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Letter to the editor

Duloxetine: An emerging evidence for fibromyalgia

Fibromyalgia (FM) is a controversial syndrome, characterized by persistent widespread musculoskeletal pain, multiple tender points, abnormal pain sensitivity, and additional symptoms such as fatigue, depressed mood, decreased volition, and sleep disturbance [1]. The prevalence of FM is approximately 2% in the general population, ranked the third most common diagnosis in rheumatology clinics [2].

Antidepressants have been widely used for the treatment of FM, although the pathophysiology of FM remains poorly understood. Justification for antidepressant treatment of FM relates to the epidemiological and biological relationship between FM and common psychiatric disorders such as anxiety and mood disorders. In one study, 46% of FM patients reported a previous diagnosis of depression and 23% reported a family history positive for depression [2]. Fifty years of research has associated depression with deficits in serotonin and norepinephrine neurotransmission, and medications for depression have in common the ability to enhance such neurotransmission. Similar research has implicated deficits in the serotonin and norepinephrine systems in the development of variable pain disorders such as FM. Among antidepressants, tricyclic antidepressants (amitriptyline), selective serotonin uptake inhibitors (SSRIs, e.g., citalopram, fluoxetine, and paroxetine controlled release), and serotonin and norepinephrine reuptake inhibitors (SNRIs, e.g., duloxetine and milnacipran) have demonstrated beneficial effects in the treatment of FM through double blind, placebo-controlled clinical trials (RCTs) [3–14]. These RCTs have been tried to find proper treatment regimen for treating FM like medications having analgesic property for several decades.

Duloxetine is the first antidepressant medication to receive approval by the United States Food and Drug Administration (FDA) for a pain disorder. Duloxetine is currently indicated for the treatment of diabetic peripheral neuropathic pain [15], and it has demonstrated benefit in the treatment of FM in two pivotal RCTs. Hence, this commentary will evaluate the strengths of this medication and explore the various outcome measures for which it has shown efficacy for FM.

In the first RCT of duloxetine for FM [14], a total of 207 subjects meeting the American College of Rheumatology criteria for primary FM were enrolled. Subjects were randomly assigned to receive duloxetine 60 mg twice a day (BID) ($n = 104$) or placebo ($n = 103$) for 12 weeks. Co-primary outcome measures were the Fibromyalgia Impact Questionnaire (FIQ) total score (score range 0–80, with 0 indicating no impact) and FIQ pain score (score range 0–10). The duloxetine-treated group demonstrated significant improvement ($P = 0.027$) on the FIQ total score, with a treatment difference of −5.53, but not significantly more on the FIQ pain score ($P = 0.130$) compared to the placebo-treated group. Additionally, the duloxetine-treated group showed significantly greater reductions in all secondary efficacy measures compared to the placebo-treated group. Interestingly, this trial suggested a potential gender difference in FM response to duloxetine favoring females: duloxetine-treated male subjects ($n = 12$) failed to improve significantly on any efficacy measure. In this RCT, duloxetine was well tolerated, and there were no significant differences in the number of patients who discontinued due to adverse events.

The second RCT of duloxetine for FM recruited 354 women with FM with or without current MDD [3]. Similar to the first RCT, subjects were randomly assigned to receive duloxetine 60 mg once daily (QD) ($n = 118$), duloxetine 60 mg BID ($n = 116$) or placebo ($n = 120$) for 12 weeks. The primary outcome measure was the Brief Pain Inventory (BPI) average pain severity score, and treatment response was defined as 30% reduction. Compared to placebo, both dosages of duloxetine (60 mg QD and BID) demonstrated greater reduction in mean changes on the BPI average pain score at endpoint (−1.23, $P < 0.001$ and −1.24, $P < 0.01$, respectively). Also, both duloxetine groups achieved significantly higher percentages of treatment responders compared to the placebo-treated group (duloxetine 60 mg QD (55%; $P < 0.001$); duloxetine 60 mg BID (54%; $P = 0.002$); placebo (33%)). With regard to safety and tolerability, side effects of duloxetine were considered to be of mild to moderate severity in most patients, although the dropout rate due to adverse events was higher in duloxetine-treated groups than in the placebo-treated group.

A recent pooled data analysis from the two RCTs provides greater statistical power and more clearly illustrates the efficacy of duloxetine for pain, functional impairment, and quality of life in FM patients [16]. The pooled data set included patients treated with duloxetine 60 mg QD or 60 mg BID ($n = 326$) vs. placebo ($n = 212$). *Compared with the placebo group, the duloxetine group showed significantly greater*

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improvement in the BPI average pain severity score ($P < 0.001$) and the FIQ total score ($P < 0.001$) beginning at week 1 and continuing through week 12. Duloxetine also established superiority to placebo on all efficacy measures (including mean tender point threshold, Clinical Global Impression of Severity, Patient Global Impression of Improvement, and average interference from pain scores) and measures of quality of life and functional outcome (including each domain of the Medical Outcomes Study Short Form-36 (SF-36)). There were no significant treatment group differences in the incidence of serious adverse events (SAE) (0.6% duloxetine-treated patients; 0% placebo-treated), although significantly more duloxetine-treated patients reported treatment-emergent adverse events (90.8% in duloxetine-treated and 77.8% placebo-treated group, $P < 0.001$). The target dose of duloxetine in the two RCTs was 60 mg/day or 120 mg/day, and 60 mg/day was better tolerated.

An SNRI comparable to duloxetine for the treatment of FM is milnacipran, which is officially approved for the treatment of major depressive disorder in European and Asian countries, but not by the United States FDA. A New Drug Application (NDA) for milnacipran in the treatment of FM filed in December of 2007 includes data from phase III trials of milnacipran involving more than 2000 patients. The phase II trial [12,13] of milnacipran has also demonstrated its potential for treating FM, showing that milnacipran potentially has a promising effect not only on pain but also on several of the other symptoms associated with FM. In this RCT of milnacipran, the effect size of milnacipran on the reduction of pain was similar to those previously found with TCAs and comparable to those in the duloxetine RCTs. The target dose of milnacipran was 200 mg/day. Of note, statistically greater improvement in pain reduction was seen in the non-depressed group than in depressed group, adding to the literature suggesting that the analgesic effect of SNRIs is independent of any antidepressant effect.

TCAs have been the most well studied in patients with FM. However, TCAs are effective in only about 40% of patients with FM and have a number of well-known tolerability and safety issues, while newer antidepressants such as duloxetine and milnacipran have demonstrated improvement in key FM outcomes in about 60% of patients [4].

The only medication currently approved by the U.S. FDA for FM is pregabalin (300 or 450 mg/d, June 2007) [17], which had previously obtained FDA-approval for the treatment of neuropathic pain associated with diabetic peripheral neuropathy and post-herpetic neuralgia and as adjunctive therapy for adults with partial onset seizures. Pregabalin is considered an effective and safe analgesic, antiepileptic, and anxiolytic medication. Hence, it is expected that duloxetine should be the first antidepressant to receive approval from U.S. FDA.

There are no formally recommended doses of antidepressants in FM, which is same to duloxetine. Available evidence indicates that the target dose of SSRIs and SNRIs is in the range considered efficacious in the treatment of depression. In contrast, the effective dose range for TCAs in FM appears to be about 25–50 mg/d of amitriptyline or its equivalent, which is lower than the therapeutic dose in depression; however trials of higher dose TCA are warranted if therapeutic response is inadequate at low doses, and combinations of different antidepressants should be attempted if response is insufficient with maximal dose of monotherapy [4]. These issues will need further evaluation.

Further studies are needed to investigate adequate duration of treatment with antidepressants for FM patients as well. In particular, longer-term studies will determine the durability of therapeutic response and overall tolerability, which are important issues due to the chronicity of this disorder. Studies directly comparing medications may help elucidate the best medication for patients with FM in terms of overall risk/benefit profile and ultimately lead to an algorithmic approach to FM treatment. The treatment of FM should be comprehensive and not simply concerned with reduction of the core symptom ‘‘pain’’. Associated symptoms such as fatigue and insomnia are relevant targets for pharmacotherapy and cognitive behavioral therapy (CBT). Physical reconditioning is of benefit, and coping skills and level of functioning should be serially measured and optimized. Research combining pharmacotherapy with non-biological interventions is lacking, and studies of duloxetine treatment in combination with CBT may produce better results than either intervention alone. Also, there have been few systematic studies examining clinical predictors of response to antidepressant treatment in patients with FM, although it has been suggested that identification of subgroups based on specific clinical characteristics may be useful for maximizing treatment efficacy in FM patients [18,19]. Information about treatment response predictors would allow clinicians to devise medication plans more effectively. Finally, it has been shown that patients with FM plus depression are high users of healthcare services. Incremental costs for patients with FM plus MDD were found to be more than additive of costs for each condition alone [20]. Hence, clinicians should pay careful attention to psychiatric comorbidity in their FM patients to reduce suffering, functional impairment, and healthcare utilization.

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