Treatment of fibromyalgia: a changing of the guard

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Fibromyalgia remains one of the most common and enigmatic musculoskeletal disorders among patients with pain and, until recently, few effective treatments have been discovered. This review will briefly consider the rationale supporting traditional treatment options and their efficacy, including the role of exercise and pharmacotherapy. Juxtaposed with these common approaches to relieve fibromyalgia pain and fatigue are the promising new medications that are being developed, such as pregabalin, milnacipran, duloxetine, sodium oxybate, ropinirole and pramipexole. Outcomes from recent randomized trials will be reviewed and compared.

Few medical disorders generate as much controversy as fibromyalgia syndrome (FMS). Its enigmatic pathogenesis and plethora of ineffective treatment strategies confound physicians and frustrate afflicted patients and their families. Despite the introduction of the term fibrositis in 1904 by Gower [1], progress in understanding FMS has been slow. However, recent innovative strategies and broader investigation of its cause beyond a myopic focus on psychiatric or musculoskeletal research have finally led to a new expectation of improved treatment outcome.

Firm confidence in a diagnosis is essential before formulating and implementing an effective treatment strategy in any medical condition. For many clinicians, the diagnosis of FMS remains confusing despite validated criteria published by the American College of Rheumatology in 1990 (**Box 1**) [2]. While specific tenderness, or tender points, have been promoted as diagnostic evidence of this disorder, honest debate and, at times, unruly skepticism, is evident even among rheumatologists. While helpful as inclusion criteria for research studies, fibromyalgia tender-point intensity can still vary from day to day in clinical practice, leading to diagnostic uncertainty. Nevertheless, clinicians can readily recognize and attempt to treat the common presentation of chronic, unexplained, widespread pain, tenderness and fatigue of fibromyalgia.

There is no consensus regarding pathogenesis, but an abnormality of centrally mediated pain processing has gained greater acceptance [3]. Functional magnetic resonance imaging (fMRI) [4] and pain-testing studies [5] have significantly strengthened this concept of centrally amplified pain perception. Observations of abnormal sleep-stage architecture [6] and induction of FMS symptoms with specific disruption of deep, non-rapid eye movement (nREM), stage IV sleep [7], have encouraged consideration of how sleep affects a variety of CNS functions influencing pain, fatigue and cognitive behavior. Sophisticated measurements of autonomic regulation with validated tools, including heart rate variability and tilt-table testing, have increased the awareness that patients with FMS fail to maintain normal sympathetic homeostasis [8–14]. In turn, perturbed sleep, psychiatric arousal (e.g., post-traumatic stress disorder, bipolar disorder and anxiety disorder), peripheral vasomotor tone, cardiac rhythm and bowel motility focus future research directly on new autonomic mechanisms that may lead to an improved understanding of FMS.

Almost 85% of FMS cases occur in women, but men are often undiagnosed. In fact, the divergent presentation of FMS in men compared with women has been well reported [15]. Pain and muscular spasm are generally more diffuse and vague in men. It appears that the hallmark diagnostic finding in FMS, 11 of 18 specific tender points, becomes apparent to the clinician and male patients much later in its clinical course. Response rates (RRs) to a variety of pharmacologic options are also less robust in men. The cause of these gender differences in presentation and response is uncertain, but may relate to behavioral differences, comorbidities or hormonal variations, including clinically amenable testosterone deficiency in men receiving chronic opioids.

The variability and unpredictability of treatment response has fueled clinician skepticism regarding FMS as a specific disorder, and gender differences also enhance this debate. Some

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future medicine

Box 1. The 1990 American College of Rheumatology criteria for the classification of fibromyalgia*.

- History of widespread pain. Definition:
  - Pain is considered widespread when all of the following are present:
  - Pain in the left side of the body
  - Pain in the right side of the body
  - Pain above the waist
  - Pain below the waist
  - In addition, axial skeletal pain (cervical spine or anterior chest or thoracic spine or low back) must be present. In this definition, shoulder and buttock pain is considered as pain for each involved side. Low back pain is considered lower segment pain
- Pain in 11 of 18 tender point sites on digital palpation. Definition:
  - Pain, on digital palpation, must be present in at least 11 of the following 18 tender point sites:
  - Occiput: bilateral, at the suboccipital muscle insertion
  - Low cervical: bilateral, at the anterior aspects of the intertransverse spaces at C5–C7
  - Trapezius: bilateral, at the midpoint of the upper border
  - Supraspinatus: bilateral, at origins, above the scapula spine near the medial border
  - Second rib: bilateral, at the second costochondral junctions, just lateral to the junctions on upper surfaces
  - Lateral epicondyle: bilateral, 2 cm distal to the epicondyles
  - Gluteal: bilateral, in the upper outer quadrants of buttocks in anterior fold of muscle
  - Greater trochanteric: bilateral, posterior to the trochanteric prominence
  - Knee: bilateral, at the medial fat pad proximal to the joint
  - Digital palpation should be performed with an approximate force of 4 kg. For tender point to be considered positive the subject must state that the palpation was painful. Tender is not to be considered painful

**For classification purposes, patients will be said to have fibromyalgia if both criteria are satisfied. Widespread pain must have been present for at least 3 months. The presence of a second clinical disorder does not exclude the diagnosis of fibromyalgia.*
Adapted from [2].

explain this paradox by considering FMS as a family of disorders and suggest defining FMS subsets to improve treatment outcomes for specific medications [16]. Unfortunately, the importance of comorbidities accompanying FMS and interfering with the treatment response has been given little consideration. Due to the general vagueness of fatigue and widespread pain as symptoms, most clinicians find teasing apart comorbidities particularly difficult in patients with FMS. Nevertheless, defining all accompanying causes of pain when treating FMS, such as arthritis, myelopathy, bursitis, tendonitis and migraine to name a few, is as important as identifying all risk factors for cardiovascular disease.

Pain and tenderness should be widespread in all four limbs and the axial spine. FMS is not a diagnosis of exclusion. One must be confident of the diagnosis and even more aware of comorbidities before considering treatment or evaluating a treatment response. Effective treatment of other causes of pain, stress, insomnia and autonomic dysfunction are equally important to the overall outcome as the choice of treatment for FMS.

Traditional treatment

Treatment of FMS has been effectively reviewed over the past few years, but these authors tend to favor more traditional approaches [17]. Until the 'magic bullet' is discovered, a balanced and comprehensive approach appears reasonable. Many different clinical specialties, including clinicians, chiropractors, naturopaths, massage therapists, physiotherapists, acupuncturists and psychologists, are inundated with patients searching for assistance. Often these modalities have provided a benefit.

Even among nonbelievers, most clinicians encourage exercise for patients with FMS. In 1988, a randomized trial of exercise demonstrated improvement in FMS pain threshold compared with flexibility training after 20 weeks [18]. Aerobic exercise [19], muscle strengthening, pool exercises [20] and spa therapy [21] have been found to be helpful. Many studies supportive of exercise vary in methodology and have significant limitations, including inadequate blinding and small sample size. However, a thorough review by Goldenberg and colleagues concluded that all patients with FMS should begin a cardiovascular program [22].

Analysis of these exercise studies reveals important limitations, including appropriate matching of specific therapies with heterogeneous patients and consistent adherence to exercise regimens [23]. In addition, while statistical significance was routinely achieved, the magnitude of the benefit (25–30% improvement) would not be considered robust. Most clinicians note that many of their patients with FMS fail to respond to exercise and many decline, or are unable to participate in such structured programs implemented at an experienced research facility. Regrettably, outcomes from many exercise trials simply do not translate into clinical practice.

The notion of exercise as an effective therapeutic options for FMS may have arisen from the observation that aerobic fitness may be preventative. In 1975, Moldofsky induced widespread pain suggestive of FMS by disrupting stage IV sleep with an auditory arousal for 4 nights in healthy college students [6]. Similar results did not occur when he repeated the experiment in fit military recruits or after disruption of REM sleep stages [7]. It is not clear how fitness preserves the benefits of stage IV sleep, but incorporation of aerobic exercise into an FMS treatment strategy remains popular.

Evidence that other nonpharmacologic remedies are effective is debatable, yet accepted by many clinicians. Soft-tissue injection with saline, local anesthetics and/or corticosteroids have been offered to patients with FMS, but placebo-controlled trials are unavailable. Acupuncture may reduce pain and analgesic requirements, but of three controlled studies [24–26], only one demonstrated a significant treatment benefit compared with placebo. Massage [27], ultrasound [28] and mineral baths [29] demonstrate a benefit for pain compared with placebo, but sustained meaningful improvement is unusual. Cognitive behavioral therapy has become a logical and helpful therapeutic approach for FMS [30], but many patients lack access to skilled therapists.

In 2004, Goldenberg and colleagues provided an evidence-based review of FMS management [22]. Their assessment of FMS studies based on study size, design and reproducibility is clearly the most thorough review of traditional treatment options for FMS to date. The greatest improvement in pain as an outcome variable compared with placebo was also reported by Goldenberg in 1996, in a study of fluoxetine (20 mg each morning) combined with amitriptyline (25 mg at bedtime) [31]. In this four-arm, 6-week, double-blind, crossover study, fluoxetine alone and amitriptyline alone improved pain and global function, but not fatigue or tender-point score. Combined, in the fourth arm, improvement in pain and fibromyalgia impact questionnaire (FIQ) score improved maximally (34%). Other studies with amitriptyline alone have confirmed a statistically significant decrease in FMS pain of approximately 30% [32]. Uncontrolled reports of serotonin (5-hydroxytryptamine [5-HT]) reuptake inhibitors, including sertraline [33], also suggest modest efficacy.

The second most frequently studied drug for the treatment of FMS is cyclobenzaprine. Dosed at 10–30 mg at bedtime, a meta-analysis of randomized studies demonstrated a benefit similar to amitriptyline [34]. Even doses as low as 1–4 mg at bedtime have demonstrated some analgesic efficacy and improved sleep-stage architecture [35]. Decreased levels of cerebrospinal fluid (CSF) neuroamines and substance P were reported by Russell with tizanidine 4–24 mg each day [36]. Carisoprodol dosed at 1200 mg/day decreased FMS pain compared with placebo in one study [37], but this result has not been confirmed. Other muscle relaxants are routinely used by clinicians without literature support.

Other classes of medication available to treat FMS have not demonstrated efficacy compared with placebo, including ibuprofen (2400 mg/day for 3 weeks) [38], naproxen (1000 mg/day for 6 weeks) [39] or prednisone (15 mg/day for 2 weeks) [40]. Temazepam (15–30 mg at bedtime for 12 weeks) demonstrated a modest statistical benefit [41], but alprazolam (0.5–3.0 mg at bedtime) was not superior to placebo [42]. Finally, a randomized 13-week trial of tramadol in combination with acetaminophen in 315 subjects demonstrated significant analgesic efficacy without any serious adverse effects [43].

A controlled trial of zolpidem (Ambien®, Sanofi-Synthelabo) may provide an important illustrative example. As a sedative hypnotic, zolpidem induces stage II rather than stage IV sleep. Subjects noted improved sleep duration and decreased sleep latency, but did not note improved FMS pain or fatigue compared with subjects receiving placebo [44]. Perhaps, if the medication effectively restored depleted stage IV sleep, an improvement in FMS symptoms may have been found.

Finally, although controlled trials are unavailable, the safety of clonazepam and lorazepam in 160 patients over 12 months was encouraging [45]. Patients did not escalate their bedtime dose (2.0 mg) or note significant adverse events, including withdrawal seizures. Contrary to other benzodiazepines, lorazepam and clonazepam effectively reduce restless legs syndrome (RLS) symptoms [46], a common source of arousal fragmenting sleep quality in patients with FMS.

New pharmacologic treatment options

Research in fibromyalgia has grown exponentially and new, meaningful treatment options are now at hand. Every clinician brave enough to accept patients with FMS recognizes many obstacles that interfere with successful treatment. However, embracing a team approach, identification of important comorbidities and consideration of novel medications are improving outcomes. In addition, large pharmaceutical companies are engaged in a race to discover an effective treatment. Pregabalin (Lyrica™, Pfizer), milnacipran (Dalcipran®, Cypress Bioscience), duloxetine (Cymbalta®, Eli Lilly), sodium oxybate (Xyrem®, Orphan Medical/Jazz Pharmaceuticals) and the dopamine agonists, ropinirole (Requip®, GlaxoSmithKline) and pramipexole (Mirapex®, Boehringer-Ingelheim) head the list of promising new therapies for FMS.

Pregabalin

In the largest controlled trial for FMS to date with 528 patients, pregabalin demonstrated significant improvement in pain score, sleep quality, fatigue and global measures of change [47]. Pregabalin, a precursor of gabapentin (Neurontin®, Pfizer), has analgesic, anxiolytic and antiepileptic effects in animals. It is a ligand for α2-δ subtype 1 and 2 receptors that adheres to voltage-gated calcium channels without affecting γ-aminobutyric acid (GABA) receptors [48]. Its activity is limited to neurons and it does not affect vascular calcium channels. Reduction of calcium influx at the neuron reduces release of substance P, glutamate and norepinepherine (NE) [49], which is thought to mediate its analgesic and anxiolytic actions.

Subjects were assigned (1:1:1:1) to placebo or one of three pregabalin doses (150, 300 or 450 mg/day) for 8 weeks. Demographics for each group were similar, including 90% women, 95% Caucasian, with an FMS duration of 8 years and mean pain score of 7 (range: 1 [no pain]–11[worst pain]). Patients discontinued prior medications and 77% completed the trial. All active arms improved within approximately 2 weeks and demonstrated sustained improvement through to week 8. Treatment with pregabalin was associated with statistically significant dose-dependent improvement. However, improvement in pain score was modest, even in the 450 mg arm (-0.93, 1–11 scale), and the p-value ($p = 0.0009$) reflected the large size of the study. Adverse events were common, but mild and transient, including dose-dependent dizziness (49% in the 450 mg arm vs 11% for placebo). Somnolence (28%), dry mouth (13%), peripheral edema (11%) and weight gain (7%) were also more common with pregabalin than placebo.

Pregabalin represents an extension of the neuropathic/anticonvulsant therapeutic approach to FMS. While psychiatric medications have been the mainstay of FMS pharmacopeia, many pain centers have addressed pain, and FMS specifically, as a neuropathic pain [50]. Narcotic analgesic efficacy for FMS has been mixed [51], but anticonvulsant medications have become very popular based on anecdotal evidence. In fact, off-label use of gabapentin has been so widespread in North America that the US Food and Drug Administration (FDA) fined its original manufacture, Warner-Lambert (Parke-Davis division, NJ, USA), for promoting unapproved uses [101]. To date, there are no FDA-approved medications indicated for the treatment of FMS, and evaluation of innovative off-label FMS therapies has become more difficult in the USA following this reprimand.

Milnacipran

The dual 5-HT and NE reuptake inhibitors (SNRIs) have received widespread attention as the next breakthrough for patients with FMS. While a controlled study of venlafaxine (Effexor®, Wyeth) was inconclusive [52], two case reports suggested a significant benefit at higher dosage [53,54]. Milnacipran, a popular antidepressant in Japan, is a novel SNRI that favors reuptake inhibition of NE over 5-HT. Reduction of pain in a variety of animal models may be related to the roles of NE and 5-HT in pain-modulating systems via the descending inhibitory pathways in the brain and spinal cord [55]. Tricyclic antidepressants mediate pain through 5-HT and NE neurotransmission and reduce FMS pain. This potential mechanism of pain amplification supports the consideration of SNRIs, which may be better tolerated than tricyclics, for the treatment of FMS.

In a 12-week, double-blind, placebo-controlled Phase II trial, 125 patients with FMS were randomized (3:3:2) to receive milnacipran once or twice daily (up to 200 mg/day) or placebo [56]. RR was defined as the percentage of subjects who achieved a 50% or greater pain reduction by visual analog scale on an electronic diary. For this outcome milestone, the intention-to-treat (ITT) analysis RR for twice daily dosing was 37%, 22% for once-daily and 14% for placebo. Only the twice-daily dose response was statistically superior to placebo ($p = 0.04$), but both twice- and once-daily outcomes on a secondary efficacy measure, the patient global impression of change (PGIC), were superior to placebo ($p = 0.003$). Multiple components of the FIQ and the short-form McGill pain questionnaire (SF-MPQ) also showed statistically significant superiority over placebo for both the once- and twice-daily dosing arms.

Adverse events were unremarkable. A Phase III trial has been completed, but details have not yet been reported. Milnacipran is not yet available in the USA, but this focus on SNRIs and the role of 5-HT and NE in pain modulation, and for FMS specifically, represents a hopeful and increasingly popular approach.

Duloxetine

Two large controlled trials of duloxetine have been recently reported in patients with FMS, demonstrating interesting results. Duloxetine is a SNRI approved by the FDA in 2005 for the treatment of major depressive disorder and neuropathic pain associated with diabetic peripheral neuropathy. Its inhibition of 5-HT and NE reuptake is relatively balanced without interacting with opioid, muscarinic, histamine-1, α_1-adrenergic, dopamine, 5-HT1A, 5-HT1B, 5-HT1D, 5-HT2A and 5-HT3C receptors. Once again, in animal models, this SNRI reduced pain behavior and did so with greater potency than venlafaxine, amitriptyline or desipramine.

These two trials illustrate important issues in FMS research. The first trial, reported in 2003, randomized (1:1) 207 subjects to duloxetine 60 mg twice daily for 12 weeks or placebo [57]. Demographic variables were equally distributed in the two arms and included 87% women (85% Caucasian), with 38% having major depression. The coprimary outcomes were FIQ total score (0–80) and FIQ pain subscore (0 [no pain]–10 [severe pain]).

Compared with placebo, duloxetine reduced total FIQ significantly (-5.53, 95% confidence interval [CI]: -10.43, -0.63 [$p = 0.027$]), but did not reduce the FIQ pain subscore ($p = 0.13$). Many other secondary measures of pain were found to be statistically improved, including the brief pain inventory (BPI), PGIC, number of tender points, FIQ stiffness subscore and several quality of life measures. A subanalysis revealed that men with FMS failed to respond to duloxetine, and that comorbid depression did not influence FMS treatment response. Reported adverse events were typical of SNRI therapy and included insomnia, dry mouth and constipation more frequently than placebo. Duloxetine intolerance was mild-to-moderate and did not lead to significant withdrawal from the study.

The study was repeated with the exclusion of men, the primary outcome was changed and the sample enlarged to favor a statistically significant treatment response [58]. The FIQ became a secondary outcome measure and the BPI became the primary outcome. In this new 12-week study, 354 women with FMS were randomized (1:1:1) to receive duloxetine 60 mg daily, 60 mg twice daily or placebo. Pain decreased significantly in subjects treated with duloxetine (daily and twice daily) compared with placebo ($p < 0.001$), as assessed by the BPI. RR was defined as a 30% (rather than 50%) reduction in pain and was achieved by 55% in the daily arm, 54% in the twice-daily arm and by 33% in the placebo arm. The size of the study ensured that these differences were statistically significant. The authors' conclusion, that duloxetine is an efficacious and safe treatment for FMS, is not unreasonable. However, scrutiny of the two study designs, including exclusion of nonresponders (men) and changing to a more favorable outcome variable emphasizes the importance of careful review of study design.

Sodium oxybate

A third treatment approach for FMS focuses directly on sleep physiology and is based on the importance of α-wave fragmentation of stage IV sleep more than on SNRI- or anticonvulsant-mediated modulation of pain neurotransmission. Diminished slow-wave sleep has been identified as an important feature in FMS and different types of α-wave intrusion of stage IV sleep have been identified [59,60]. Sodium oxybate is a commercially available form of γ-hydroxybutyrate (GHB), a naturally occurring CNS

metabolite primarily found in the hippocampus and basal ganglia. It is the only compound known to increase growth hormone secretion and deep, slow-wave stage IV sleep and is FDA-approved for the treatment of cataplexy in patients with narcolepsy.

A double-blind, crossover trial of sodium oxybate in 24 patients was conducted over 1 month intervals with a 2-week washout period [61]. A total of 18 subjects completed the trial of sodium oxybate (6.0 mg at bedtime) compared with placebo and were monitored by polysomnogram (PSG), tender-point index and subjective measurements of improvement in daily diaries. A variety of pain and fatigue scores improved by 29–33% in the active arm compared with 6–10% in the placebo arm ($p < 0.005$). Tender-point score decreased by 8.4 points with sodium oxybate compared with an increase of 0.4 points in the placebo arm ($p = 0.008$). PSG measures of inappropriate CNS arousal, including α-intrusion, sleep latency and REM decreased with treatment, while stage III and IV slow-wave sleep increased compared with placebo ($p < 0.005$).

This study provided preliminary yet compelling evidence that FMS pain and fatigue improve with increased slow-wave sleep and decreased α-wave intrusion. A larger, multicenter, controlled study has recently been completed and should be reported soon. The therapeutic role of restoring stage IV deep sleep to address FMS symptoms provides another important approach quite different from treating FMS with analgesics, anticonvulsants or SNRIs. Based on Moldofsky's landmark sleep deprivation studies [6,7] and these sodium oxybate results, a renewed emphasis on the restoration of normal sleep-stage architecture has gained more attention as a primary, rather than secondary, therapeutic goal.

Ropinirole

Most FMS reviews do not mention dopamine agonists (e.g., ropinirole and pramipexole), as initial reports were anecdotal until late 2004. These medications were FDA-approved for the treatment of Parkinson's disease in 1997 and the reasoning behind their use is far afield of traditional approaches to FMS. Ropinirole is a dopamine receptor agonist with specificity for the dopamine $(D)_2$ and $_3$ subreceptors (D_2, D_3). It is metabolized in the liver by the cytochrome P450 (CYP)C1A isoenzyme and has negligible affinity for muscarinic, acetylcholine, α_1, α_2, opioid or 5-HT receptors.

In 2003, the first use of ropinirole for the treatment of FMS was reported in an open-label assessment of 17 patients who noted a 64% decrease in tender-point pain score over 4 months at a mean dose of 6.0 mg at bedtime [62]. While the approved maximum dose for RLS is 4.0 mg at bedtime, the typical dose for Parkinson's disease is 1–8 mg orally three times daily. In 2004, in a controlled trial of 30 patients with FMS [63], 20 patients were randomized to ropinirole and ten were assigned to the placebo arm. Ropinirole was gradually increased over 14 weeks to 8 mg at bedtime. Although 45% of patients receiving ropinirole achieved a 50% or greater reduction in 10 cm visual analog pain score compared with 30% of placebo patients, the results of this small, pilot study were not statistically significant ($p = 0.31$). All other measures of efficacy (tenderness, fatigue and function) also showed a trend towards the efficacy of ropinirole compared with placebo.

The most common adverse events were typical intolerances seen with dopaminergic therapy, including mild-to-moderate nausea. Interestingly, sudden, uncontrolled daytime sleepiness (sleep attacks) as well as orthostatic hypotension, experienced by patients with Parkinson's disease treated with daily dopamine agonists, were not seen in this FMS trial. Another controlled FMS trial with a new delayed-release ropinirole formulation dosed at bedtime has been completed in Europe, but results are not yet available.

The rationale for using a dopamine agonist begins with a greater appreciation of the higher incidence of RLS in patients with FMS (31%) compared with normal controls (3%) [64]. In May 2005, ropinirole became the first and only medication approved for the treatment of RLS by the FDA. This RLS arousal inhibits deep sleep and ties in with the Moldofsky findings. While sedating medications are commonly offered to promote deep sleep by overwhelming arousal in FMS, the dopamine agonist was intended to reduce arousal fragmenting normal sleep.

Interestingly, dopamine agonists are not sedating and their mechanism of action in FMS is under investigation. Abnormal sympathetic arousal has been documented in FMS, and these patients maintain poor autonomic homeostasis. Excessive fight-or-flight responses as well as specific arousals such as intense chronic pain, frustration, post-traumatic stress disorder and anxiety have been well documented in FMS. Any of these arousals can chronically disrupt deep, restorative sleep.

D_3 receptors are primarily found in the limbic system, including the hippocampus, but not in the sympathetic arousal centers in the brainstem. The hippocampus attenuates and balances sympathetic arousal [65]. Inadequate dopaminergic control of autonomic drive from the hippocampus has been suggested as a fundamental issue in FMS pathogenesis [66]. In fact, preliminary magnetic resonance imaging (MRI) volumetric assessment has demonstrated hippocampal atrophy in patients with FMS compared with normal controls [67,68]. Consequently, a medication capable of decreasing RLS and restoring normal hippocampal dampening of brainstem autonomic arousal would be a logical therapeutic option for FMS.

Pramipexole

Although pramipexole is indicated only for the treatment of Parkinson's disease by the FDA, it also effectively reduces RLS [69]. Its profile is similar to that of ropinirole, except that it is renally metabolized and has mild affinity for central adrenergic α-$_2$ receptors (the target of tizanidine and clonidine) in addition to D_2 and D_3 receptors.

Following two positive open-label reports [70,71], a controlled trial of pramipexole for FMS in 60 subjects (57 women, 3 men) was recently presented [72]. Over 14 weeks, subjects were randomized (2:1) to a weekly fixed dose escalation of pramipexole from 0.25 to 4.5 mg at bedtime or placebo. Significant reductions in visual analog pain, fatigue, total FIQ score and global function at week 14 were found. The mean pain score decreased by 36% in the active arm compared with 9% for placebo by ITT analysis ($p = 0.008$). A pain reduction of 50% or greater was seen in 42% of patients receiving pramipexole compared with 14% receiving placebo. All other secondary outcome measures trended better for the active arm, including tender-point index, Beck anxiety score and Hamilton depression scale, without achieving statistical significance.

The most common adverse event was nausea, occurring in 79% of the active arm and 71% of the placebo arm. Nausea did not lead to discontinuation of pramipexole and was addressed by concomitant use of proton pump inhibitors. A mean weight gain of 3 lbs was seen in the placebo arm, while 40% of patients in the active arm noted 5–25 lb weight loss at week 14 ($p = 0.001$). Transient increased anxiety (14%) and vomiting (16%) were seen in the active arm but were not reported in the placebo arm. One episode of transient amnesia (< 24 h) required hospitalization for evaluation, but the patient fully recovered and completed the trial (double-blinded) 6 weeks later.

This study was very atypical for a FMS study. Subjects were allowed to maintain stable doses of other medications and psychiatric and pain comorbidities were allowed. A total of 53 of the 59 patients who completed the trial maintained stable doses of other medications, including 50% requiring daily narcotic analgesics. For any addition of a new medication during the study, the final untainted assessment was used as the final outcome. In addition, 30% of subjects were disabled, of whom one returned to work during the study (active arm).

Most FMS clinical trials only include patients without comorbidities who are willing to wash out all other medications and risk receiving a placebo for many months. This bias may affect interpretation of results and question the relevance of study conclusions for the clinician caring for patients with comorbidities and more severe FMS. It is unlikely that future pregabalin, milnacipran, sodium oxybate or ropinirole FMS trials will assess a similarly disabled and narcotic dependent FMS cohort, but perhaps a more traditional trial with pramipexole as monotherapy will be completed. Then, results from these different trials may be compared more fairly.

Conclusion

Potential new therapies for FMS from divergent approaches are developing at an unprecedented pace. A comparison of different medications is shown in **Table 1**. Scientific principles of FMS are becoming clearer as basic scientists study neuropharmacology and clinicians observe unexpected benefits and confirm them in randomized trials. Application of traditional, conservative treatments remains an option, but greater RRs have emerged with the use of medications capable of manipulating 5-HT, NE and dopamine. As with any review of randomized trials, only longer and larger studies can confirm or refute these early findings. However, a changing of the guard is clearly occurring in FMS treatment.

Future perspective

Competition among pharmaceutical companies to discover an effective treatment for the millions of patients with FMSa is already leading to dramatic changes in how the medical community views this cryptic disorder. Larger

Table 1. Comparison of new medications proposed for the treatment of fibromyalgia.

Medication	Subjects who achieved ≥ 50% reduction of pain (%)			p value
	(N/dose/duration)	Active arm	Placebo arm	
Pregabalin	(528 pts/450 mg/8 weeks)	29%	11%	0.001
Milnacipran	(125 pts/200 mg/12 weeks)	37%	14%	0.04
Duloxetine	(207 pts/120 mg/12 weeks)	28%	17%	0.06
Duloxetine	(354 pts/120 mg/12 weeks)	41%	23%	0.003
Sodium oxybate	(18 pts/6 mg/4 weeks)	NR	NR	NR
Ropinirole	(30 pts/8 mg/14 weeks)	45%	30%	0.31
Pramipexole	(60 pts/4.5 mg/14 weeks)	42%	14%	0.008

NR: Not reported; pts: Patients.

and bolder studies designed to test these hypotheses related to central pain processing, autonomic regulation and sleep stage architecture, enhance the scientific legitimacy of fibromyalgia.

As clinicians finally accept the existence of FMS, a broader array of individuals may become involved in finding a solution rather than expending energy to rationalize it away with mythology. Some of the most vociferous opponents of fibromyalgia are our most gifted clinicians and researchers. Dedicated fibromyalgia researchers are a small group who need to be expanded. Bickering over its existence only adds to the tragedy of fibromyalgia.

For a variety of medications, study of their impact on sleep stages and central pain processing is also expanding our knowledge of human physiology well beyond fibromyalgia. Scientists are discovering the nature of autonomic regulation and its varied impact on human function unrelated to pain and fatigue. Central limbic system influence on behavior, autonomic function, analysis of pain transmission and receptor dynamics are expanding our basic knowledge of the CNS and suggesting novel applications for many drugs currently used for a variety of different disorders.

Future fibromyalgia studies may begin to consider the impact of comorbidities on therapeutic outcome results. Exclusion criteria may become much more important after we begin to understand the mechanisms of action of these new medications. Just as diet affects insulin response in diabetics and multiple risk factors affect long-term outcomes in cardiovascular trials, the same is true for comorbidities with fibromyalgia. Untreated obstructive sleep apnea was excluded in the pramipexole and ropinirole trials and added as an exclusion criterion in a new sodium oxybate trial. Theoretically, the profound autonomic arousal of untreated obstructive sleep apnea could have a significantly negative effect on a fibromyalgia treatment paradigm designed to restore deep sleep stages.

Conversely, comorbidities could explain a positive treatment response. Cervical myelopathy, an autonomic arousal documented in animal models, was also excluded in the pramipexole trial. Hypothetically, such a significant arousal would limit dampening of autonomic fragmentation of normal sleep by a dopamine agonist. However, treatment of fibromyalgia with pregabalin might be enhanced in the same subset of patients with fibromyalgia and comorbid cervical irritation from cord compression. Stabilization of neural membrane activity might be a more effective treatment in this cohort, but such an evaluation of comorbidity was not a consideration in the pregabalin study.

Of course, all of these studies require validation through larger and longer trials but, unlike most medical challenges, future research must be rigorous indeed to overcome the emotionally charged and controversial nature of fibromyalgia. Yet while the challenge remains daunting, the potential application of eventual discoveries seems almost limitless. Even this modest success will be infectious. Interest in fibromyalgia research and acceptance of fibromyalgia as a genuine entity is expanding. As clinicians finally see meaningful clinical improvement and even recovery, an explosive potential emerges to encourage greater dedication to finally solving the fibromyalgia problem for patients and clinicians alike.

Information resources

- Fibromylagia clinical trials
  www.Clinicaltrials.gov
  (Accessed October 2005)

Executive summary

Fibromyalgia overview

- Fibromyalgia syndrome (FMS) is a specific musculoskeletal condition affecting 10 million Americans validated by specific criteria published by the American College of Rheumatology in 1990.
- Diagnosis is based on demonstration of widespread pain for at least 3 months and specific tenderness to gentle palpation symmetrically at tender points.
- FMS tender points are located at the occiput, trapezius, medial clavicle, lateral epicondyle, sacroiliac, greater trochanteric and medial knee regions.
- FMS is not a diagnosis of exclusion and important comorbid pain can complicate the presentation and require independent diagnosis and treatment.

Pathogenesis

- FMS symptoms have been reproduced after auditory fragmentation of stage III/IV sleep for 4 nights.
- Similar experiments in athletes and disruption of rapid eye movement (REM) sleep did not lead to FMS symptoms.
- Pain and tenderness have been attributed to amplified central pain processing, but the specific mechanism has not yet been identified.
- Abnormal regulation of autonomic control is a prominent feature of FMS and may explain the strong association of irritable bowel syndrome, irritable bladder, palpitations and vasomotor instability with FMS.
- Inadequate hippocampal attenuation of autonomic arousal fragmenting sleep appears to be a fundamental feature of FMS.
- Dopaminergic control of hippocampal function suggests a novel treatment approach to FMS.

Traditional treatment options

- Exercise, usually aerobic and carefully graded, consistently reduces FMS symptoms for some patients, but fails to address FMS pathogenesis.
- Controlled trials with acupuncture, massage, ultrasound, mineral baths and cognitive behavioral therapy demonstrate 30% reduced pain.
- Fluoxetine (20 mg), amitriptyline (25 mg), sertraline (50 mg), cyclobenzaprine (1–30 mg), tizanidine (4–24 mg), carisoprodol (1200 mg) and temazepam (15–30 mg) demonstrated a clinical benefit in controlled trials.
- Ibuprofen (2400 mg), naproxen (1000 mg), prednisone (15 mg) and alprazolam (0.5–3.0 mg) failed to benefit FMS patients in controlled trials. Zolpidem (5–15 mg) improved sleep, but not FMS pain.

Neuropathic approach

- Pregabalin, a precursor of gabapentin, is a ligand for $\alpha 2$-δ subtype 1 and 2 receptors affecting CNS voltage-gated calcium channels.
- In the largest FMS trial to date (528 patients), pregabalin (450 mg) significantly reduced FMS pain over 8 weeks.
- A total of 29% of patients receiving pregabalin achieved more than 50% decreased pain compared with 11% receiving placebo.

Psychiatric approach

- Milnacipran and duloxetine are mixed 5-hydroxytryptamine (5-HT) and norepinepherine reuptake inhibitors (SNRI) indicated for the treatment of depression.
- In a Phase II trial, 37% of patients with FMS receiving milnacipran noted a greater than 50% pain reduction compared with 14% receiving placebo. Adverse events were unremarkable.
- In two large trials, duloxetine did not reduce pain in men, but effectively reduced many FMS symptoms, including pain, in women. In the first trial, including men, 28% receiving duloxetine noted greater than 50% decreased pain compared with 17% receiving placebo.

Stage IV sleep induction approach

- Sodium oxybate induces stage IV sleep and is a commercial form of g-hydroxybutyrate (GHB), a naturally occurring CNS metabolite. It is indicated for the treatment of narcolepsy in patients with cataplexy.
- In a pilot controlled trial in 24 patients, sodium oxybate significantly increased stage IV sleep duration, decreased arousals fragmenting sleep and reduced FMS pain and fatigue by 29–33%.

Dopamine agonist approach

- Ropinirole and pramipexole are selective dopamine D_3 receptor agonists developed for the treatment of Parkinson's disease and commonly used for the treatment of restless legs syndrome.

Executive summary (Cont.)

- Much higher doses demonstrate efficacy for FMS when given at bedtime. Typical dopamine intolerances, including nausea, are noted and often require concomitant treatment.
- In a pilot trial in 30 patients, ropinirole (8 mg) safely reduced pain without achieving statistical significance. A large European study at higher doses has just been completed.
- Over 14 weeks, 42% of patients receiving pramipexole (4.5 mg at bedtime) noted more than 50% decreased pain compared with 14% receiving placebo. Significant improvements in fatigue, function and global assessment were also noted.
- The most common adverse events were mild nausea and weight loss in the pramipexole arm and nausea and weight gain in the placebo arm.

Future research

- Identifying the role of autonomic regulation of sleep stage architecture, the importance of hippocampal control of autonomic arousal and the mechanism of central amplified pain will be central themes.
- Combination therapy with these varied treatment approaches to FMS and identifying the influence of comorbidities will make the treatment of FMS more complex, but also more successful.

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