

PHARMACOLOGICAL THERAPY IN FIBROMYALGIA

(Adapted from: Rao, S.G., Bennett, R.M. "Pharmacologic therapies in fibromyalgia" In Pain Best Practice & Research Compendium 2007)

A wide variety of medications are used, with varying degrees of success, in the treatment of FMS, and several excellent articles have recently been published that review the efficacy of various agents in this syndrome (3-9).

The management of fibromyalgia patients involves a complex interplay between pharmacological management of pain and associated symptoms and the use of non-pharmacological modalities. As the elimination of all FMS symptoms (i.e. a cure) is not currently possible; the philosophy of management is symptom palliation and functional restoration. The presentation of fibromyalgia symptomatology is highly variable and each patient must have an individualized evaluation before deciding on an initial treatment plan (10). Regular follow-up and modification of the initial management strategy is usually required, depending upon the response pattern. As in other chronic pain states there is often an existential crisis that goes through distinctive phases from denial, searching for "the cure" to eventual acceptance. The early phases of management (usually the first 2 years) require more "hand holding," until the patient has come to terms with their new existence.

FIBROMYALGIA: SYMPTOMS AND COMORBID SYNDROMES

Chronic, widespread pain is the defining feature of FMS, as reflected in the FMS classification criteria adopted by the American College of Rheumatology in 1990 (11). Fibromyalgia patients display quantitative abnormalities in pain perception under experimental conditions, in the form of both allodynia (pain with innocuous stimulation) and hyperalgesia (increased sensitivity to painful stimuli) (12). Taken together, these data are suggestive of a state of sensitized pain perception in FMS (12).

FMS patients typically have a number of complaints beyond pain; a list of commonly associated symptoms is presented in Table 1. Fatigue is cited as a significant cause of morbidity for the vast majority of FMS patients (13). The potential causes of fatigue in these patients are manifold, but recent evidence suggests that sleep disturbances may play a particularly important role (13). Sleep disturbances in the form of nonrestorative sleep are reported to occur in over three-quarters of FMS patients (14). Sleep electroencephalography has demonstrated a number of abnormalities in the sleep architecture of FMS patients; particularly abnormalities in slow-wave sleep (SWS) (14). Other associated sleep syndromes seen commonly in FMS patients include periodic limb movements of sleep/restless leg syndrome and sleep apnea (reviewed in9).

Patients with FMS also frequently meet the diagnostic criteria for a number of other syndromes, particularly the class of conditions loosely referred to as the "functional somatic syndromes" (FSS), as reviewed by Manu (15). Such syndromes include irritable bowel syndrome (IBS), subsets of chronic low back pain, temporomandibular disorder, chronic fatigue syndrome, interstitial cystitis, certain headache syndromes, and multiple chemical sensitivity. These conditions are fundamentally characterized by a discrepancy between the degree of patient suffering and objective, clinical findings. As a group, FSS are typically more common in women than men, and

they share a number of clinical features, including pain, psychological distress/affective disorders, sleep abnormalities, and fatigue.

Low back pain represents one of the most common problems seen in primary care, with up to 70% of adults having at least one episode of such pain during the course of their lifetimes (16). Most episodes are acute and self-limited in nature. However, chronic low back pain (CLBP), as defined by pain persisting beyond 3 months, results in a great deal of morbidity and societal costs.

Irritable bowel syndrome (IBS) is a common disorder characterized by abdominal pain, bloating, and disturbed defecation (17). Irritable bowel syndrome remains the most common disorder encountered by gastroenterologists, representing nearly 50% of visits to gastroenterologists. The incidence of IBS is estimated to be 15% to 20% in the general population, with a strong female (18). Three subtypes of IBS are recognized—diarrhea, constipation, and discomfort/pain predominant—and classification significantly impacts therapy, as we will see below (18).

Increased levels of psychological distress resulting in psychiatric syndromes are a common accompaniment of many painful chronic illnesses (19). Approximately 20-30% of FMS patients have significant current depression (i.e., meeting DSM IV criteria) and about 60% have a lifetime prevalence of depressive illness (20). Finally, recent work suggests that post-traumatic stress disorder (PTSD) and other anxiety disorders may also represent an important cause of psychological distress in fibromyalgia (21, 22).

Temporomandibular joint disorders (TMJDs) are a cluster of common chronic orofacial pain syndromes of unknown etiology. Patients are most often classified into one of three groups: myofascial, joint disorders, and combined (23). Patients in the latter two groups are similar to those with other FSS, as they are more typically women and report greater pain and distress than patients with purely anatomical abnormalities (reviewed in 23). TMJDs are extremely common, with an overall estimated prevalence of 3.7% and 12% in men and women, respectively (24).

Chronic tension-type headaches (CTTH) represent one of the most common forms of chronic headaches (25). As reviewed in Redillas et al. (26), the CTTH are defined by the occurrence of bilateral headaches that are mild to moderate in intensity, occurring more 15 days/month for more than 6 months. The pain has a tightening or pressing quality that is not aggravated by physical activity. Associated symptoms include nausea, photophobia, and phonophobia. The prevalence of chronic daily headache is estimated at 2-3% in the general population.

Finally, other syndromes that are somewhat less frequently comorbid with FMS include chronic fatigue syndrome (CFS), interstitial cystitis (IC), chronic pelvic pain (CPP), and multiple chemical sensitivity (MCS) syndrome. CFS is characterized by severe fatigue, plus 4 of 8 of the following symptoms: myalgia, arthralgia, sore throat, tender neck, cognitive difficulty, headache, postexertional malaise, and/or sleep disturbance. The overall prevalence of this syndrome is estimated at 1% of the general population with approximately 70% of those affected being women (27). Interstitial cystitis (IC) is a chronic, debilitating disease characterized by bladder and pelvic pain, irritative voiding symptoms (i.e., urgency, frequency, nocturia, dysuria), and sterile

urine. Prevalence is estimated at 0.3% of the general population, with 90% of the patients being women (28). Multiple chemical sensitivity (MCS) is characterized by sensitivity to numerous environmental exposures, with resultant unexplained symptoms in multiple organ systems. Women appear to be more commonly affected, though overall prevalence data have not been compiled (27). Finally, as reviewed in Engel (29), unexplained chronic pelvic pain is common in women in the reproductive age group and results in significant disability and distress. The pathogenesis of such pain is poorly understood.

FIBROMYALGIA: TREATMENT STRATEGIES

Several recent publications have reviewed the current state of FMS therapy. Highlighted are more recent results from double blind, randomized, controlled trials that were not included in the previous reviews. It should be noted that no therapeutic currently holds an approval specifically for FMS. Further, the number of randomized, controlled trials published to date is relatively small compared to other chronic pain conditions such as neuropathic pain or even irritable bowel syndrome. This review will focus on the major classes of drugs used in the management of fibromyalgia and its associated problems.

Antidepressants

The majority of FMS clinical trials have involved antidepressants of one class or another. Trials studying the oldest class of agents, tricyclic antidepressants are most abundant, though several recent studies have focused on selective serotonin reuptake inhibitors and “atypical antidepressants” including dual reuptake inhibitors and monoamine oxidase inhibitors. Despite the multiplicity of antidepressant classes, practically all of the agents that are currently in clinical use in the United States either directly or indirectly increase neurotransmission mediated by the monoamine neurotransmitters, particularly serotonin (5-HT) and/or norepinephrine (NE; also called noradrenaline) ((2). These activities are thought to underlie the antidepressant activity of these compounds, and such activities also appear to be an important mechanism by which these compounds effect centrally-mediated analgesia (2).

Tricyclic Antidepressants (TCAs)

Most TCAs increase the concentrations of 5-HT and/or NE by directly blocking their respective reuptake. However, TCAs typically possess myriad other pharmacological activities, including the abilities to block certain cation channels as well as histamine-, acetylcholine-, and N-methyl-D-aspartate (NMDA)-mediated glutamatergic neurotransmission. Cation channel blockade can result in analgesia by generally decreasing neuronal excitability; indeed, this activity may underlie the analgesic efficacy of certain antiepileptic drugs. Increased NMDA receptor mediated glutamatergic neurotransmission has been implicated in the pathogenesis of chronic pain, and blocking this activity has been efficacious in relieving such pain in a variety of models and clinical states (2).

Unfortunately, the anticholinergic and antihistaminergic activities of TCAs contribute to the relatively poor side effect profile of these agents. This point may be particularly relevant to the FMS patient population, due to the relatively high prevalence of comorbid MCS. Despite these tolerability issues, the use of TCAs (particularly amitriptyline) to treat the symptoms of pain, poor sleep, and fatigue associated with FMS is supported by several

randomized, controlled trials (4, 9). Surprisingly, the story is less clear regarding the mood elevating effects of these agents in the context of FMS, perhaps as a result of the fact that most trials have evaluated sub-antidepressant doses of TCAs (4, 9). In most forms of major depressive disorder, however, the efficacy and remission rates of TCAs are equal or superior to those of other classes of agents, perhaps as a result of their effects on both serotonergic and noradrenergic systems (30). TCAs also have an established track-record in treating various forms of chronic pain, including the pain associated with other FSS. Double blind, randomized controlled trials support the use of TCAs in IBS (31), TMD (23), and CLBP (16), though the effect size in the latter appears to be small. Finally, while TCAs are not efficacious as acute treatment for CTTH, they are an effective form of prophylaxis (26).

Selective Serotonin Reuptake Inhibitors (SSRI's)

SSRIs have revolutionized the field of psychiatry, providing safe and effective treatment of common psychiatric conditions including major depressive disorder, anxiety, and social phobia. Much of their success is attributable to the fact that SSRIs display a much-improved side-effect profile compared to TCAs, which, in turn, is a result of their much higher degree of pharmacological specificity. As implied by their name, SSRIs primarily inhibit the reuptake of 5-HT, and they typically lack the extra-monoaminergic activities that characterize TCAs. The SSRIs fluoxetine, citalopram, and sertraline have each been evaluated in randomized, placebo controlled trials in FMS (32). The results of these trials have been somewhat inconsistent, leaving some debate regarding the relative efficacy of the SSRIs, especially in comparison to TCAs. Two studies have demonstrated positive efficacy for fluoxetine when compared to either placebo or amitriptyline in treating sleep, pain, fatigue, and depression (32, 33). However, a third study failed to demonstrate any significant improvement in pain, although mild improvements were noted in sleep and depression (34). Two placebo-controlled trials of citalopram have been performed. The first was convincingly negative, with citalopram failing to demonstrate any improvements in pain, fatigue, sleep, or mood (35). The second study demonstrated that citalopram significantly improved mood, though other outcome measures did not improve significantly (36). Finally, one study comparing sertraline to amitriptyline demonstrated that the two compounds were equivalent in producing significant improvements in pain, sleep, and fatigue. Taken together, SSRIs appear to be effective for treating certain FMS symptoms, particularly mood. However, their effect sizes on pain, sleep, and fatigue appear to be less robust in comparison to TCAs.

Despite the wide use of SSRIs within the general population, surprisingly few randomized, controlled trials assessing the efficacy of these agents in the FSS have been published. SSRIs do appear to be effective in CTTH prophylaxis (26). In CLBP, the use of SSRIs is controversial (16). Finally, in CPP, sertraline was found to be effective in improving mood, though no improvements in pain were noted (29).

Dual Reuptake Inhibitors (DRIs)

DRIs are pharmacologically similar to some TCAs in their ability to inhibit the reuptake of both 5-HT and NE, a feature that may improve their analgesic efficacy (reviewed in2). Importantly, DRIs differ from TCAs in being generally devoid of significant activity at other receptor systems, and this selectivity results in diminished side effects and enhanced tolerability (2). Venlafaxine is the only DRI currently available within the U.S., and its current labeled indications are depression and anxiety. Data support its use in the management of neuropathic

pain (37), and retrospective trial data demonstrate that this compound is effective in the prophylaxis of migraine and tension headaches as well (38). An open label study suggested venlafaxine is useful in treating multiple symptoms of FMS (39). However, these results were not replicated by a more recent randomized placebo controlled trial (40). One significant difference between these two trials was drug dosage: the study by Dwight et al. pushed each patient to their maximally tolerated dose or 375mg/day (mean 167mg/day), while the study by Zijlstra et al. had a single drug arm with a dose of 75mg/day. Data suggests that venlafaxine is primarily a 5-HT reuptake inhibitor at lower doses (i.e., < 150mg), with NE effects apparent only at higher doses (9).

Milnacipran is a DRI that is presently available in parts of Europe and in Japan for the treatment of depression. Milnacipran is unique among clinically available DRIs in its preferential blockade of NE reuptake over that of 5-HT; in addition, this compound is a low affinity NMDA antagonist (41). Milnacipran is presently in clinical development for FMS in the U.S., and the results of a Phase II clinical trial were recently announced (42). In a double-blind, placebo-controlled, randomized study, treatment with milnacipran resulted in statistically significant improvements in the pain, sleep, fatigue, and mood of patients with FMS.

Monoamine Oxidase Inhibitors (MAOIs)

Unlike TCAs and SSRIs, MAOIs increase monoamine levels by blocking their breakdown after release from the neuron. Non-enzyme-specific, irreversible, MAOI, such as phenelzine and tranylcypromine, have been on the market in the U.S. for many years as antidepressants, though concerns about potentially fatal interactions with certain foods and medications have limited their widespread usage (9). Moclobemide and pirlindole represent “second generation” agents that show improved specific and reversible binding compared to the older compounds. Both of these agents have been approved in Europe as antidepressants, though they are not presently available within the U.S. Preliminary studies with moclobemide in FMS have failed to demonstrate significant analgesic activity when compared to amitriptyline (43). However, a more recent study has demonstrated the efficacy of this compound in CFS, though effects were primarily limited to fatigue (44). The results of a randomized, double-blind, placebo controlled trial of pirlindole were more promising, with beneficial effects upon sleep, pain, fatigue, and mood (45). It is of interest to note that MAOIs show greater efficacy than TCAs in treating atypical depression, a particular depression subtype which is relatively common in patients with chronic pain conditions (46). Finally, while MAOIs have not been tested extensively in other FSS, they do appear to be effective in prophylaxis against CTTH (26).

Norepinephrine Reuptake Inhibitors (NRIs)

Reboxetine is an NRI antidepressant available in a number of European countries, though, it is currently unavailable within the US. A recent open-label trial of reboxetine in 25 FMS patients suggests this compound maybe useful for treating pain and fatigue (47), though more extensive follow-up studies are needed on this point. Another NRI—atomoxetine—has recently been introduced to the U.S. market for the treatment of attention-deficit hyperactivity disorder. However, no data of the efficacy of this compound in pain are presently available.

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs; including COX-2-selective agents) and acetaminophen are used by a large number of FMS patients (48). However, numerous studies have failed to confirm their effectiveness as analgesics in FMS, though there is limited evidence that patients may experience enhanced analgesia when treated with combinations of NSAID's and other agents (5). This phenomenon may be a result of the fact that painful, inflammatory conditions—including osteoarthritis, rheumatoid arthritis, and lupus—are frequently comorbid with FMS. NSAIDs have been found to be moderately effective in the treatment of CLBP (49). Well-controlled studies do not support the use of NSAIDS in TMJD, though some patients do obtain short term relief (24). Finally, it should be noted that NSAID overuse may result in chronic daily headaches (50).

Antiepileptic Drugs

The majority of the antiepileptic drugs (AEDs) increase the seizure threshold through sodium and/or calcium channel blockade or by increasing inhibitory neurotransmission; this mechanism of action appears to underlie their analgesic activity as well (reviewed in9). Indeed, these compounds are widely used in the treatment of various chronic pain conditions, including postherpetic neuralgia and painful diabetic neuropathy (reviewed in51). Pregabalin—an AED presently in clinical development—demonstrated efficacy in a phase II trial against pain, sleep disturbances, and fatigue in FMS patients (52). The precise mechanism of action of pregabalin and a related is unknown, although its analgesic activities may result from the agent's ability to block certain calcium channels (52). Neurontin, a compound with similar pharmacology to pregabalin, is specifically indicated for the treatment of postherpetic neuralgia and studies support its use in the symptomatic treatment of a variety of pain states as well as headache prophylaxis (26, 51). Another AED compound, clonazepam, has demonstrated efficacy in treating TMJD associated jaw pain (51) and is also a useful medication in the treatment of restless leg syndrome (53). However, the widely used AED phenytoin was found to have no effect in an IBS study (51).

Sedative-hypnotics

Sedative-hypnotic compounds are widely used by FMS patients (48). A handful of studies have been published on the use of certain non-benzodiazepine hypnotics in FMS, such as zopiclone and zolpidem. These reports have suggested that these agents can improve the sleep and, perhaps, fatigue of FMS patients, though their effects upon pain were not significant (5).

Several other agents typically classified as sedative-hypnotics have shown promise in the symptomatic treatment of FMS in open-label studies. Gamma-hydroxybutyrate (GHB), a precursor of GABA with powerful sedative properties, may be useful in improving fatigue, pain, and sleep architecture (9). Melatonin, a dietary supplement, was shown to improve sleep and reduce tender point counts (9). Pramipexole is a dopamine agonist indicated for Parkinson's disease that has also shown utility in the treatment of PLMS (4). Recent studies suggest that this compound may improve both pain and sleep in FMS patients (54). Finally, patients with significant anxiety symptoms, including PTSD or panic attacks, may benefit from the use of benzodiazepines,

particularly in the early stages of management while waiting for the effects of antidepressant medications to optimize (55).

Muscle relaxants

Cyclobenzaprine is a muscle relaxant that was originally shown to be of some benefit in the management of fibromyalgia in the mid-1980s (5). Although typically classified as a muscle relaxant, cyclobenzaprine shares structural and pharmacological similarities with the TCAs (2). The mechanism of action underlying cyclobenzaprine's muscle relaxing action is unclear, though it may be mediated by blockade of 5-HT₂ receptors (2). Data generally support its use in FMS, particularly in treating sleep and pain, and there is some data suggesting synergism when used with fluoxetine (5, 56). The major problems patients report with cyclobenzaprine are morning "hangover" and dry mouth, in this respect a recent report by Moldofsky on the efficacy of low dose cyclobenzaprine (1mg to 4mg) is of special note (57). Finally, while one study suggests that cyclobenzaprine is effective in treating IBS symptoms in the context of FMS (56), randomized, controlled trials specifically targeting other FSS have not yet been performed.

Tizanidine is a centrally acting alpha-2 adrenergic agonist that is FDA approved for the treatment of muscle spasticity associated with multiple sclerosis and stroke. Literature suggests that this agent is a useful adjunct in treating several chronic pain conditions, including chronic daily headaches and low back pain (4). A recent 8 week long, open-label study of 25 fibromyalgia patients receiving a total daily dose of 4 – 24 mg reported significant improvements in several parameters, including sleep, pain, and measures of quality of life (58). Of particular interest was the demonstration that treatment with tizanidine resulted in a reduction in substance P (SP) levels within the cerebrospinal fluid (CSF) of patients with FMS. SP is an excitatory neurotransmitter that is thought to play a role in pain perception (reviewed in 2), and multiple studies have confirmed elevated levels of SP in the CSF of patients with FMS.

Opiates

Typical opiate agonists like morphine act at some combination of the mu, delta, and kappa opiate receptors. These receptors are located throughout the CNS, and all three receptors appear to play a role in analgesia (2). A recent study has reported reduced levels of beta-endorphin in peripheral blood mononuclear cells of fibromyalgia, with the implication that fibromyalgia patients may have a suboptimal endogenous opioid system (59). Morphine and morphine-like compounds are widely used in many chronic pain states, including TMJD (24), and subsets of CLBP (49). Despite a continuing lip service against the use of opiates in fibromyalgia, a survey of academic medical centers in the US reported that opiates were used in about 14% of patients (48). The main problems related to long-term use of opioids are the effects on cognition, reduced motivation to pursue non-pharmacological treatment modalities, aggravation of depression and negative stigmatization by the medical profession and society in general (4). The usual cited concerns regarding addiction are now known to be unfounded – only occurring in about 0.5 percent of opioid treated chronic pain patients (4). All patients taking

opioids can be expected to develop dependency; this however is not the same as addiction, but implies that this class of medications cannot be abruptly stopped without the patient experiencing withdrawal symptoms.

There have been only a few controlled clinical trials for these agents in FMS. Interestingly, acutely administered IV morphine was not found to be effective in treating FMS pain (60). Tramadol is another widely used analgesic that has a unique mechanism of action: weak mu agonist activity combined with 5-HT/NE reuptake inhibition (4). Tramadol appears to be useful in treating the chronic pain associated with several conditions, including chronic daily headaches and low back pain (4). Three double-blinded studies have demonstrated the efficacy and tolerability of tramadol in the management of fibromyalgia pain, as an isolated compound (61, 62) and as combination with acetaminophen (i.e., "Ultracet") (63).

Other compounds

Finally, a few classes of agents that are not widely used clinically but that have shown promise in controlled trials bear mentioning: 5-HT₃ antagonists, NMDA antagonists, and growth hormone.

5-HT₃ antagonists

Anti-emetics that pharmacologically block serotonin 3 receptors (e.g., ondansetron) have been approved in the U.S. for several years. Tropisetron, another 5-HT₃ antagonist, has been tested extensively in FMS patients, and it has been found to be modestly effective for the treatment of pain and sleep disturbances, though only within certain dose ranges (4). As reviewed in Moynihan, 2002 (64), the 5-HT₃ antagonist alosetron (Lotronex™) has been shown to be of use in managing the pain and diarrhea in women with irritable bowel syndrome. Unfortunately, due to indiscriminate prescribing, some patients developing severe ileus, and there were several deaths; alosetron, was therefore withdrawn for the market in United States November of 2000. It was reintroduced by the FDA in June 2002, though its use is now strictly limited. Physicians wishing to prescribe alosetron must now register with the GlaxoSmithKline "Prescribing Program for Lotronex."

NMDA antagonists

As mentioned above, certain TCAs are known to be NMDA receptor antagonists, though their activity in this regard is relatively weak (i.e., they are low affinity agents) (2). Three studies have demonstrated that high-level NMDA receptor blockade (effected by the use of high affinity agents or large doses of low affinity compounds) can improve pain symptoms in FMS patients (60, 65, 66). However, such high-level blockade is associated with significant cognitive side-effects, thus potentially limiting utility of this approach.

Growth Hormone

Finally, it has been shown in numerous studies that FMS patients display a variety of neuroendocrine abnormalities, including low levels of insulin-like growth factor-1 (IGF-1; also known as somatomedin-C) (reviewed in 67). IGF-1 is a factor produced in the liver, primarily in response to GH secretion. Bennett *et al.* conducted a randomized, placebo-controlled double-blind study of the clinical effects of GH therapy in 50 women with FMS and pre-determined low IGF-1 levels (68). The GH-treated group achieved a significant improvement in FIQ scores and tender point counts at 9 months compared to baseline, whereas no significant

improvement was observed in the placebo group. Unfortunately, while GH therapy would appear to offer this subgroup of patients some symptomatic improvement, financial considerations limit the viability of GH as a long-term therapy in this population.

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