The FIBRO System: a rapid strategy for assessment and management of fibromyalgia syndrome

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Abstract: Fibromyalgia syndrome (FMS) is a complex disorder of widespread pain and tenderness associated with numerous other symptoms including fatigue, cognitive dysfunction, nonrestorative sleep, depression, anxiety, and stiffness. While new diagnostic criteria and previous management guidelines require quantitation of the severity of associated FMS symptoms experienced by individual patients, no system for rapid patient assessment has been made available to provide a basis for diagnosis, treatment selection and follow-up for clinicians in busy practices who have limited time. This review presents the FIBRO System, an easily remembered system for FMS symptom quantitation using the FIBRO mnemonic along with verbal questions on simple 0–10 scales to assess symptom severity (the FIBRO Problem Scale) and response to treatment (the FIBRO Change Scale) along with recommendations for pharmacologic and nonpharmacologic therapies to address individual FIBRO symptoms. This symptom-based approach can improve the care of FMS patients by providing a comprehensive, focused assessment in limited time.

Keywords: fibromyalgia, therapeutics, outcome assessment, review, exercise, adverse effects

Introduction

Fibromyalgia syndrome (FMS) is a disorder of chronic widespread pain (CWP) and tenderness associated with a number of other symptoms including fatigue, cognitive dysfunction ('fibrofog'), nonrestorative sleep, depression, anxiety, and stiffness of muscles and joints [Wolfe *et al.* 1990]. FMS is a common disorder, occurring in developed countries worldwide with prevalence rates of up to 5% [Neumann and Buskila, 2003]. However, these rates likely underestimate the true prevalence of FMS since they are based on fulfillment of the American College of Rheumatology (ACR) classification criteria which fail to identify approximately half of clinically diagnosed FMS patients [Katz *et al.* 2006]. Since FMS prevalence rates are highest in those aged 60–79, the overall prevalence is likely to increase significantly now that the baby-boom generation are in their 60s [Wolfe *et al.* 1995]. FMS is of particular importance to those who care for patients with rheumatic disease, as 10–20% of new patients presenting to rheumatology clinics are afflicted with the disorder and FMS disproportionately affects patients commonly cared for by rheumatologists including

women, the elderly, and patients with inflammatory autoimmune conditions [Wolfe *et al.* 1995]. One in five patients with rheumatoid arthritis (RA) and half of systemic lupus erythematosus patients suffer from FMS, and the presence of FMS has a detrimental effect on disease outcomes for patients with inflammatory disorders [Wolfe and Michaud, 2004; Middleton *et al.* 1994]. FMS is a significant cause of morbidity, resulting in high costs due to a level of healthcare utilization and disability comparable to that seen in patients with RA [Silverman *et al.* 2009].

FMS differs from other forms of widespread pain (such as generalized osteoarthritis) by its lack of responsiveness to classical analgesic medications such as opioids or nonsteroidal anti-inflammatory drugs (NSAIDs). This lack of responsiveness is likely due to differences in disease pathophysiology. While the exact etiology of FMS remains unknown, growing evidence has implicated dysfunctional central nervous system (CNS) pain processing that results in central pain amplification caused by alterations in neurotransmitter levels [Buskila, 2009; Russell and Larson, 2009]. FMS patients have higher CNS levels of

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excitatory neurotransmitters such as glutamate and substance P that mediate pain signaling [Harris *et al.* 2009; Vaeroy *et al.* 1988] and lower CNS levels of serotonin and norepinephrine that contribute to descending inhibitory pain pathways [Russell *et al.* 1992]. There are currently three pharmacologic therapies indicated by the United States (US) Food and Drug Administration (FDA) for the management of FMS: duloxetine (Cymbalta), milnacipran (Savella) and pregabalin (Lyrica). These medications are thought to treat FMS by increasing the activity of descending inhibitory pain pathways (duloxetine and milnacipran) and decreasing the activity of excitatory pain pathways (pregabalin).

Despite the availability of effective treatments, diagnosis and management of FMS patients is challenging. While all FMS patients have pain, they vary widely in the associated FMS symptoms from which they suffer. New ACR diagnostic criteria for FMS require quantitation of the severity of symptoms of fatigue, fibrofog and nonrestorative sleep [Wolfe *et al.* 2010]. Effective FMS management requires an individualized treatment regimen that addresses not only pain but all associated FMS symptoms [Carville *et al.* 2008]. A symptom-based management approach improves patient outcomes and limits treatment failures that are common when the exclusive focus is on treating pain. However, assessment is often hampered by the inability of many patients to effectively articulate their symptom burden and the inability of clinicians to interpret the patient's complaints into a coherent intellectual framework from which to make diagnostic and treatment decisions. While self-report questionnaires to quantify symptom severity exist, including the fatigue severity scale for fatigue [Krupp *et al.* 1989], the Everyday Cognition Scale for fibrofog [Farias *et al.* 2008], the Athens Insomnia Scale for insomnia [Soldatos *et al.* 2000], the Physicians Health Questionnaire-9 for depression [Kroenke *et al.* 2001], the Generalized Anxiety Disorder-7 for anxiety [Spitzer *et al.* 2006], and the Brief Pain Inventory for pain [Cleeland, 1989], their length and complexity often preclude use in busy clinical practices.

The FIBRO System for diagnosis and management FMS

To improve the care of FMS patients by busy practitioners, a brief questionnaire for

quantitation of problematic symptoms was needed. The questionnaire is composed of modified visual analog scales (VASs) from the original fibromyalgia impact questionnaire (FIQ) to provide a rapid assessment of symptom burden that can provide a basis for developing an individualized treatment plan [Boomershine and Crofford, 2009]. The FIQ is the most widely used measure for quantifying global fibromyalgia disease severity through a combination of 11 activities of daily living (ADL), two day-of-the-week (DOW), and seven VAS questions [Bennett, 2005]. However, the ADL questions have been criticized for their gender bias and on psychometric grounds [Zachrisson *et al.* 2002; Wolfe *et al.* 2000], and the length and scoring complexity of the ADL and DOW questions make the FIQ difficult to use in routine clinical care. While the FIQ has recently been revised to address some of its limitations [Bennett *et al.* 2009], it is still too long and complex for many clinicians to use routinely. The modified FIQ VAS scores are each on a 0–10 scale that can be easily summed to produce a global disease severity score highly correlated with the full FIQ global score and used in isolation to quantify the severity of individual fibromyalgia symptoms [Boomershine *et al.* 2008].

However, the modified FIQ VAS questionnaire remains too burdensome for some clinicians due to the requirement for patients to complete a paper questionnaire. While the modified FIQ VAS questions can be asked verbally with patients answering on a 0–10 scale, the nonuniform wording of the questions and anchors makes them difficult to recall. Also, the original FIQ did not provide a VAS to assess fibrofog, which is necessary for diagnosis utilizing the new ACR criteria [Wolfe *et al.* 2010]. Finally, while VASs perform well for initial evaluation and for measuring therapeutic improvement, they perform poorly in detecting side effects of treatment at follow up since they are often unable to measure symptom worsening [Farrar *et al.* 2001]. This deficit is significant, as FMS treatments can improve some symptoms while worsening others. To further simplify assessment and improve the ability to measure treatment effects over time, the FIBRO System has been developed. The FIBRO System utilizes the FIBRO Problem Scale for initial assessment (Box 1) and the FIBRO Change Scale for follow up (Box 2). The FIBRO Problem Scale questions were based on wording from a VAS that is at least as well correlated with clinical variables as

Box 1. The FIBRO Problem Scale.

Directions: For each of the following questions, select the number that best indicates how much of a problem each symptom is on a scale from 0 to 10 where 0 indicates no problem and 10 indicates a totally disabling problem.

FATIGUE: How much of a problem is fatigue or feeling tired?

0 1 2 3 4 5 6 7 8 9 10
No problem A totally disabling problem

FIBROFOG: How much of a problem is memory and/or concentration?

0 1 2 3 4 5 6 7 8 9 10
No problem A totally disabling problem

INSOMNIA: How much of a problem is getting a good nights sleep?

0 1 2 3 4 5 6 7 8 9 10
No problem A totally disabling problem

BLUES: How much of a problem is depression or feeling sad?

0 1 2 3 4 5 6 7 8 9 10
No problem A totally disabling problem

How much of a problem is anxiety or feeling nervous?

0 1 2 3 4 5 6 7 8 9 10
No problem A totally disabling problem

RIGIDITY: How much of a problem is stiffness in muscles and/or joints?

0 1 2 3 4 5 6 7 8 9 10
No problem A totally disabling problem

Ow!: How much of a problem is pain?

0 1 2 3 4 5 6 7 8 9 10
No problem A totally disabling problem

Box 2. The FIBRO Change Scale.

Directions: For each of the following questions, select the number that best indicates change in how much of a problem each symptom is **NOW COMPARED TO YOUR LAST VISIT** on a scale from 0 to 10 where 0 indicates very much improved, 10 indicates very much worse, and 5 indicates no change.

FATIGUE: How have problems of fatigue or feeling tired changed?

0 1 2 3 4 5 6 7 8 9 10
Very much improved No change Very much worse

FIBROFOG: How have problems with memory and/or concentration changed?

0 1 2 3 4 5 6 7 8 9 10
Very much improved No change Very much worse

INSOMNIA: How have problems with getting a good nights sleep changed?

0 1 2 3 4 5 6 7 8 9 10
Very much improved No change Very much worse

BLUES: How have problems of depression or feeling sad changed?

0 1 2 3 4 5 6 7 8 9 10
Very much improved No change Very much worse

How have problems of anxiety or feeling nervous changed?

0 1 2 3 4 5 6 7 8 9 10
Very much improved No change Very much worse

RIGIDITY: How have problems of stiffness in muscles and/or joints changed?

0 1 2 3 4 5 6 7 8 9 10
Very much improved No change Very much worse

Ow!: How have problems of pain changed?

0 1 2 3 4 5 6 7 8 9 10
Very much improved No change Very much worse

longer scales [Wolfe, 2004] and are consistent with assessments required under the new ACR diagnostic criteria for FMS [Wolfe *et al.* 2010]. The FIBRO Change Scale questions were based on wording from the patient global impression of change, the most commonly used and validated measure of a patient's response to treatment [Guy, 1976]. Both scales assess FMS symptoms with seven questions recalled using the FIBRO mnemonic were F stands for fatigue and fibro fog, I for insomnia (waking unrefreshed), B for blues (depression and anxiety symptoms), R for rigidity (stiffness) and O for 'Ow!' (pain). These clinical domains of FMS have been identified by expert opinion as well as clinician and patient Delphi exercises as being among the most important to assess in FMS patients [Mease *et al.* 2008]. The FIBRO Problem Scale utilizes a 0–10 numeric rating scale with similar wording and identical anchors for each question with 0 = 'no problem' and 10 = 'a totally disabling problem' to simplify recall. The FIBRO Change Scale uses a 0–10 numeric rating scale ranging from 0 = 'very much improved' to 10 = 'very much worse' with 5 = 'no change'. The FIBRO Problem Scale assesses current symptom levels and the FIBRO Change Scale assesses symptom levels compared with the last clinic visit. The FIBRO Problem Scale items can be used individually to identify problematic FMS symptoms for use in diagnosis and to develop an individualized therapeutic regimen and summed to provide a global measure of

FMS symptom severity. The FIBRO Change Scale is used to assess treatment response and monitor for the development of side effects from therapy. By facilitating communication between clinicians and patients, these scales can improve diagnosis, delivery of care and shorten office visits with FMS patients.

Nonpharmacologic treatments

Nonpharmacologic treatments form the foundation for managing FMS and it is recommended that nonpharmacologic therapies be used in managing FMS patients [Carville *et al.* 2008]. While nonpharmacologic treatments used to treat FMS vary widely, those with proven efficacy in FMS symptoms include graduated aerobic and resistance exercise, education, psychological, physical, and manual therapies [Thieme and Gracely, 2009; Mannerkorpi and Henriksson, 2007]. While certain modalities, such as water aerobics in a heated pool or cognitive behavioral therapy, are ideal for many patients, they are often not practical due to limited availability or cost. However, many sources of information exist that allow patients to perform self-directed treatments at little or no cost within their own homes. The combination of education, aerobic, and resistance exercise has been shown to be superior to the use of any of these therapies in isolation [Rooks *et al.* 2007], so combination therapy utilizing these approaches is recommended as outlined in Box 3. Daily stretching

Box 3. Online sources for patient educational information.

General exercise recommendations:
<http://www.nia.nih.gov/HealthInformation/Publications/ExerciseGuide/>

Stretching recommendations:
http://www.nia.nih.gov/HealthInformation/Publications/ExerciseGuide/04e_flexibility.htm

Aerobic exercise recommendations:
http://www.nia.nih.gov/HealthInformation/Publications/ExerciseGuide/04b_endurance.htm

Resistance exercise recommendations:
http://www.nia.nih.gov/HealthInformation/Publications/ExerciseGuide/04c_strength.htm

Sleep hygiene recommendations:
<http://www.stanford.edu/~dement/howto.html>

General fibromyalgia Information
<http://www.knowfibro.com>

Fibromyalgia support groups and general fibromyalgia Information
<http://www.FMaware.org>

Arthritis foundations programs and general fibromyalgia information
<http://www.arthritis.org>

upon awakening is recommended combined with alternating days of aerobic and resistance exercise performed for 30 minutes six days a week. An excellent source for exercise recommendations is the National Institute on Aging website (<http://www.nia.nih.gov>) which provides stretching (http://www.nia.nih.gov/HealthInformation/Publications/ExerciseGuide/04e_flexibility.htm), aerobic (http://www.nia.nih.gov/HealthInformation/Publications/ExerciseGuide/04b_endurance.htm) and resistance (http://www.nia.nih.gov/HealthInformation/Publications/ExerciseGuide/04c_strength.htm) exercises. To maximize compliance and limit worsening of symptoms, it is recommended that patients begin with *very* light activity and gradually increase both the intensity and duration of exercise. It is recommended that patients begin aerobic exercise using low-impact aerobic activities (e.g., walking or using elliptical or stationary bicycle machines) at 50–60% of the patient's age-adjusted maximum heart rate (calculated as 220 minus age) and resistance exercise using very light resistance bands or very small weights (2.5–5 lb). While many sources for FMS patient education exist, their quality can vary widely. Recommended online sources for FMS educational information include Know Fibro (www.knowfibro.com), the National Fibromyalgia Association (www.FMaware.org) and the Arthritis Foundation (www.arthritis.org). It is also recommended that all FMS patients follow sleep hygiene recommendations to help maximize sleep quality (available from www.stanford.edu/~dement/howto.html) [Kryger *et al.* 2005].

Pharmacologic treatments

FDA approved medications

Four general points should be considered before using pharmacologic treatments in FMS patients. First, primary disorders that can mimic FMS must be ruled out before symptomatic therapies are used including vitamin deficiencies, anemia, and metabolic, oncologic, psychologic, or inflammatory disorders. Second, since many FMS patients are hypersensitive to drug effects, medications should be started individually at low dose and slowly uptitrated and/or combined only if necessary to ensure tolerability. Third, since over half of FMS patients suffer from multiple medication intolerances [Slotkoff *et al.* 1997], clinicians must have great patience since multiple individual medications or medication combinations often need to be tried before finding a

regimen the patient will tolerate. Finally, while the focus of this review is on pharmacologic treatments, medications are only moderately effective in treating FMS symptoms in the majority of patients (pregabalin and duloxetine meta-analyses). Also, while some FMS patients may have an excellent initial response to pharmacologic therapy, many do not remain on medications in the long term due to the development of side effects or loss of therapeutic efficacy. Since FMS is typically a life-long disorder with disease exacerbations (so-called fibromyalgia ‘flares’) triggered by stressful life events, patients must develop strategies to manage their symptoms. Therefore, medications have a limited role in FMS treatment: reducing symptoms to allow patients to develop disease management strategies by participating in nonpharmacologic therapies including exercise, education, and cognitive behavioral therapies [Carville *et al.* 2008].

Since pregabalin (Lyrica), duloxetine (Cymbalta), and milnacipran (Savella) are FDA approved for FMS management, it is reasonable to consider these ‘anchor’ drugs analogous to methotrexate for treating RA. While all three drugs have shown similar efficacy in ameliorating pain, their ability to manage other FMS symptoms differ along with their pharmacodynamic and side-effect profiles, so this often makes one drug a better initial choice for an individual patient than the others. Since thorough, open-access reviews detailing the risks and benefits of using each drug for the management of FMS are available [Boomershine, 2010; Ormseth *et al.* 2010; Scholz *et al.* 2009], each is only briefly described here.

Pregabalin is an $\alpha_2\delta$ calcium channel antagonist that acts by limiting neuronal release of excitatory neurotransmitters [Boomershine, 2010]. It has many properties that make it amenable to combination therapy, including low protein binding, few drug–drug interactions, and negligible hepatic metabolism [Pfizer Inc., 2009]. Pregabalin has shown an ability to decrease sleep latency and modify sleep architecture by enhancing slow-wave sleep, making it a particularly good choice for FMS patients with sleep complaints [Hindmarch, 2005]. While the approved FMS dosage is 300–450 mg divided twice daily [Pfizer Inc., 2009], I recommend beginning pregabalin treatment with a single small dose (between 25 and 75 mg) in the evening and uptitrating in weekly intervals as dictated by

therapeutic effect up to a maximum of 225 mg. While many FMS patients respond to once-daily dosing at night, patients with significant peripheral neuropathy or allodynia often benefit from a second smaller dose in the morning. Pregabalin has multiple possible side effects including dizziness, somnolence, weight gain, and peripheral edema that are more prevalent as the dose is increased. For this reason, the minimum effective dose should be used for treatment. Pregabalin-treated patients should also be closely monitored for worsening of fatigue and/or fibrofog symptoms since these are common, especially in patients treated with pregabalin during the day. Since pregabalin is an adjunctive anti-epileptic medication, it should be discontinued gradually since abrupt stopping could precipitate seizures in susceptible patients.

Duloxetine and milnacipran belong to the serotonin–norepinephrine reuptake inhibitor (SNRI) class of antidepressants thought to improve FMS pain by increasing the activity of noradrenergic and serotonergic antinociceptive pathways [Ormseth *et al.* 2010; Scholz *et al.* 2009]. While both drugs have similar mechanisms of action, duloxetine is biased more toward serotonin-reuptake inhibition compared with milnacipran which is more noradrenergic-reuptake inhibition biased. Owing to these differences, the drugs differ in their therapeutic effects and each may be more beneficial for specific subsets of FMS patients.

Duloxetine is the recommended first-line pharmacologic agent for treating FMS patients with significant depression and/or anxiety symptoms since it is also FDA approved for these indications [Eli Lilly and Company, 2010]. While the indicated dose of duloxetine is 60 mg once daily [Eli Lilly and Company, 2010], starting with 20 mg in the morning is recommended with 20-mg dosing increases after 1–2 weeks only if necessary. This is because side effects increase with dose and many patients treated with 20 mg have significant symptom improvement [Russell *et al.* 2008]. Common side effects of duloxetine include nausea and decreased appetite which may make duloxetine a better choice for obese FMS patients. Duloxetine can also cause insomnia in some FMS patients, the reason morning dosing is recommended for most patients. However, some FMS patients experience somnolence when taking duloxetine and these patients should take it at night. Owing to its hepatic metabolism and drug–drug interactions,

duloxetine should be avoided in patients with significant hepatic or renal impairment and caution is advised when combining duloxetine with other agents. As with all serotonin-activating medications, duloxetine may increase risk of bleeding and/or suicidality and should be used with caution in patients with a history or at risk of these conditions.

Milnacipran is the recommended first-line drug for FMS patients with predominant fatigue or fibrofog symptoms since milnacipran can significantly improve these symptoms at indicated doses [Mease *et al.* 2009]. While milnacipran has been indicated for treatment of major depressive disorder in Europe and Japan for the past decade at a dose of 25 mg twice daily, its sole indication in the US is for management of FMS at indicated doses of 50 or 100 mg twice daily [Forest Pharmaceuticals Inc., 2009]. Use of a dose titration pack is recommended to gradually increase milnacipran dose to limit side effects. The dose titration pack recommends uptitration to 50 mg twice daily after 1 week by starting with 12.5 mg on day 1, 12.5 mg twice daily on days 2 and 3, 25 mg twice daily on days 4, 5, 6, and 7. However, side effects using this dosing scheme are common and include nausea, headache, constipation, dizziness, insomnia, hot flush, hyperhidrosis, vomiting, palpitations, increased heart rate, dry mouth, and hypertension. Patients may tolerate milnacipran better if titration is slowed using the dose titration pack to take a 12.5 mg tablet once daily in the morning for 5 days, then 25 mg once daily in the morning for 8 days, and then 50 mg once daily in the morning for 7 days before increasing to 50 mg twice daily. Milnacipran dose is only increased if necessary to manage patient symptoms, and milnacipran is available in 12.5, 25, 50, and 100 mg tablets to allow for dosing flexibility. While some patients respond to once-daily dosing, milnacipran trials have shown the majority of patients benefit more from twice-daily dosing [Vitton *et al.* 2004]. Milnacipran hepatic metabolism is negligible and its serum protein binding is much lower leading to fewer drug–drug interactions than with duloxetine. Milnacipran can also be used in patients with severe renal impairment, in contrast to duloxetine. As with all serotonin-activating medications, milnacipran use may increase the risk of bleeding and/or suicidality and should be used with caution in patients with a history or at risk of these conditions.

Given the differing therapeutic mechanisms and side-effect profiles of pregabalin and the SNRIs, synergy through a combination strategy may benefit patients who fail to respond to monotherapy with pregabalin or one of the SNRIs. Combination therapy with the SNRI venlafaxine (Effexor) and the $\alpha_2\delta$ calcium channel antagonist gabapentin (Neurontin) has been shown to improve symptoms of pain, fatigue, mood disturbance, and insomnia in neuropathic pain patients who had previously failed gabapentin monotherapy [Simpson, 2001]. While combination therapy was well tolerated in the neuropathic pain trial [Simpson, 2001], the potential for additive adverse effects in FMS patients is possible and randomized combination trials are needed to better understand the risks and benefits of combining pregabalin with the SNRIs. Since duloxetine and milnacipran work by similar mechanisms of action, combination therapy with these agents is not recommended.

Generic alternatives to FDA approved medications

While pregabalin, duloxetine, and milnacipran are the only medications FDA approved for the management of FMS syndrome, many patients cannot afford these brand-name medications. Fortunately, generic medications with similar mechanisms of action to the indicated drugs exist with efficacy in treating FMS, which can instead be used in these patients. Gabapentin (Neurontin), an $\alpha_2\delta$ calcium channel antagonist with the same mechanism of action as pregabalin, has shown efficacy in treating FMS in a single open-label trial [Arnold *et al.* 2007]. The median effective gabapentin dose in the trial was 1800 mg/day divided three times daily, and gabapentin improved pain and global FMS symptoms as well as sleep. Owing to frequent somnolence, patients should be started on gabapentin using a single low dose (100–300 mg) at bedtime with additional small doses at breakfast and lunch made at weekly intervals if needed. Other side effects are similar to those seen with pregabalin including dizziness, fatigue, and weight gain. As with pregabalin, patients should be slowly tapered off gabapentin due to the risk of precipitating seizures in susceptible patients.

Since duloxetine and milnacipran act by inhibiting reuptake of both norepinephrine and serotonin, similar therapeutic effects can be achieved using antidepressants with SNRI activity. First-generation selective serotonin reuptake inhibitors

(SSRIs) have norepinephrine reuptake inhibition at higher doses. Fluoxetine at a mean dose of 45 mg/day has been shown to significantly improve FMS symptoms [Arnold *et al.* 2002]. Amitriptyline, a tricyclic antidepressant (TCA) that provides balanced reuptake inhibition of serotonin and norepinephrine, has been shown in multiple meta-analyses to be effective in patients with FMS [Nishishinya *et al.* 2008; Uceyler, 2008]. However, a common problem with gabapentin, SSRI or TCA monotherapy in treating FMS is medication intolerance of the high doses typically required for efficacy. One way to improve tolerability is through the use of combination therapy. As stated previously, the combination of gabapentin with the SNRI venlafaxine has shown synergy in treating FIBRO symptoms in patients with neuropathic pain [Simpson, 2001]. The combination of amitriptyline 25 mg at night with fluoxetine 20 mg in the morning provides synergy for treating FMS symptoms with minimal side effects [Goldenberg *et al.* 1996].

Medications for management of specific FIBRO symptoms

While some FMS patients have good response to all FIBRO symptoms using the ‘anchor’ medications described above, many fail treatment or continue to have a significant FIBRO symptom despite good response in others. In the following section, we describe the use of medications to manage specific FIBRO symptoms. However, clinicians should be warned that all uses described are off-label and limited published data exists for the use of these agents in treating FMS.

Fatigue and fibrofog treatment with wakefulness-promoting agents and stimulants

Many FMS patients experience debilitating fatigue symptoms which manifest physically as severe exhaustion and mentally as ‘fibrofog’ with difficulties in memory and concentration. While long-term management of fatigue in FMS should rely on improving fitness through graduated aerobic and resistance exercise, stimulants and wakefulness-promoting agents can improve symptoms of fatigue in FMS patients. Modafinil (Provigil) is a wakefulness-promoting agent pharmacologically distinct from stimulants and currently FDA-approved for the treatment of somnolence associated with obstructive sleep apnea, narcolepsy, and shift-work syndrome [Kumar, 2008]. Modafinil has shown efficacy in

improving fatigue associated with multiple disorders, and three published reports have shown it can improve fatigue in FMS patients [Schwartz *et al.* 2007; Pachas, 2003; Schaller and Behar, 2001]. Effective doses in FMS patients ranged from 50 to 400 mg/day given primarily as a single morning dose but with a second, smaller dose added at noon if fatigue symptoms returned late in the day. Modafinil affects multiple cytochrome P450 isoenzymes and has the potential for interacting with numerous drug classes. Dose reductions should be considered in the elderly and patients with hepatic or renal disease. While modafinil is structurally distinct from stimulants, its adverse effects are shared with the stimulants and patients with insomnia, hypertension, and anxiety disorders should be closely monitored for worsening of their signs and symptoms [Kumar, 2008]. Armodafinil (Nuvigil), is a newer and longer-lasting enantiomer of modafinil [Cephalon, 2010]. Armodafinil shares the same FDA indications with modafinil and, while no published data exists, is expected to have similar efficacy in treating FMS fatigue but with the benefit of once-daily dosing. It is important to note that all wakefulness-promoting agents and stimulants have addiction potential. Use of these medications in patients with a history of addiction to alcohol or drugs is strongly discouraged, and urine drug screening both before and during treatment is encouraged. Also, given the prevalence of bipolar disorder in patients with FMS symptoms [Wallace and Gotto, 2008], it is recommended that patients be screened for bipolar disorder with the Mood Disorder Questionnaire [Hirschfeld *et al.* 2000] prior to beginning treatment with stimulants or wakefulness-promoting agents and be closely monitored for the development of mania during treatment.

Since they are not indicated for FMS management, both modafinil and armodafinil can be difficult to obtain under insurance coverage and they are expensive, limiting their use for most patients. For these FMS patients, stimulants may be considered for managing fatigue and fibrofog since they are inexpensive and often have few insurance restrictions for their use. Since FMS patients have similar cognitive deficits to those seen in adult attention deficit hyperactivity disorder (ADHD) patients [Glass, 2008], and adult ADHD patients with coexisting FMS have improvement in their FMS symptoms when treated with stimulants for their ADHD [Young and Redmond, 2007], it is reasonable to use

stimulants in an analogous manner for treating FMS as for ADHD. Since excellent reviews for the management of adult ADHD with stimulant therapies including discussions of methylphenidate, dexamethylphenidate, amphetamine salts, and atomoxetine have recently been published [Culpepper and Mattingly, 2008; Rostain, 2008], a thorough discussion of these agents will not be made here. However, if the practitioner elects to use stimulants I recommend a 'start low and go slow' approach with a small dose of short-acting stimulant given upon waking and an additional dose added at noon if necessary before once-daily extended release formulations are used in case patients have side effects. An example would be to start immediate-release methylphenidate at a dose of 5 mg once in the morning before adding a second dose at noon or increasing to 10 mg once or twice daily before transitioning to the 20 mg once-daily sustained release pill.

Insomnia treatment with sleep aids

Improving sleep quality is important for disease management in a majority of FMS patients. Over 90% of FMS patients have sleep problems, and disordered sleep has been implicated in FMS pathogenesis [Moldofsky, 1976, 1975]. It is recommended that all FMS patients be screened for underlying sleep disorders before treating with symptomatic pharmacologic therapies. Patients can be screened for the presence of obstructive sleep apnea-hypopnea (OSA) syndrome using Berlin Questionnaire criteria that include persistent snoring, daytime somnolence and the presence of hypertension or obesity [Netzer *et al.* 1999]. All patients at risk for OSA syndrome should be referred for formal sleep evaluation. Since one third of FMS patients have restless leg syndrome (RLS) [Yunus and Aldag, 1996], all should be screened for RLS using the four question International RLS Study Group criteria [Walters, 1995]. Patients with RLS should be treated for their RLS before other sleep medications are used. Pramipexole and ropinirole are dopamine agonists currently FDA approved for treating RLS and both have demonstrated efficacy in managing FMS [Holman and Myers, 2005; Holman, 2003]. It is recommended that dopamine agonists be started at low dose (0.125 mg for pramipexole and 0.25 mg for ropinirole) 2 hours before bedtime and gradually increased in weekly intervals until RLS symptoms resolve or patients become intolerant. While the recommended maximum daily doses

for RLS treatment are 0.5 mg for pramipexole and 4 mg for ropinirole, higher doses are often needed to improve FMS symptoms with a mean dose of 4.5 mg for pramipexole and 6 mg for ropinirole [Holman and Myers, 2005; Holman, 2003]. Owing to the high cost of pramipexole and ropinirole, generic carbidopa/levodopa (25 and 100 mg, respectively) combination tablets can be used to treat RLS in FMS patients who cannot afford the indicated medications.

If FMS patients have difficulty falling asleep, FDA approved pharmacologic therapies should be considered after patients fail psychological and behavioral insomnia treatment modalities [Morgenthaler *et al.* 2006]. While benzodiazepines have historically been the mainstay of insomnia therapy, due to their detrimental effects on sleep architecture, cognition, and addiction, potential use in FMS patients is not recommended. Nonbenzodiazepine FDA approved therapies for insomnia, including ramelteon (Rozerem) and eszopiclone (Lunesta), are recommended. Ramelteon is a selective melatonin receptor agonist taken as a single, 8 mg tablet 30 minutes before bedtime. Eszopiclone is a nonbenzodiazepine hypnotic taken as a 1, 2, or 3 mg tablet immediately before bedtime. Administration of both ramelteon and eszopiclone with fatty foods should be avoided since absorption is slowed and efficacy is decreased. As with all sedatives, patients should be closely monitored for worsening depression or suicidal ideation and use with other sedatives should only be considered with caution. While side effects with ramelteon are uncommon, eszopiclone can cause headache and an unpleasant taste that can limit use. Sedating antidepressants may also be beneficial for FMS patients with depressive symptoms, and are discussed in the next section.

While some FMS patients experience insomnia, others have nonrestorative sleep where they sleep well but do not wake feeling refreshed. This nonrestorative sleep phenomenon requires medications that improve sleep *quality*, not quantity [Moldofsky, 2008]. Pregabalin is the recommended first-line agent for patients with nonrestorative sleep since it can improve sleep architecture at doses FDA approved for managing FMS [Hindmarch *et al.* 2005]. However, improvements in sleep restoration with pregabalin are often transient, making pregabalin a poor long-term choice for many FMS patients.

While chlorpromazine (Thorazine) 100 mg at bedtime can increase slow wave sleep and improve pain and mood symptoms in FMS patients [Moldofsky and Lue, 1980], poor tolerability has limited its clinical use. Quetiapine (Seroquel), an atypical antipsychotic agent known to enhance sleep architecture [Cohrs *et al.* 2007], improves sleep quality and numerous other FMS symptoms at doses of 25 and 100 mg per day [Hidalgo *et al.* 2007]. Since quetiapine doses of 100 mg per day have been associated with increased periodic limb movements, the lowest effective dose should be used. Sodium oxybate (Xyrem), currently FDA approved for cataplexy management, improves sleep and other FMS symptoms at a dose of 6 mg given half at bedtime and half 4 hours later [Scharf *et al.* 2003]. However, sodium oxybate use is tightly regulated due to its significant abuse potential and routine clinical use cannot be recommended at this time.

Blues treatment with antidepressant and anxiolytic medications

Identification and treatment of mood disorders is important in FMS treatment since one third of FMS patients complain of major problems with depression and/or anxiety that can severely hamper disease management and significantly increase suicidality risk [White *et al.* 2002; Ratcliffe, 2008]. Since duloxetine carries FDA indications for not only FMS management but also major depressive disorder and generalized anxiety disorder [Eli Lilly and Company, 2010], it is the recommended first-line treatment for patients with mood disorders. While daily doses of duloxetine as high as 120 mg are often used to treat mood disorders, doses >60 mg per day are poorly tolerated by FMS patients and not recommended [Russell *et al.* 2008]. While milnacipran has had an indication for treating major depressive disorder in Europe and Japan for the past decade, it lacks this indication in the US and therefore cannot be recommended as a first-line treatment for depressed FMS patients. Venlafaxine is a generic SNRI with efficacy in FMS management at 75 mg per day that is a reasonable alternative in patients who cannot afford branded SNRIs [Sayer *et al.* 2003]. Older SSRIs, including fluoxetine and paroxetine, have efficacy in FMS because they also inhibit norepinephrine reuptake at high doses (i.e. 40–80 mg per day), but these doses are often poorly tolerated [Clauw, 2008]. SNRI or SSRI medications should be not be rapidly discontinued as rebound increases in

depression and/or discontinuation symptoms such as anxiety, dizziness, confusion, headache, lethargy, insomnia, tinnitus, and seizures can occur.

Sedating antidepressants can be particularly beneficial for depressed FMS patients with insomnia. TCAs, including amitriptyline and the structurally related cyclobenzaprine (Flexeril), have long been used to treat pain and insomnia with low doses in the evening (5–10 mg cyclobenzaprine or 10–50 mg amitriptyline). While intolerance to high doses often makes TCA monotherapy insufficient to manage mood disorders, combining low-dose amitriptyline 25 mg at night with fluoxetine 20 mg in the morning can provide synergy for treating FMS symptoms with minimal side effects [Goldenberg *et al.* 1996]. Mirtazapine (Remeron) enhances serotonergic and noradrenergic neurotransmission via a novel mechanism that may allow use in patients who do not tolerate traditional SNRIs. Doses of 15–30 mg at night can improve symptoms of pain, insomnia, fatigue, and depression in FMS patients [Samborski *et al.* 2005]. Somnolence with mirtazapine is inversely proportional to dose, so patients with excess sedation at 15 mg should increase the dose to 30 mg. As the most sedating second-generation antidepressant, trazodone (Desirel) is best suited for patients with insomnia refractory to other drugs. While no studies using trazodone to treat FMS patients exist, an evening dose of 100 mg has been shown to improve sleep architecture in patients with somatoform pain disorder [Saletu *et al.* 2005].

Rigidity treatment with muscle relaxants

Stiffness of muscles and joints is problematic for the majority of FMS patients [Wolfe *et al.* 1990]. The etiology of these symptoms remains unknown, but likely results from inactivity and deconditioning combined with the CNS abnormalities thought to underlie FMS. Managing stiffness is important so that patients can maintain employment and participate in physical activity that is vital for long-term FMS management. Stretching exercises that enhance range-of-motion and fitness such as yoga, tai chi, and qigong are recommended for managing stiffness in all FMS patients. Centrally acting muscle relaxants (MRs) can be helpful adjuncts in managing patients with significant stiffness. An excellent review that thoroughly describes the risks and benefits of MR use is available [See and

Ginzburg, 2008], so in this section we focus on the use of MRs in treating FMS.

Cyclobenzaprine (Flexeril) is the most widely used MR for treating FMS and has many properties that make it particularly well suited for this purpose. Structurally, cyclobenzaprine is a TCA and so it can improve mood and pain symptoms in addition to its improvement of stiffness. While sedation from cyclobenzaprine use can be problematic during the day, it can improve insomnia when used at night. A meta-analysis has shown cyclobenzaprine significantly improves pain, sleep, tenderness and global function in FMS patients while maintaining excellent tolerability [Tofferi *et al.* 2004]. Cyclobenzaprine can be particularly useful in managing FMS ‘flares’, but often requires 30–50 mg per day divided four times daily. A new extended-release formulation of cyclobenzaprine, Amrix, can be used at bedtime to allow for once-daily dosing [Cephalon, 2008], but many patients find it too sedating. FMS patients treated with cyclobenzaprine should be monitored for worsening fatigue, counseled to avoid other CNS depressants, and monitored for anticholinergic side effects (e.g. dry mouth, constipation, urinary retention). Tizanidine (Zanaflex) is a MR with similar sedative properties to cyclobenzaprine. Tizanidine is dosed starting with a 4 mg dose at night and can be used on an as-needed basis to a maximum of 36 mg per day. Along with anticholinergic side effects, tizanidine can also cause hepatotoxicity and laboratory monitoring is required making its use less attractive than cyclobenzaprine. Methocarbamol (Robaxin) and metaxalone (Skelaxin) are less sedating MRs that can be used in patients that do not tolerate cyclobenzaprine, but evidence for their effectiveness in managing FMS symptoms is limited. Benzodiazepines should be avoided in FMS patients due to addiction potential and worsening of sleep architecture. There is no evidence to support the use of antispasmodics (such as baclofen or dantrolene) in FMS, but patients with spasticity may benefit from these agents. Tramadol (Ultram) can also significantly improve FMS stiffness and is discussed in the next section.

Ow! Analgesic medications to treat FMS pain

While acetaminophen (Tylenol) is commonly used to treat FMS pain, evidence for its efficacy is sparse since placebo-controlled trials are lacking [Carville *et al.* 2008]. Personal experience has shown that the acetaminophen dose required to

treat FMS pain is often near the maximum recommended 4000 mg per day, and patients are noncompliant with the necessary frequency of administration. Assuming patients have normal renal and hepatic function, dosing with extended-release formulations can improve compliance, however, concerns of possible increased risk of hepatotoxicity have been raised for extended-release formulations of acetaminophen [Graudins *et al.* 1995]. Also, the majority of FMS patients prefer NSAIDs to acetaminophen [Wolfe *et al.* 2001]. While all NSAIDs have similar analgesic effects, evidence for the efficacy of NSAIDs in FMS management is lacking and, due to the risk of side effects, NSAIDs are not recommended as primary therapy for the treatment of FMS [Carville *et al.* 2008]. However, FMS patients with concomitant inflammatory conditions or osteoarthritis may benefit from NSAIDs since these conditions can serve as 'pain generators' that can worsen FMS symptoms.

Tramadol is a narcotic medication that combines a μ -opioid agonist and SNRI activities recommended for managing FMS [Carville *et al.* 2008]. One or two tramadol/acetaminophen 37.5/325 mg tablets taken four times daily have been shown to significantly improve pain, stiffness, and work interference in FMS patients [Bennett *et al.* 2005]. Common side effects of tramadol include nausea, pruritus, and constipation. While the risk of abuse and dependence with tramadol is low, it is still a concern. Since 97% of abuse cases occur in patients with a prior history of substance abuse [Cicero *et al.* 1999], patients should be screened for a history of drug abuse prior to receiving tramadol. Tapentadol (Nucynta) is a new narcotic medication similar to tramadol that combines μ -opioid receptor agonist activity with norepinephrine reuptake inhibition [PriCara, 2010]. Tapentadol is currently FDA indicated only for the relief of acute pain, and FMS trials are needed to determine whether it could be beneficial in managing FMS. Traditional narcotics should be avoided for FMS treatment since their efficacy is poor and it can be very difficult to wean patients off them due to the rebound pain phenomenon (analogous to the phenomenon of rebound headaches).

Conclusions

While multiple meta-analyses have shown FMS can be effectively treated and there are currently three medications FDA approved for FMS

management, effective FMS management requires an individualized treatment approach that can be challenging to provide in a busy clinical practice. Also, new ACR diagnostic criteria require quantification of symptoms of fatigue, fibrofog and sleep quality. The FIBRO System provides a rapid, symptom-based method for assessment and pharmacologic management of FMS suitable for use by clinicians in numerous settings. By providing a system that focuses on individualized symptom identification and management, the FIBRO System promotes an integrated, patient-centered assessment of disease that may improve delivery of care regardless of the patient's underlying disorder.

Conflict of interest statement

The author works as a consultant for Eli Lilly and Co., Forest Laboratories Inc., and Pfizer Inc. Dr Boomershine receives research funding from Pfizer Inc. The author reports no conflict of interest in this work.

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