MD CONFERENCE EXPRESS

Fibromyalgia — Are we there yet?

EULAR Best Practices and Recommendations

The EULAR working group on fibromyalgia (FM) performed a systemic review of all of the randomized control trials in FM. Dr. Ernest H.S. Choy from Kings College Hospital in London presented the findings. Nine recommendations for the management of FM were developed using a systematic review and expert consensus by a Delphi process. Optimal treatment requires a multidisciplinary approach with a combination of non-pharmacological and pharmacological treatment modalities, tailored to the individual needs of the patient, according to pain intensity, function, and associated features such as depression, fatigue and sleep disturbance.

In the category of non-pharmacological interventions, heated pool treatment with or without exercise, individually tailored exercise programmes including aerobic exercise and strength training, cognitive behavioural therapy, and therapies such as relaxation, rehabilitation, physiotherapy and psychological support may be effective.

Pharmacological treatments include tramadol, tropisetron, pramipexole, and pregabalin. Simple analgesics such as paracetamol are recommended for the management of FM-related pain. Antidepressants such as amitriptyline, fluoxetine, duloxetine, milnacipran, moclobemide and pirlindole, reduce pain and often improve function. Evidence for the effectiveness of corticosteroids and strong opioids is weak and as such, they are not recommended.

Dr. R.M. Bennett from the Oregon Health and Science University, Portland, OR, stated that "most scientific articles on the subject of fibromylagia (FM) and chronic pain commence with –'the causes of FM are unknown,'" which he believes is untrue. "We know that FM symptomatology results from an amplification of incoming sensory impulses in the CNS and it involves an interaction of augmented sensory processing and peripheral pain generators." This neural dysfunction is commonly called "central sensitization." This occurs when impulses from the first order neurons are 'gated' by an up-regulation in the sensitivity of dorsal horn neurons. This phenomenon, first described as "wind-up" results from the stimulation of unmyelinated type-C neurons by repetitive nociceptive input. At the biochemical level, wind-up is dependent on

Highlights from the
European League Against Rheumatism 2006 Annual Meeting

the activation of NMDA receptors by glutamate and substance P. FM patients display wind-up from both the skin and muscle, and have two-fold increased sensitivity to pain compared with normal subjects.

Functional magnetic resonance imaging (fMRI) shows that FM patients have an increased activation of the somatosensory cortices and limbic system for a pain stimulus.

Though depression and pain share the same receptor system, treating patients for depression does not necessarily reduce the patient's sensitivity to pain. However, agents that block receptors that inhibit the release of glutamate and substance P appear to modulate pain somewhat. Also, the newer antidepressants (SNRIs) that inhibit the reuptake of norepinephrine and serotonin appear to be more effective than SSRIs, which only modulate serotonin receptors.

FM is a complex chronic pain condition that affects nearly 6 million people in the United States, approximately 80% to 90% of whom are women. Symptoms of FM include widespread and localized pain, disrupted sleep, fatigue, visceral pain and other pain syndromes, neurological symptoms (e.g., dizziness, numbness, tingling, and impaired cognition), depression, anxiety, and exercise-induced pain. Current treatments are palliative rather than curative and are usually directed at improving function, not abolishing pain. New approaches are needed.

Dr. Choy suggested that a change in the prognosis of FM could impact outcomes. He quoted data from Wolfe et al (*Arthritis Rheum*, 1997; 40:1560-70) showing that the diagnosis of FM has increased significantly since the American College of Rheumatology (ACR) classification criteria were published in 1990. FM patients averaged almost 10 outpatient medical visits per year. When nontraditional treatments were considered, this number increased to approximately 1 visit per month. Patients were hospitalized at a rate of 1 hospitalization every 3 years. In each 6-month study period, patients used a mean of 2.7 fibromyalgia-related drugs. Costs increased over the course of the study. The mean yearly per-patient cost in 1996 dollars was $2,274. If left undiagnosed, a cycle of chronic pain, stress, and psychological arousal often generates a set of secondary symptoms.

Compared to patients with other rheumatic disorders, those with FM were more likely to have lifetime surgical interventions, including back or neck surgery, appendectomy, carpal tunnel surgery, gynecologic surgery, abdominal surgery, and tonsillectomy, and were more likely than other rheumatic disease patients to report comorbid or associated conditions. However, following diagnoses, the number of FM related tests, prescriptions written, and referrals made, decreased.

Dr. Choy concluded that the pain and healthcare burden of FM is real. Using diagnosis constructively, encouraging exercise, the use of appropriate medications, and having a positive attitude can help patients cope with this long-term condition.

Dr. Richard Morriss from the University of Nottingham, UK, addressed the issue of whether FM and wide spread pain (WSP) was mainly a physical or psychiatric problem, i.e., should the treating physician focus on psychological treatments or pain relief?

Psychiatric problems associated with chronic pain, such as depression and disruptive sleep patterns, share common pathogenic pathways involving serotonin, noradrenaline and the hypothalamic-pituitary axis (HPA). There are also early adverse childhood experiences that appear to impact the onset of FM. Psychological factors, disruption of HPA, and sleep patterns often precede the onset of chronic pain.

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Dr. L.A. Fitzpatrick, Amgen, Thousand Oaks, CA, reported on the efficacy of denosumab (AMG 162; a fully human monoclonal antibody that binds to and inhibits RANKL) in postmenopausal women with low BMD. Subjects treated with denosumab for 24 months had significantly greater increases in lumber spine, total hip, distal 1/3 radius, and total body BMD compared with placebo treated patients ($p<0.001$). Denosumab also caused significant sustained suppression of bone turnover markers serum C-telopeptide and urine N-telopeptide/ creatinine compared with placebo ($p<0.001$).

Dr. Wim Goettsch, PHARMO Institute, Utrecht, Netherlands, presented evidence showing that low persistent use of bishosphonates for one year resulted in a significant, 26% lower, fracture rate, whereas 2 year use resulted in a 32% lower rate in women hospitalized for previous osteoporotic fractures.

Osteoporosis is a multifaceted disease that until recently has been both under-diagnosed and under-treated. New emphasis on the disease and recent developments in the field of osteoporosis research has provided clinicians with new treatments and prevention strategies.

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Treating depression in FM often does not diminish reporting of pain and medically unexplained symptoms, but it may improve social function. Graded exercise produces improvements in functional work capacity and fatigue, while fluoxetine improves depression only (*Br J Psychiatry*. 1998;172:485-90).

Disrupted sleep appears to complicate the course of FM. For the most part, sleep complaints are either attributable to the lifestyle of FM patients, or seem inherent to the underlying condition of FM. They are generally unrelated to depression or anxiety in FM.

The correlation between tissue pathology and the perceived severity of the chronic pain experience is poor or even absent. More importantly, chronic pain seldom responds to the therapeutic measures that are successful in treating acute pain.

Dr. Morriss concluded by saying that "psychological treatments focused on the needs of the FM patients can improve clinical care, but research evidence does not support a complete shift of focus away from pain relief." Thus, for optimal management of FM, he recommends a blend of multidisciplinary group therapy and individualized clinician-based treatment.

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The endpoint of the study was the number of patients in remission defined as no swollen joints plus 2 out of 3 of the following criteria: number of tender joints ≤ 3, ESR ≤ 20 mm/hr1st, and VAS general well-being ≤20 mm fulfilled at three subsequent visits measured at three monthly intervals.

Sixty-three (41%) of the patients in the intensive strategy group achieved remission for at least 6 months versus 24% of the patients in the conventional strategy group ($p= 0.002$). Mean time until first remission was 10 months for the intensive strategy group compared with 13 months for conventional strategy group. Median (IQ 0.25-0.75 range) AUC of all clinical variables were significantly better for the intensive strategy group when compared to the conventional strategy group.

Tailoring the MTX treatment to the individual patient is significantly more beneficial than the conventional approach. Furthermore, a computer assisted approach, to make more objective decisions on dosage changes, may be beneficial.