# Fibromyalgia Pain: Is It Treatable?

**Gordon D. Ko, MD, CCFP(EM), FRCPC, FABPMR, FABPM**

Patients with widespread pain are initially seen by the family physician, and subsequently referred to a specialist (usually a rheumatologist) to confirm the diagnosis, and to ensure that some other condition is not overlooked. Once a diagnosis is confirmed, the family physician should ideally provide continued care, but may be limited by knowledge and time constraints.[1]

## *Treatment Paradigms*

Treatment should target other symptoms in addition to pain, such as unrefreshing sleep, fatigue, and mood and cognitive impairments. The physician and patient need to agree on SMART goals (specific, motivating, attainable, relevant, tangible) that improve function: activities of daily living, return-to-work or school, and household and social responsibilities. The locus of control should shift to the patient participating more actively in self-management (even via internet resources).[2]

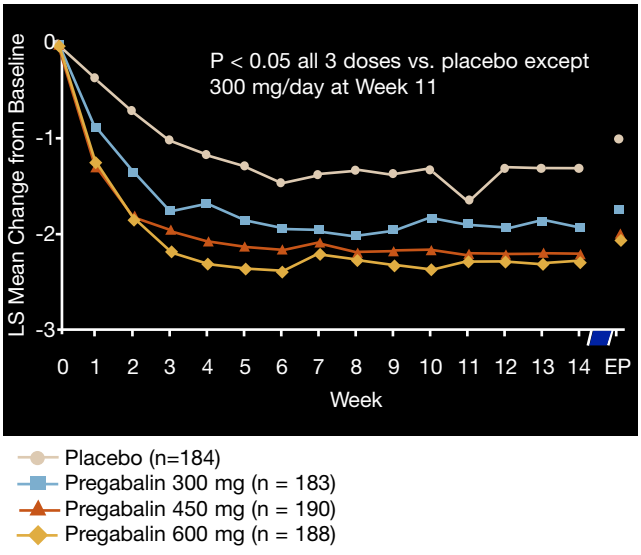


Figure 1: Pregabalin FMS Study: Significant Improvement in Pain[8]

Functional outcomes can be documented with the Brief Pain Inventory (BPI) or the revised Fibromyalgia Impact Questionnaire (FIQ),[3] although their use in clinical practice is limited.

Guidelines for management of fibromyalgia (FM) have been published by the American Pain Society (APS) in 2005,[4] the European League against Rheumatism (EULAR) in 2008,[5] and a German consensus group in 2009.[6] A Canadian task-force previously provided a clinical case definition with overview of published treatments.[7] A new eight member group headed by Dr. Mary-Ann Fitzcharles (which includes this author) will produce updated evidence-based guidelines and treatment algorithm later this year.

## *Pharmacological treatments*

As patients with FMS frequently report excessive sensitivity to medications, pharmacologic treatments should be introduced at a low dose, with a plan to gradually increase dosage to therapeutic levels. This way, better tolerability may be achieved and treatments are more likely to be continued.

Pharmacologic treatments for FMS have focused mainly on pain modulation, using drugs that affect peripheral/central sensitization, such as gabapentinoids (α-2-ligands), or that augment descending pain inhibitory mechanisms, such as antidepressant and dopaminergic agents. Current guidelines indicate strong evidence in support of tricyclic antidepressants (TCAs), dual serotonin and norepinephrine reuptake inhibitors (SNRIs), such as duloxetine and milnacipran, and α-2-ligands, such as pregabalin. At present, pregabalin and duloxetine are the

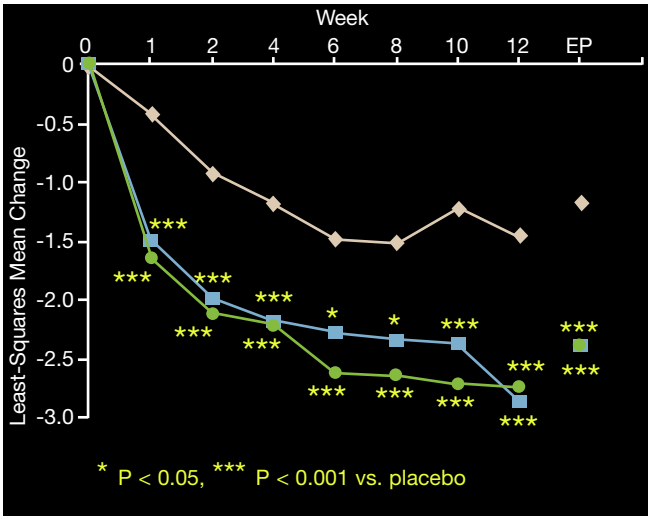


Figure 2: Duloxetine FMS 3-Month Phase III RCT
BPI Average Pain Severity vs. Time Course of Efficacy[9]

only pharmacological agents with a Health Canada-approved FM pain indication.

Amitriptyline is still the most commonly prescribed drug for FMS. Although relatively inexpensive and on most provincial formularies, use is limited by side effects (*e.g.*, weight gain, anticholinergic effects) and lack of sustained efficacy beyond two months.[10] Nortriptyline is an alternative with fewer side-effects, but less potency.

A recent meta-analysis found that the FMS-approved medications were superior to placebo for pain and other symptoms in FM, with the exception of pregabalin for depression, duloxetine for fatigue, and milnacipran (FDA-approved only) for sleep disturbance.[11]

Another meta-analysis of pregabalin and gabapentin trials found strong evidence for pain reduction, improved sleep and quality of life. There was some improvement in fatigue and anxiety. Pregabalin was effective at higher doses (300 to 450mg q.d.) based on monotherapy.[12] In clinical practice, particularly where polypharmacy is used, lower doses are often effective. Common side effects include dizziness, drowsiness (hence, begin with nighttime dosing only), and more rarely edema and weight gain (dose dependent). Both medications have no significant effects on protein binding and cytochrome P450 enzyme activity; thus, drug interaction risk is minimal.

The postulated mechanism of SNRIs is to enhance the diffuse noxious inhibitory control (DNIC) system via augmentation of serotonin and norepinephrine. Duloxetine's effect on pain is independent of its effect on mood.[13] Long term use may be limited by side effects including nausea, vomiting, insomnia, diarrhea and dizziness.[14] These agents have a reported potential for interactions with other serotonin-elevating agents such as tramadol, SSRIs, and St. John's wort. However, serotonin syndrome is rare, and with appropriate monitoring it should not be an obstacle when selecting an effective pain-relief strategy.[15]

Studies of opioid use for pain management in FMS are lacking. There is conflicting evidence, with reports of down- as well as up-regulation of opioid receptors, elevated levels of enkephalin in cerebrospinal fluid, and variable response to naltrexone, an opioid antagonist that affects CNS microglial activity. However, clinical experience suggests that opioids may be useful in selected patients, but only with caution regarding side effects, and concerns of misuse and addiction. The long-term effects of chronic opioid use in non-malignant pain are not yet fully clarified, but effects on mood, cognitive and

**Dr. Ko** is Medical Director, Physiatry Fibromyalgia Integrative Treatment Clinics at Sunnybrook Health Sciences Centre, University of Toronto, and the Canadian Centre for Integrative Medicine, Markham, Ontario; and Assistant Professor, Department of Medicine, University of Toronto, Toronto, Ontario

hormonal function need to be constantly reevaluated. Extended-release formulations are believed to have a better tolerability profile than short-acting agents, but there is limited evidence.

Tramadol (molecularly very similar to venlafaxine) is an analgesic with SNRI action, as well as an effect on the μ-opioid receptor. Two studies have shown positive pain relief, with associated quality of life benefits.[16,17]

NSAIDs are not generally effective against FMS pain, but may be used to treat pain associated with other co-existing conditions, such as osteoarthritis, heeding the usual precautions regarding potential gastrointestinal and cardiovascular toxicity.

## *Emerging pharmacological treatment options*

Novel treatments for FMS include the dopamine agonist pramipexole, the sleep-inducing agent sodium oxybate, and the cannabinoids exemplified by the synthetic form nabilone. Administering pramipexole 4.5 mg q.h.s. as "add-on" treatment reported improvements in pain, fatigue, function, and global status in a 14-week RCT.[18] An RCT of sodium oxybate, 4.5 g and 6 g, observed reduction of pain and improvements in sleep quality.[19] A small RCT of nabilone (0.5 mg q.h.s. to 1 mg b.i.d. over four weeks) reported improvements in VAS and FIQ scores.[20] Long-term efficacy and safety of these novel agents require additional study. Injection therapies with botulinum toxin type-A (BTX-A), using a biomechanical approach, have also been reported to help in FMS and myofascial pain palliation, but require further RCTs.[21,22] Recent FDA approval was granted for its use in migraine prophylaxis. Dx

For a complete list of references, please see
**www.stacommunications.com**

## Additional Comments and Take-Home Message

- Treatment plans should incorporate non-pharmacological (discussed next month) and pharmacological treatments tailored to the individual. Drugs that impact more than one FMS symptom are preferred over agents that improve one aspect
- Amitriptyline (start with a dose of 10 mg q.h.s., titrated to a maximum of 75 mg q.h.s.) is the most commonly prescribed drug for FMS, but is problematic in a population with high drug intolerances. It is essential to monitor weight gain and anticholinergic side-effects; nortriptyline, though less potent, may be better tolerated. Avoid use of tricyclics (including cyclobenzaprine) in the daytime with FMS patients, as this adds to their cognitive impairment and confusion
- Duloxetine is Health Canada-approved for FMS pain (as well as depression and painful diabetic neuropathy). Begin with a starting dose of 30 mg q.d. with food (nausea side-effect) and titrate up after one week to 60 mg q.d. For the sensitive patient, try 1/4 to 1/2 of the opened capsule, mixed in apple sauce, with gradual upward titration. Warn about the risk for serotonin syndrome, particularly if combining with other serotonergic agents (tramadol, triptans, SSRIs, St. John's wort)
- Pregabalin is also Health Canada-approved for FMS pain, painful diabetic neuropathy, shingles, and spinal cord injury pain. Begin with a starting dose of 75 mg h.s. (dizziness, drowsiness side-effect) and titrating up to 300-450 mg per day (dose b.i.d. or t.id.) For the sensitive FMS patient, try 25 mg q.h.s with gradual upward titration. For ODB coverage, one must document failure of response to both amitriptyline 75 mg q.h.s. and gabapentin 1800 mg q.d.
- Opioids should be reserved for patients with symptoms at the severe end. The 2010 National Opioid Guidelines suggest referral to a specialist if doses exceed 200 mg q.d. of morphine equivalents
- Novel oral agents include dopamine agonists (mirapex), sodium oxybate and the cannabinoids (nabilone, dronabilone and the Sativex spray). Nabilone has been studied in two RCTs. Begin with a low starting dose of 0.5mg q.h.s. and titrate up to a maximim of 6 mg per day (b.i.d. dosing). Like pregabalin, it also helps with sleep and should be used primarily at night. Botulinum toxin-A injections may also be useful for associated migraines, chronic musculoskeletal and neuropathic pain

References
1. Shir Y, Fitzcharles MA. Should Rheumatologists Retain Ownership of Fibromyalgia? J Rheumatol 2009;36(4):667-70.
2. Williams DA, Kuper D, Segar M, et al. Internet-enhanced Management of Fibromyalgia: A Randomized Controlled Trial. Pain 2010;151(3):694-702.
3. Bennett RM, Friend R, Jones KD, et al. The Revised Fibromyalgia Impact Questionnaire (FIQR): Validation and Psychometric Properties. Arthritis Res Ther 2009;11(4):R120
4. Burkhardt C, Goldenberg DL, Crofford LJ, et al. "Guideline for the Management of Fibromyalgia Syndrome Pain in Adults and Children." APS Clinical Practice Guidelines Series, No. 4;2005
5. Carville SF, Arendt-Nielsen S, Bliddal H, et al. EULAR Evidence-based Recommendations for the Management of Fibromyalgia Syndrome. Ann Rheum Dis 2008;67(4):536-41.
6. Häuser W, Thieme K, Turk DC. Guidelines on the Management of Fibromyalgia Syndrome - A Systematic Review. Eur J Pain 2009 Mar 3. [Epub ahead of print]
7. Jain A, Carruthers BM, van de Sande MI, et al. Fibromyalgia Syndrome: Canadian Clinical Working Case Definition, Diagnostic and Treatment Protocols– A Consensus Document. J Musculoskel Pain 2003;11(4):3-107.
8. Arnold LM, Russell IJ, Diri EW, et al. A 14-week, Randomized, Double-blinded, Placebo-controlled Monotherapy Trial of Pregabalin in Patients with Fibromyalgia. J Pain 2008;9(9):792-805.
9. Arnold LM, Rosen A, Pritchett YL, et al. A Randomized, Double-blind, Placebo-controlled Trial of Duloxetine in the Treatment of Women with Fibromyalgia With or Without Major Depressive Disorder. Pain 2005;119(1-3):5-15.
10. Nishishinya B, Urrutia G, Walitt B, et al. Amitriptyline in the Treatment of Fibromyalgia: A Systematic Review of its Efficacy. Rheumatology Oxford 2008;47(12):1741-6.
11. Häuser W, Petzke F, Sommer C. Comparative Efficacy and Harms of Duloxetine, Milnacipran, and Pregabalin in Fibromyalgia Syndrome. J Pain 2010;11(6): 505-21.
12. Häuser W, Bernardy K, Uceyler N, et al. Treatment of Fibromyalgia Syndrome with Gabapentin and Pregabalin – A Meta-analysis of Randomized Controlled Trials. Pain 2009;145(1-2):69-81.
13. Arnold LM, Hudson JI, Wang F, et al. Comparisons of the Efficacy and Safety of Duloxetine for the Treatment of Fibromyalgia in Patients with versus without Major Depressive Disorder. Clin J Pain 2009;25(6):461-8.
14. Chappell AS, Littlejohn G, Kajdasz DK, et al. A 1-year Safety and Efficacy Study of Duloxetine in Patients with Fibromyalgia. Clin J Pain 2009;25(5):365-75.
15. Wedge MK. The Truth behind Tramadol and Antidepressants: An Interaction of Concern? Can Pharm J 2009;142:71-3.
16. Bennett RM, Kamin M, Karim R, et al. Tramadol and Acetaminophen Combination Tablets in the Treatment of Fibromyalgia Pain: A Double-blind, Randomized, Placebo-controlled Study. Am J Med 2003;114(7):537-45.
17. Russell IJ, Kamin M, Bennett RM, et al. Efficacy of Tramadol in Treatment of Pain in Fibromyalgia. J Clin Rheumatol 2006:250-57.
18. Holman AJ, Myers RR. A Randomized, Double-blind, Placebo-controlled Trial of Pramipexole, a Dopamine Agonist, in Patients with Fibromyalgia Receiving Concomitant Medications. Arthritis Rheum 2005;52(8):2495-505.
19. Russell IJ, Perkins AT, Michalek JE; Oxybate SXB-26 FM Syndrome Study Group. Sodium Oxybate Relieves Pain and Improves Function in Fibromyalgia Syndrome: A Randomized, Double-blind, Placebo-controlled, Multicenter Clinical Trial. Arthritis Rheum 2009;60(1):299-309.
20. Skrabek RQ, Galimova L, Ethans K, et al. Nabilone for the Treatment of Pain in Fibromyalgia. J Pain 2008;9(2):164-73
21. Ko GD, Whitmore S, Huang D, et al. Effective Pain Palliation in Fibromyalgia Syndrome Patients with Botulinum Toxin Type-A: Case Series of 25. J Musculoskel Pain 2007:55-66.
22. Qerama E, Fuglsang-Frederiksen A, Jensen TS. The Role of Botulinum Toxin in Management of Pain: An Evidence-based Review. Curr Opin Anaesthesiol 2010;23(5):602-10.