregabalin may increase the risk of suicidal thoughts or behavior in any patients regardless of indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

In controlled clinical trials, the incidence of peripheral edema was 6% in the pregabalin group compared with 2% in the placebo group. In short-term trials of

patients without clinically significant heart or peripheral vascular disease, there was no apparent association between peripheral edema and cardiovascular complications such as hypertension or congestive heart failure. Peripheral edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function.

In pregabalin-controlled clinical trials of up to 14 weeks, a gain of 7% or more over baseline weight was observed in 9% of pregabalin-treated patients and 2% of placebo-treated patients. Pregabalin associated weight gain was related to dose and duration of exposure but did not seem to be associated with baseline body mass index, gender, or age. Weight gain associated with pregabalin was not just limited to patients with edema.[43]

Physical dependency and abuse

In a study of recreational users of sedative/hypnotic drugs, including alcohol, pregabalin (450 mg, single dose) received subjective ratings of ''good drug effect,'' ''high'' and ''liking'' to a degree that was similar to diazepam (30 mg, single dose). In controlled clinical studies in over 5500 patients, 4% of pregabalin and 1% of placebo group overall reported euphoria as an adverse reaction. Pregabalin is a Schedule V controlled substance but is not known to be active at receptor sites associated with drugs of abuse.

Future direction in pregabalin

The exact molecular mechanisms underlying FM remain unclear thus rendering most of clinical management relatively ineffective. The onset and maintenance in FM may be related to both nociceptive and central pain processing systems. These systemic abnormalities in FM are thought to be responsible for the loss of cephalic gray matter density observed in FM patients groups studied to date. The current scope of FM treatment focuses largely on analgesia and does not evidently address any potential neuroprotective strategies.

Recla et al[44] proposed a combined treatment of pregabalin and memantine to decrease the pain and rate of gray matter atrophy associated with FM. This dual–drug therapy targeted the 2 primary components of human nociceptive and pain processing systems that involve VGCC and NMDA receptor, respectively.

Translational models of FM

Milnacipran and duloxetine, serotonin/NE reuptake inhibitors, and pregabalin, an alpha2-delta ligand in calcium channel, are effective treatments for FM. Bardin et al[45] compared these compounds in rat models of acute inflammatory pain and stress-induced ultrasonic vocalization. Milnacipran, duloxetine, and pregabalin possess analgesic activity in the formalin test on the paw licking/late phase (corresponding to inflammatory pain with a central sensitization component). In the ultrasonic vocalization model, milnacipran was found to be the most potent and efficacious compound. Bardin et al[45] proposed to use reduction of formalin-induced paw licking/late phase as a useful indicator of potential activity against inflammatory and centrally sensitized pain as might be expressed in FM.

Glucocorticoid

Clark et al[46] enrolled 20 patients into a double blinded crossover study to compare the effects of prednisone vs. placebo. Each patient was randomly assigned to either prednisone 15 mg/day or placebo for 14 days of therapy and then therapy was switched for a further 14 days. The following measurements were assessed at baseline, end of week 2, and end of week 4 such as analogue scores for pain, sleep disturbance, morning stiffness and fatiguability, and dolorimetry readings of pain tolerance over 14 representative tender points. Most of the measured variables showed no improvement but a trend towards deterioration with prednisone treatment.

Ernberg et al[47] investigated whether the treatment effect of intramuscular glucocorticoid injection differs between 25 patients with FM and 25 patients with localized myalgia of the masseter muscle concerning pain, tenderness to digital palpation, pressure pain threshold, pressure pain tolerance level, maximum voluntary occlusal force, or intramuscular temperature. In the FM group, there was a reduced tenderness to digital palpation in response to the treatment. The localized myalgia group responded with a general improvement of symptoms and a significant reduction of pain intensity and tenderness to digital palpation. Ernberg et al[47] demonstrated that patients with FM and localized myalgia in many respects showed a similar response to local glucocorticoid treatment.

Nonsteroidal anti-inflammatory drugs

Although the use of NSAIDs and acetaminophen are very popular, there is little objective evidence to assess the efficacy of analgesia in FM. Patients with FM and coexisting peripheral pain generators such as osteoarthritis, rheumatoid arthritis, and tendonitis may contribute to aggravation of central sensitization and pain. Thus the use of NSAIDs and acetaminophen could contribute to symptomatic relief in those individual with other painful conditions in addition to FM.

Yunus et al[48] evaluated therapeutic effects of ibuprofen in 46 patients with FM. Several features of FM,

including number of pain sites, fatigue, swelling feeling, and tender points all significantly improved over time in both groups. However, no significant differences were found between the ibuprofen and placebo groups. Improvements in FM features might have occurred as a result of physician or study interactions as intervention effect. An important observation in this blinded study was that tender point sites among patients with FM were significantly consistent at 3 and 6 weeks when compared with the baseline.

NSAIDs are not very effective, even if commonly used, in primary FM, whereas cyclobenzaprine has proved to be quite useful. Fossaluzza compared cyclobenzaprine 10 mg alone or in combination with ibuprofen 1600 mg in 32 female patients suffering from FM. All patients received the drugs orally at night and were evaluated at baseline and at days 5 and 10. Assessment of efficacy included the number of tender points, muscle tightness, sleep difficulty, visual analogue scale and duration of morning stiffness. At the end of the study, all symptoms were found to be improved to the same extent in both treatment groups. An exception was morning stiffness, which became significantly more reduced in the patients taking both drugs. No patient discontinued the trial owing to adverse side effects. In conclusion, cyclobenzaprine 10 mg and ibuprofen 1600 mg given concomitantly at night proved to be safe and advantageous in relieving the short-term discomfort of FM.[49]

Russell et al[50] published an 8-week, OL study in which 52 FM patients received both ibuprofen and alprazolam (xanax) and further documented improvement in outcome measures. These data indicate that treatment with a combination of ibuprofen and alprazolam can be beneficial for some patients with FM.

Sixty-two patients with FM were randomly assigned to receive 25 mg of amitriptyline at night, 500 mg of naproxen twice daily, both amitriptyline and naproxen, or placebo in a 6-week, double-blind trial. Amitriptyline was associated with significant improvement in all outcome parameters, including patient and physician global assessments, patient pain, sleep difficulties, fatigue on awakening, and tender point score. Patients with combined naproxen and amitriptyline regimen experienced minor but not significant improvement in pain when compared with amitriptyline alone. Goldenberg et al[51] concluded that either amitriptyline or amitriptyline and naproxen were effective therapeutic regimens for patients with FM.

Tramadol

Tramadol is a centrally acting synthetic analgesic that binds weakly to the mu-opioid receptors (MORs) and also inhibits the re-uptake of NE and serotonin. There have been several clinical trials in FM supported the use of tramadol as a mixed analgesic.

Bennett et al[52] demonstrated the efficacy of a combination analgesic tablet (37.5 mg tramadol and 325 mg acetaminophen) for the pain management of 315 FM patients in a 91-day RCT. The mean dose of tramadol/acetaminophen was 2–6 tablets/day without any serious adverse effects. The primary outcome variable was cumulative time to discontinuation (Kaplan–Meier analysis). Secondary measures at the end of the study included pain, pain relief, total tender points, myalgia, health status, and FIQ scores. Tramadol/acetaminophen-treated subjects also had significantly less pain at the end of the study and better pain relief and FIQ scores. The indexes of physical functioning, role-physical, body pain, health transition, and physical component summary have improved significantly in the tramadol/acetaminophen-treated subjects.

Russell et al[53] supported the efficacy of tramadol 50–400 mg/day over a period of 6 weeks in a RCT for the treatment of FM pain in 100 patients who had been determined to tolerate it (69%) and then perceived a benefit vs. placebo.

Kim et al[54] observed potentiation of the antihyperalgesic effect when both milnacipran and tramadol were administered in combination on the pain threshold in an animal model of FM pain induced by acidic saline. Further research may shed light on the potential efficacy with combination of various pharmacological treatments of FM in humans.

Opioids

Health care providers may feel like being in the hot seat while assessing severe flare up or breakthrough pain in patients with FM. Patient with FM often exhausts the analgesic options of NSAIDs and acetaminophen or even tramadol in managing the widespread pain. Even if any 1 of 3 FDA approved medications (pregabalin, duloxetine, and milnacipran) is effective in FM, the pain relief may not be sufficient in the process of titration or acute flare up. Patient and their loved ones may bring up the issue of trying short-acting or long-acting opioids for pain control in FM. However, there has been no available randomized controlled research on pure mu-opioid agonists to validate the efficacy in FM despite the popularity in clinical practice.

Opioid therapy for chronic pain (including FM) has become more accepted. However, a concern arose that the analgesic efficacy of opioids may not always preserve over long-term treatment despite dose escalation and steady pain. The idea that pain relief could diminish over time may have a significant impact on

the decision of initiating any opioid therapy in vulnerable individuals. Potential loss of analgesic efficacy is concerning and dependence may make it harder to withdraw opioid therapy even in case of inadequate analgesia. Ballantyne and Shin[55] concluded that existing evidence suggests that analgesic efficacy is not always sustained during long-term opioid therapy. Ballantyne and Shin[55] proposed several mechanisms for loss of analgesic efficacy such as pharmacologic tolerance, opioid-induced hyperalgesia, subtle and intermittent withdrawal, and a number of psychological factors including loss of the placebo component. Opioid-induced hyperalgesia is often characterized by insidiously escalating pain in response to the increasing dose of opioid analgesics.

The underlying neurophysiology of acute pain is fairly well characterized, whereas the central mechanisms operative in chronic pain states are less well understood. FM is a common chronic pain condition characterized by widespread pain that may originate largely from altered central neurotransmission. Harris et al[56] compared a sample of 17 FM patients and 17 age- and sex-matched healthy controls, using (MOR) positron emission tomography. FM patients displayed a reduced MOR binding potential within several regions known to play a role in pain modulation, including the nucleus accumbens, the amygdala, and the dorsal cingulate. MOR binding potential in accumbens and throughout cingulate and striatum of FM patients was negatively correlated with the affective pain ratings. Harris et al[56] reported altered endogenous opioid analgesic activity in patients with FM as a possible reason to explain why the exogenous opiates seem to have reduced efficacy in FM.

FM is a chronic pain disorder that is characterized by diffuse musculoskeletal pain and sensitivity to mechanical stimulation. Younger et al[57] studied the effectiveness of low-dose naltrexone on symptomatic management of FM in a pilot clinical trial of 10 FM women. Naltrexone at low doses of 4.5 mg may inhibit the activity of microglia and reverse central and peripheral inflammation. The low-dose naltrexone reduced the symptoms of FM in the entire cohort with a greater than 30% reduction of symptoms over placebo. The mechanical and heat pain thresholds were improved by naltrexone during the laboratory visits. Baseline erythrocyte sedimentation rate predicted over 80% of the variance in drug response. Individuals with higher erythrocyte sedimentation rate (indicating a general inflammatory process) had the greatest reduction of symptoms in response to naltrexone. Younger et al[57] proposed that low-dose naltrexone (4.5 mg) might be an effective and highly tolerable treatment for FM.

Healthcare cost of FM in newly or establishe cases

In 2004, the American Pain Society issued evidence-based recommendations for treatment on FM. The objective of this claims database analysis was to describe the prescription and medical use in patients with newly diagnosed and established FM. Use of the American Pain Society guideline medications increased across stages: SSRIs (20.6%–25.3%), SNRIs (4.58%–9%), pregabalin/gabapentin (5.4%–8.8%), benzodiazepines (19.0%–24.2%), nonbenzodiazepine sedatives (9.1%–13.7%), and opioids (39.5%–43.9%). Office visits to providers increased, on average, after diagnosis: primary care (70.9%–76.3%), chiropractors (28.8%–53.3%), and rheumatologists (4.2%–10.5%), mental health (6.4%–8.3%). Average health care costs rose after diagnosis of FM in the newly diagnosed group ($6555 to $8654). White et al[58] published a study on prescription drug and medical care use with respect to stages of diagnosis in FM. Established patients use more medical resources and have higher rates of concomitant medication use than newly diagnosed FM patients. These findings may help educating and guiding clinicians on the optimal drug treatment patterns in FM.

NMDA antagonist

Central mechanisms related to referred muscle pain and temporal summation of muscular nociceptive activity are facilitated in FM patients. Graven–Nielsen demonstrated that the mechanisms involved in referred pain, temporal summation, muscular hyperalgesia, and muscle pain at rest were attenuated in FM patients via NMDA-antagonist. There seemed to be a link between central hyperexcitability and the mechanisms for facilitated referred pain and temporal summation in a subgroup of the FM patients.[59]

There is strong evidence that intravenous (IV) administration of ketamine based on a standard protocol could be used as diagnostic test for a central sensitization in the central nervous system in patients with FM. The combination of a weak opioid and an NMDA-receptor antagonist with few side effects represented a promise for treatment of pain in a subgroup of patients with FM. The response to IV ketamine may help select specific patients with FM for the treatment modality.[60]

Temporal summation of second pain at least partly reflects temporal summation of dorsal horn neuronal responses, and both have been termed windup, a form of the nociception-dependent central sensitization. Animal and human experiments have shown that both forms of windup depend on the NMDA and substance P receptor systems. Windup of second pain in patients with FM is enhanced comparing to normal control

subjects. Staud et al[61] demonstrated that FM patients showed abnormal windup of second pain WU (SP) during thermal and mechanical stimulation compared with normal control. Because oral doses of the NMDA-antagonist dextromethorphan attenuated thermal and mechanical WU (SP) similarly in FM patients and normal control, there must be other mechanisms than the WU (SP) to be considered for the widespread pain of FM patients. These potential mechanisms might include tonic nociceptive input from the peripheral tissues and/or enhanced descending facilitation.[61]

FM is a challenging pain syndrome without definite or reliable pharmacotherapy. Recent clinical studies suggested that NMDA receptors might play a role in the pathogenesis of FM. Cohen et al[62] reported the response to an IV ketamine infusion (0.1 mg/kg) might help predicting subsequent response to an oral dextromethorphan treatment regimen in 34 FM patients with an observed agreement of 83%. Considering the common refractory nature of FM to conventional pain treatments, this IV ketamine test might enhance patient care by saving time and reducing any unnecessary treatment trials.

The pain amplification of central sensitization can be either inhibited or attenuated by the NMDA receptor antagonists. There are 2 NMDA receptor antagonists (ketamine and dextromethorphan) studied in FM and resulted in beneficial effects on spontaneous pain and allodynia. There were about 50% of FM patients benefited from ketamine. Ketamine clearly identified either responsive or unresponsive subjects among comparable FM patients. However, the value of ketamine as a therapeutic agent in FM has been further limited by psychological disturbances (eg, feelings of unreality, altered body image perception, modulation of hearing, and vision), dizziness, anxiety, aggression, and nausea.[63]

Dopamine agonist

Recent advances have shed insight on FM and led to the conclusion that disturbances of pain-related processes within the CNS, termed central sensitization, represent its most likely source. The phenomenon of central sensitization depends on plasticity in function of NMDA subtype glutamate receptors. However, recent insights into the pharmacology have cast doubt on a direct contribution of NMDA receptors and add credence to a model of the disorder that suggests that the primary pathology of FM is a suppression of the normal activity of dopamine-releasing neurons within the limbic system. The current lack of a demonstrable pathology underlying the pain of FM has hampered progress toward adequate treatment of this mysterious disorder. Accumulating evidence suggested that FM might represent a dysregulation of dopaminergic neurotransmission, which may provide insights to guide both rational clinical interventions as well as system-specific research models.[64]

Pramipexole (Mirapex) is a nonergot dopamine D3-receptor selective agonist indicated for Parkinson disease (PD) that has also shown some efficacy in the treatment of restless leg syndrome.

Holman et al[65] demonstrated that a 14-week RCT on treatment with pramipexole 4.5 mg was safe and well-tolerated in a subset of 60 patients with FM on improvement of scores on assessments of pain, fatigue, function, and global status compared with placebo. The most common adverse events associated with pramipexole were transient anxiety and weight loss. There was no patient withdrew from the study because of inefficacy or an adverse event related to pramipexole.

The strongest evidence suggested the effective treatment of FM with duloxetine and milnacipran. There were studies also reported efficacies with pregabalin, gabapentin, pramipexole, tramadol, and IV tropisetron.[3]

Distler et al[66] assessed the efficacy and safety of terguride, a partial dopamine agonist, in 99 patients with FM in a 12-week RCT. The dosage was titrated to a maximum daily dose of 3 mg of terguride in 3 weeks and this fixed dosage was continued over 9 weeks. During the study, patients were evaluated for the presence of cervical spine stenosis by magnetic resonance imaging. Cervical spine stenosis was detected in 22% of the patients. Terguride treatment did not improve pain, the FIQ score, the TPS, or the Hamilton Depression Scale score in the total study population. However, a subgroup of patients with cervical spine stenosis seemed to benefit particularly from terguride treatment.

Compulsivity has been associated with use of dopamine agonists used to treat PD. Escalating use of dopamine agonists to treat FM raises the concern for compulsivity in a new group of subjects. Holman conducted a retrospective review of 3006 patients with FM treated between 2002 and 2006, 1356 had taken atleast 1 dose of a dopamine agonist (>95% pramipexole). There were 21 patients being identified with compulsive gambling (33%), shopping (40%) or both (27%) after taking a 4.5 mg mean dose of pramipexole at bedtime. The compulsivity resolved in 3–10 days for 19 of 21 patients and by 3 months for all 21 patients after a monitored and mandatory tapered discontinuation over 7 days. Although the biologic aspects of PD and FM differ significantly, the compulsive gambling and shopping related to dopamine agonists have become main concerns for patients with FM and their treating clinicians.[67]

Beta-blockade

In patients with FM and TMD, stress and pain may chronically enhance sympathetic activity, altering cardiovascular responses and worsening pain. Light et al[68] examined cardiovascular, epinephrine (EPI), NE, cortisol and clinical pain responses in 54 female patients with these disorders and 34 controls. FM patients showed lesser heart rate increases to posture challenge but greater blood pressure (BP) increases to postural and speech tasks than controls, as well as higher overall BP and greater total vascular resistance (TVR) than TMDs or controls.

TMDs showed higher overall cardiac output and lower TVR than controls

Both FM and TMD groups showed lower baseline NE than controls, and TMDs showed lower overall EPI and NE levels. Group differences in heart rate, EPI, and NE were abolished after propranolol although BP, CO, and TVR differences persisted. In both FM and TMD, the number of painful body sites and ratings of total clinical pain obtained 4 times during each session were significantly lower after beta-blockade vs. placebo. Light et al[68] reported that FM and TMD may frequently involve the dysregulation of beta-adrenergic activity that contributes to the altered cardiovascular and catecholamine responses and to severity of clinical pain; acute treatment with low-dose propranolol led to short-term improvement in all these domains.

Nonbenzodiazepine as sedative hypnotics

Sedative hypnotic medications are commonly used by FM patients. There were clinical studies published on the use of certain nonbenzodiazepine hypnotics such as zopiclone and zolpidem in FM. These agents may improve sleep and reduce fatigue in FM without significant benefit on pain relief.

Grönblad et al[69] enrolled 33 patients with FM in an 8-week RCT with zopiclone (brand name Imovane in Canada and Zimovane in the United Kingdom). The subjective sleep quality showed improvement in more than 90% of zopiclone patients at 4 weeks and nearly 80% at 8 weeks as compared with improvement in more than 60% of placebo control. However, 50% of patients in both treatment and placebo groups showed improvement at 8 weeks. The effects of zopiclone treatment were at the same level as those of placebo in reports on widespread tenderness, visual analogue scales, and drawings for pain and other subjective feelings of discomfort.

Moldofsky et al[70] conducted a RCT to examine whether zolpidem (ambien) would improve the disturbed sleep, fatigue, mood, and pain symptoms in patients with FM. The total of 16 patients who completed the study reported no significant differences in ratings of pain, number of tender points, mood, sleep quality, morning fatigue, morning sleepiness, or ability to concentrate. Compared with the placebo group, patients treated with zolpidem recorded significantly reduced time to fall asleep, increased sleep time, reduced awakenings, overall improvement in sleep, and daytime energy except a lower rating for evening energy. Zolpidem at the 10 mg dose was rated most acceptable for sleep. Short-term treatment with zolpidem (5–15 mg) was useful for sleep and daytime energy in patients with FM without other benefit of pain and symptomatic relief.

Sodium oxybate

In general, about 50% of all treated patients with FDA approved medications in FM seem to experience a 30% reduction of symptoms, suggesting that many patients with FM will require additional therapies. Thus, other forms of treatment, including exercise, cognitive behavioural therapies and self-management strategies, may be necessary to achieve satisfactory treatment outcomes in FM. Despite promising results of pilot trials, RCTs with dopamine receptor agonists (pramipexole) and sodium channel antagonists have so far been disappointing for patients with FM. However, Staud[71] reported promising outcome on new pharmacological approaches using sodium oxybate for the treatment of pain and insomnia in FM.

FM is commonly associated with the sleep phenomenon of alpha intrusion and with low growth hormone secretion. Gamma-hydroxybutyrate, also known as sodium oxybate, is a precursor of GABA with powerful sedative hypnotic activities. Sodium oxybate has been shown to increase both slow-wave sleep and growth hormone levels. Sodium oxybate 6.0 g/day effectively reduced the symptoms of pain and fatigue in 18 patients with FM in a RCT. Sodium oxybate dramatically reduced the sleep abnormalities (alpha intrusion and decreased slow-wave sleep) associated with the nonrestorative sleep characteristic of FM.[72]

Sodium oxybate (Xyrem) may influence both presynaptic and postsynaptic GABA-B receptors. This scheduled drug was originally approved by FDA for the treatment of narcolepsy with cataplexy and excessive daytime sleepiness. Russell et al[73] reported therapy with sodium oxybate 4.5 gm or 6 gm for 8 weeks was well tolerated and provided significant improvement of sleep quality and other symptoms of FM. The most common reported adverse events include dose-related headache, nausea, dizziness, and somnolence that may resolve with continuation of treatment.

Tropisetron

Tropisetron is a 5-HT3 antagonist that has been subjected to controlled study in Europe for the treatment of FM. A responder group has been distinguished from a nonresponders group exhibiting a rapid and steady decrease in pain intensity. Treatment with tropisetron was well tolerated and limited only by gastrointestinal side effects.

Stratz et al[74] conducted a RCT on IV injection of 2 mg of the 5-HT3 receptor antagonist tropisetron once daily for 5 days that produced a longer lasting therapeutic effect on FM symptoms than did peroral daily treatment with 5 mg of this drug.

Substance P has been found at an elevated level in the cerebrospinal fluid of FM patients. Treatment with tropisetron leads in a subgroup of FM patients to pain reduction. Stratz et al[75] reported that 10 of 20 FM patients had a good or very good influence on their pain (responders). In these responders, the means of the serum substance P levels were higher in comparison with the nonresponders, though the difference was not significant. In the responders, 5-HT3 receptor antagonist tropisetron produced a significant decrease in the serum substance P levels, whereas this did not occur in the nonresponders. It is possible that the responders to tropisetron represent a subgroup of patient with FM for whom the substance P and 5-HT3 receptors play key roles in the development of the pain symptoms.

In 223 FM patients in a rheumatology practice, a follow-up postal survey was carried out 0.5–2 years after a 5-day IV treatment with 5 mg of the 5-HT3 receptor antagonist tropisetron daily on the effect of this treatment. There were 60.2% of patients contacted for whom an assessment of the tropisetron treatment was possible. A good to very good effect of the treatment on the pain was reported by 45% of the patients, and only 25% reported an unsatisfactory effect. The effect of tropisetron lasted between one day and 12 weeks. Sleep and general condition were also assessed as good or very good by almost half of the patients. Tropisetron was rated as more efficacious in almost half of the cases in comparison with the current treatment and the best treatment with other drugs ever received. The unsatisfactory effect of IV tropisetron compared with other treatments was reported in 30% of the cases. IV tropisetron treatment represents a promising option for the treatment of FM according to this open respective study. Whether the success of IV tropisetron treatment can be improved further with a longer lasting treatment or a selection of the FM patients still needs to be settled.[76]

Substance P (NK-1) receptor antagonists

The discovery of substance P and its potent biological activities have lead to discovery of other tachykinins and NK1 receptor. Blockade of the NK1 receptor may have potentially beneficial effects in medical care in drug-induced emesis and the treatment of depression. The analgesic potential of NK1 receptor antagonists has not met the early expectations despite its promising theory. However, there is future clinical application of more potent NK1 receptor antagonists in the management of FM.[77]

Tender point injection

FM is characterized by widespread pain and hyperalgesia to mechanical, thermal, and electrical stimuli. Despite convincing evidence for central sensitization of nociceptive pain pathways, the role of peripheral tissue impulse input in both initiation and maintenance of FM is unclear. Staud et al[78] published a RCT of 22 female normal controls and 28 female FM subjects and tested the effects of trapezius muscle tender point injections with 1% lidocaine on local pain thresholds and on remote heat hyperalgesia at the forearm. The lidocaine injections increased local pain thresholds and decreased remote secondary heat hyperalgesia in FM patients. However, neither lidocaine nor saline injections significantly affected the clinical pain ratings of FM. Staud[78] et al emphasized the important role of peripheral impulse input in maintaining the central sensitization in FM similar to other pain conditions such as irritable bowel syndrome and complex regional pain syndrome.

FM pain is often widespread and does not seem to be restricted to only the tender points in ACR criteria. There may be multiple areas of deep tissue pain (trigger points TrP) with adjacent much larger areas of referred pain frequently seen in FM. Staud[79] reported that trigger point injection and analgesia over areas of extensive nociceptive input (tender points) has been found to provide often long lasting local and general pain relief. Staud[79] thus proposed that interventions aimed at reducing the local pain of FM seemed to be effective but needed to focus less on tender points but more on the trigger points and any other body areas of heightened pain and inflammation.

Trigger points are defined as specific areas of muscle that are painful to palpation and are characterized by the presence of taut bands and the generation of a referral pattern of pain. Tender points are areas of tenderness occurring in muscle, muscle-tendon junction, bursa, or fat pad. When tender points occur in a widespread manner, they are usually considered characteristic of FM. Trigger points, which typically occur in a more restricted regional pattern, are indicative of

MPS. In some patients, the 2 phenomena of both trigger and tender point may coexists, and overlap pain symptoms can also occur. There is continued controversy regarding the defining characteristics and homogeneity of myofascial pain because of the variability of the examination findings. Borg-Stein and Stein[80] proposed that myofascial trigger point injections can be helpful in decreasing pain and improving range of motion incorporated in a comprehensive exercise and rehabilitation program in appropriately selected patients.

Neuromodulation

Neuromodulation is a technique to treat pain from a variety of causes including CNS disorders and CRPS. Occipital nerve stimulation is a neuromodulation technique currently under study to treat various migraine headache disorders. Thimineur and Ridder[81] examined a technique of neurostimulation via peripheral neurostimulation of the C2 scalp area that appears to affect the pain and symptoms of 12 FM patients with comorbid headache disorder. Visual Analog Scale pain levels for FM-related pain has decreased significantly at 6 months, and pain-drawing total area and number of areas colored in also decreased dramatically. Chronic fatigue and depression as assessed by the Beck Depression Inventory and Fatigue Impact Scale were markedly improved. Overall quality of life as assessed by the Health Survey Short Form 36 (SF-36) was markedly improved. There were no infectious or technical complications reported. The stimulation over the C2 scalp area may help diminishing pain and related symptoms in patients with FM.

Complementary and alternative therapies for FM

FM is a common chronic pain disorder characterized by complex symptoms and few consistently effective treatments. Prior evidence suggests that medication and self-management approaches to care can improve symptoms; function, and well-being in FM. Studies evaluating different forms of exercise continue to support increased physical activity as an essential component of treatment plan in FM. The efficacy of acupuncture in FM showed conflicting results in studies but added to the essential knowledge for clinicians to have substantive conversations with patients. Recent studies supported the recommendation of a multimodal approach in FM with individualized, evidence-based pharmacotherapy and self-management. Treatment goals should include the improvement of symptoms, primarily pain and sleep, and the promotion of positive health behaviors with the endeavor of improving physical function and emotional well-being in FM.[82]

Assessment of complementary and alternative approaches to FM treatment is limited by a lack of clinical trials. Despite a few completed trials, they all shared the shortcoming as other studies on FM. Although acupuncture is commonly accepted by FM patients, the evidence for clinical improvement is conflicting. One randomized sham-controlled study demonstrated no subjective improvement in pain between acupuncture and sham (control) acupuncture. A more recent randomized trial, however, demonstrated that patients who received acupuncture (vs. sham acupuncture) had significantly greater improvements in FIQ scores at 1 and 7 months after treatment.

Ernst et al[83] published a systemic review of RCTs on acupuncture for FM. There were 5 studies used electroacupuncture as an adjunct to conventional treatments. Three RCTs suggested positive but short-lived effects while 2 yielded negative outcomes. Therefore, acupuncture cannot be recommended yet for treatment of FM based on the current mixed evidence.

Martin et al[84] conducted a prospective, partially blinded, randomized controlled clinical trial of acupuncture in 50 FM patients. This study paradigm allows for controlled and blinded clinical trials of acupuncture. Acupuncture was well tolerated and with minimal adverse effects. Acupuncture provided significantly improvement for symptoms of FM that was not only restricted to pain relief but most significant for fatigue and anxiety.

Martin-Sanchezetal[85]conducted a systematic review and meta-analysis and found no evidence of benefit resulting from acupuncture as a treatment for FM vs. placebo.

Targino et al[86] reported that addition of acupuncture to TCA and exercise for 58 women with FM had been beneficial for pain reduction and improvement in quality of life up to 6 months after the conclusion of acupuncture treatment.

Nonpharmacological treatments in FM

Nonpharmacological treatments should include fitness and strengthening exercise, and warm water therapy and psychological pain management techniques. Symptoms of FM can be effectively managed with both pharmacological and nonpharmacological therapies. In general, treatment benefits in FM seem largely independent of the gender difference.[3]

Comprehensive and multidisciplinary approaches seemed to result in better outcomes than any single intervention, although there were little well-controlled clinical studies.

Combined cardiovascular fitness training and flexibility program provided significantly greater improvement than a psychologically based muscle relaxation technique. Water-based exercise may be recommended

as an initial regimen because most of FM patients seemed to tolerate it better. Short-term studies of aquatherapy provided a noticeable improvement in quality-of-life measures and pain in FM.

Fors et al[87] studied prospectively the effectiveness of an attention distracting and attention focusing guided imagery and the effect of amitriptyline in 55 women with FM. The relaxation training and guided instruction in ''pleasant imagery'' were reported effective as intervention for pain relief in FM during the 28-day study period, but the amitriptyline revealed no significant advantage over placebo.

In healthy adults, expectations can modulate the activity of inhibitory bulbospinal projections, and can even block the analgesic properties of counter-irritation- a phenomenon that triggers descending inhibition. Because descending inhibition was known to be deficient in FM patients, Goffaux et al[88] tested the hypothesis that ''expectancy-mediated analgesia would improve or even kick-start deficient inhibitory responses of FM patients''. Goffaux et al[88] demonstrated that expectations of analgesia radically change the subjective experience of pain but do not eliminate evidence of spinal hyperexcitability in FM patients. The spinal activity of FM patients was abnormal even when the analgesia was experienced confirming the heightened reflex responses. Goffaux et al[88] reported the modulation of pain by expectations in FM patients failed to influence the spinal activity unlike in healthy subjects. FM patients were susceptible to expectancy induced analgesia yet this form of analgesia did not depend on recruitment of descending inhibitory projections.

Thieme and Gracely[89] studied various classes of psychological techniques and their efficacy on pain relief in FM. The highest effects for pain reduction are found after cognitive-behavioral therapy (CBT) and operant-behavioral therapy group treatments. Relaxation as a single treatment has not been proven to be useful. The psychological treatment was effective in FM pain, whereas hypnotherapy and writing intervention had demonstrated mild treatment effects. Considering the heterogeneity of FM, Thieme and Gracely[89] advocated incorporation of CBT and operant-behavioral therapy to pharmacotherapy, exercise, education, and other treatment domains.

Lera et al[90] published a RCT on the response of 83 FM patients to 2 multidisciplinary treatments with and without CBT according to the presence of concurrent symptoms. The multidisciplinary treatments in FM improved functional capability and reduced symptom impact. CBT increased slightly the effect of multidisciplinary treatments in FM patients with fatigue.

Reduction of analgesics after multidisciplinary approach in FM

Hooten et al[91] reported the favorable measurements of physical and emotional functions for 159 FM patients following a 3-week outpatient multidisciplinary pain rehabilitation that incorporates withdrawal or reduction of analgesic medications. Compared with admission, the number of patients using opioids, NSAIDs, benzodiazepines, and muscle relaxants at program dismissal was significantly reduced.

Of note, this clinical research was conducted while there was no US FDA approved medications available for FM. The ''withdrawal'' or ''reduced use'' of opioids, NSAIDs, benzodiazepines, and muscle relaxants were certainly beneficial for the detoxification of patients with FM. It will be of interest in pursuing future outcome study to optimize the benefit of pharmacotherapy with pregabalin, duloxetine, and milnacipran in conjunction with the multidisciplinary pain rehabilitation and analgesics reduction program in FM.[91]

Acute pain management in FM

Acute pain management in FM may involve surgery, trauma, or flare up of pain induced by various factors. Whenever a FM patient shows up for an urgent or emergency care, the scenario may be confusing and overwhelmed. It is very challenging to assess acute pain and formulate management plan in FM patients. The long list of pain medications and multiple comorbid conditions plus the widespread pain complaints could raise a red flag. Patient may end up being overmedicated with only escalating dose of opioids in stead of coverage with a comprehensive pharmacotherapy. Perioperative patient care could certainly be a nightmare for FM patients and clinicians without proper understanding and planning beforehand. Thanks to the recent advance in basic and clinical research, there are promising options of acute pain management for FM and perioperative care team.

Patients with FM are at high risk to experience increased acute pain and prolonged pain afterwards. Pogatzki-Zahn et al[92] have provided a general outline of pathophysiological characteristics of FM relevant for enhanced central pain processing after surgery. The treatment options in the perioperative period may be based on the specific symptoms of individual FM patients to optimize the acute pain management. Recent evidence has supported the mechanisms of FM towards the enhanced CNS sensitization and decreased descending pain inhibition. These 2 mechanisms have been identified as the main contributors to severity of acute and chronic pain conditions after surgery even in patients without FM. Other frequent

comorbidities in FM such as anxiety, depression, and somatization disorder were independently known to increase risk of acute and chronic pain after surgery or trauma.

Pogatzki-Zahn et al[92] presented an optimal treatment including substances and strategies targeting specific symptoms in FM to prevent or specifically reduce the acute and chronic pain after surgery. The multimodal approach in FM for perioperative pain management may include nonopioid analgesics (tramadol), NSAIDs, muscle relaxants, gabapentin, pregabalin, duloxetine, milnacipran, and NMDA receptor antagonists (ketamine and dextromethorphan). The regional anesthesia techniques such as nerve block and catheter infusion, plexus block, epidural, and spinal anesthesia and analgesia should be considered while indicated and available. The acute pain management in FM is very challenging and need to cover systemic symptom-based approaches to target both the enhanced central sensitization and decreased descending pain inhibition. The goal is to minimize acute pain and prevent any persistent pain after surgery or trauma and tackle comorbid and psychological syndromes to facilitate best outcome in FM.[92]

Approach to the acute and chronic pain in FM: practice-based evidence vs. evidence-based medicine

FM is a poorly-understood chronic pain syndrome characterized by the specific regions of widespread musculoskeletal pain, localized tenderness, nonrestorative sleep, fatigue, psychological distress all in the absence of apparent organic disease. Although the etiology of FM is unclear, accumulating data suggested that the disordered central pain processing likely plays a role in the pathogenesis of diverse symptoms. Although assorted pharmacotherapies have been studied and espoused for treatment, no particular agent or class of drugs has proved to be mostly useful agent in the management of FM overall.[93]

There is no standard protocol or pathway to guide acute or chronic pain management in FM. Treatment choice in FM is usually made on an empiric basis and informed by the evidence wherever possible. The first agent of choice may be TCAs with amitriptyline or nortriptyline at bedtime, starting at 10 mg and titrating incrementally up to 25–50 mg to either maximum benefit or as patients tolerated. If TCAs were not tolerated, then low-dose cyclobenzaprine at bedtime may be considered. Patients may respond to analgesics such as tramadol for widespread pain without other associated symptoms. Patients with clinical depression associated with FM may particularly benefit from SSRIs or SNRIs.

It is mandatory to set up a realistic goal before initiating any pain management in FM. The efficacies of SNRIs and alpha2-delta ligands have been demonstrated to provide pain relief gradually but not instantaneously. Most of clinical studies have only documented mild to moderate pain relief in FM that responded to treatment with SNRIs or alpa2-delta ligands. The efficiency and timeline with US FDA approved medications have shown to be quite different than other nonspecific analgesic agents in the pain management of FM.

It is an empirical decision whether to start with SNRIs or alpha2-delta ligands as first line treatment for FM. Vigilant follow-up and counseling patient on any potential drug–drug interactions are crucial to a successful launch of these standard treatments. It is prudent to start with low dose and titrates cautiously to balance the risk and benefit ratio. Duloxetine in dose >120 mg/day, milnacipran >200 mg/day and pregabalin >450 mg/day failed to provide any additional pain relief. However, higher doses of these medications may only cause more adverse events and withdrawals according to result of previous clinical studies.

Potential synergistic effect of SNRIs (duloxetine or milnacipran) and alpha2-delta ligand (pregabalin) warrant further clinical research in FM. It is crucial to validate the modern strategy with multimodal analgesia and nonpharmacologic approach to improve outcome in management of FM.

An improved understanding of the pathogenesis of FM has allowed more substantial refinements in its treatment. Patients with FM may benefit from pregabalin, duloxetine, or milnacipran and use tramadol as needed. For most of the pharmacotherapy, patients with FM need to be instructed that at least several weeks may be mandatory to appreciate noticeable benefit. An insignificant improvement after 1 medication for FM indicates a need for introduction of another agent in different category or a combination of therapies.

Clinicians should not be discouraged due to therapeutic responses to current therapies are rarely permanent for any single pharmacological agent in FM. Successful progress in FM treatment depends on the vigilant reassessment and update of treatment plan if indicated. Russell[94] has proposed a straightforward and useful acronym-ADEPT living in FM that stands for Attitude, Diagnosis, Education, Physical Modalities, Treatment.

Patients with FM are commonly encouraged to participate in low-impact exercise, such as aquatherapy. Patients and clinicians need to be reminded the common scenario of FM associated with very limited exercise capacity at the beginning. Patients and

clinicians should work together to enhance the exercise tolerance very gradually instead of overly aggressive regimen.

Education, emotional support, and reassurance are all critical to acute and chronic pain management of FM. Despite the severity of pain, patients should be reassured that FM is an otherwise benign condition that does not lead to serious mortality. Clinicians need to sympathize that patients with FM frequently have had their symptoms and signs either being ignored or dismissed. The challenge is how to establish and then maintain a compassionate rapport to carry on the comprehensive treatment program and address all aspects of illness in FM.

The emerging and promising pharmacotherapies may include NMDA receptor antagonist (ketamine and dextromethorphan), 5-HT 3 receptor antagonist (tropisetron), sodium oxybate (GABA-B receptor), substance P (NK-1 receptor) antagonist, dopamine D3-receptor selective agonist (pramipexol), and other novel agents and delivery system in the pipeline. Meticulous care and follow-up could help tackling any new onset of acute pain or flare up of chronic pain in FM. It is crucial to ensure the best outcome and improve quality of life although providing integrated care for patients with FM and their loved ones.

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