The Role of Serotonin Norepinephrine Reuptake Inhibitors in the Treatment of Fibromyalgia: A Guide for the Physician Assistant

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Abstract

Fibromyalgia is a controversial polysymptomatic syndrome of unknown etiology. Diagnosis of fibromyalgia is often problematic due to numerous concomitant conditions that mimic this disorder. Additionally, the validity of fibromyalgia as a true physiologic condition remains a point of debate within the scientific community. Fibromyalgia reportedly occurs in approximately two percent of the United States population and clinical presentation typically occurs in the primary care setting. Fibromyalgia is more common than rheumatoid arthritis and poses a significant health issue because no "curative" treatment exists. This disorder can lead to significant patient disability and economic burden especially if diagnosis is delayed. There are many pharmacological treatments for fibromyalgia, however there is no drug of choice.

As more patients are being seen in the primary care setting and are presenting with fibromyalgia, it is imperative that physician assistants remain up-to-date regarding pharmacological treatments and underlying mechanisms of action. The purpose of the paper is to describe results from various investigations on the efficacy and effectiveness of serotonin norepinephrine reuptake inhibitors in treating patients with fibromyalgia in the ambulatory primary care setting. This paper is a review article that will discuss serotonin norepinephrine reuptake inhibitors currently on the market and compare them to other pharmacological treatments used in fibromyalgia.

BACKGROUND

Fibromyalgia is a controversial polysymptomatic syndrome of unknown etiology characterized by chronic widespread musculoskeletal pain, multiple tender points, abnormal pain sensitivity, and additional symptoms such as fatigue, sleep disturbance, headache, concentration difficulties, and irritable bowel syndrome (Shaver, 2004). Comorbid conditions include, but are not limited to, migraine headaches, chronic fatigue syndrome, Raynaud's syndrome, restless leg syndrome, temporomandibular joint syndrome, panic disorder, and major depression (Hudson, Goldenberg, Pope, Keck, & Schlesinger, 1992). Diagnosis of fibromyalgia is often problematic due to numerous concomitant conditions that mimic this disorder including drug induced myopathy, connective tissue disorders, autoimmune disorders, rheumatologic disorders, and hypothyroidism (Quisel, Gill, & Walters, 2004). Additionally, the validity of fibromyalgia as a true physiologic condition remains a point of debate within the scientific community (Bohr, 1995) and the causes of fibromyalgia are unknown.

Numerous etiologies of fibromyalgia have been reported including attributing this disorder to the effects of exposure to viral infections, toxins, or physical and emotional trauma (Sierpina & Carter, 2002). Hypotheses of pathophysiology include impaired functioning of the hypothalamic-pituitary axis and alterations in specific neurotransmitters such as substance P, N-methyl-d-aspartate, norepinephrine, and serotonin. Serotonin in particular is thought to play a role in sleep, pain thresholds, as well as many of the comorbid psychiatric disorders seen in fibromyalgia (Wolfe, 1996; Juhl, 1998). Fibromyalgia reportedly occurs in approximately two percent of the United States population and current data suggests that this disorder primarily affects females of childbearing age (American College of Rheumatology, 2003). Of reported cases, fibromyalgia occurs seven times more frequently in women than in men

(American College of Rheumatology, 2003). Clinical presentation typically occurs in the primary care setting (Goldenberg, 2002) and most new diagnoses are given to patients age 55 to 79 years even though symptoms may present earlier in life (Quisel, Gill, & Walters, 2004; American College of Rheumatology, 2003).

Fibromyalgia is at least twice as common as rheumatoid arthritis and poses a significant health issue because no 'curative' treatment exists (Simms & Adams, 2002; Simms, 1994). This disorder can lead to significant patient disability and economic burden. Medical utilization, receipt of prescription drugs, and annual total costs are significantly greater among fibromyalgia patients than those without the disorder. Also, the prevalence of disability is twice as high among fibromyalgia patients. Overall, hidden costs of disability and comorbidities greatly increase the financial burden of fibromyalgia (Robinson et al., 2003).

Due to the variety of proposed mechanisms, the multiple comorbid conditions, and the heterogeneity of the patient population presenting with fibromyalgia, there are presently few gold standards available to direct and guide treatment. In fact, treatment approaches vary and include aerobic exercise, acupuncture, hydrotherapy, biofeedback, heat therapy, massage therapy, relaxation, cognitive-behavioral therapy, and combination treatment (Simms & Adams, 2002).

In addition to treatment approaches described above, there are many pharmacological treatments for fibromyalgia (Quisel, Gill, & Walters, 2004). However, consistent with the variability among the treatments provided by health care workers in ambulatory care settings, there is also no drug of choice when treating these patients. For example, numerous classes of pharmacological interventions are currently prescribed including the antidepressants, opiates, antiepileptic drugs, and antispasticity agents. These agents are typically indicated due to their analgesic effects (Rao, 2002). Other pharmacological interventions, such as sedatives and hypnotics may have a role in treating associated symptoms but not the pain in fibromyalgia. Non-steroidal anti-inflammatory drugs are often used in clinical settings; however, their effectiveness as analgesics in fibromyalgia has not been shown (Rao, 2002).

Despite the variability regarding medical treatment and pharmacological intervention, most practitioners treat fibromyalgia through a combination of pharmacological intervention by using one or more antidepressants, including a tricyclic antidepressant, in combination with aerobic exercise (Quisel et al., 2004; Arnold, Keck, & Welge, 2003). Regarding antidepressants, the proposed mechanism of action primarily involves increasing serotonin and/or norepinephrine by blocking their respective reuptake (Rao, 2002). More recently, research has demonstrated that drugs that inhibit both norepinephrine and serotonin reuptake in a balanced manner may be more effective in fibromyalgia (Littlejohn, 2004). A newer class of antidepressants, serotonin norepinephrine reuptake inhibitors (5-HT-NE dual reuptake inhibitors), may prove to be the effective in treatment of fibromyalgia through this balanced reuptake inhibition.

Serotonin norepinephrine reuptake inhibitors are very similar to tricyclic antidepressants (e.g., amitriptyline) in increasing the levels of both norepinephrine and serotonin by inhibiting their respective reuptake (Rao, 2002). However, unlike tricyclic antidepressants, the serotonin norepinephrine reuptake inhibitors generally do not have any significant activity at other receptor systems such as histaminergic and cholinergic receptor sites (Sanchez & Hyttel, 1999). This specificity has the potential to lead to reduction in the side effect profile and general tolerability of tricyclic antidepressants (Rao, 2002). Currently, only two serotonin norepinephrine reuptake inhibitors are on the market in the United States. These include Venlafaxine, and the most recently approved, Duloxetine. The United States FDA has not yet approved the use of Milnacipran (Obesity, Fitness, and Wellness Week, 2004; Rao, 2002; Milnacipran, 2004).

Fibromyalgia creates enormous challenges for primary care physicians due to logistical changes resulting from managed care (Goldenberg, 2002). Fibromyalgia treatment calls for patient education and is "labor intensive" which makes it a prime area for physician assistants to become involved (Goldenberg, 2002). It has been suggested that within the management of fibromyalgia, "there may be large cost-offset opportunities for reductions in patient, physician, and employer burdens" (Robinson et al., 2003). This may be accomplished by early diagnosis of fibromyalgia, aggressive treatment of the syndrome and its comorbidities, and improving patient education and knowledge of their disorder (Robinson et al, 2003). As more patients are being seen in the primary care setting and are presenting with fibromyalgia, it is imperative that physician assistants remain up-to-date regarding pharmacological treatments and underlying mechanisms of action. The purpose of this paper

is to describe results from various investigations on the efficacy and effectiveness of serotonin norepinephrine reuptake inhibitors on treating patients with fibromyalgia in the ambulatory primary care setting.

METHOD

Ovid MEDLINE search limited to the years 1996 to 2004 was conducted using the keyword fibromyalgia. This search resulted in 1945 journal articles being found. The search was further limited by using the keywords serotonin norepinephrine reuptake inhibitors. The results of the first search using the keyword fibromyalgia were then combined with a second search using the keywords randomized clinical trial and serotonin norepinephrine reuptake inhibitors. Nine articles were found. This same search process was used to search a different database, PsychINFO, which was limited to the years 2000 to 2004 to find six more articles. Of the fifteen articles, three were chosen based on information presented on a clinical trial basis and examination of serotonin norepinephrine reuptake inhibitors specifically in the treatment of fibromyalgia.

RESULTS

Three studies on serotonin norepinephrine reuptake inhibitors were examined for this paper and include the pharmacological agents Venlafaxine, Duloxetine, and Milnacipran (See Table 1). Each study was conducted for a twelve week time period and each patient was diagnosed with fibromyalgia.

The results of the study on venlafaxine were promising in alleviating the pain and disability associated with fibromyalgia (Sayar et al., 2003). The effect of Venlafaxine was shown to be independent of its anxiolytic and antidepressant properties. It was also demonstrated that Venlafaxine is effective as both an analgesic and an antidepressant (Sayar et al., 2003; Bradley et al., 2003). The study found that blocking both norepinephrine and serotonin reuptake appears to be more effective than blocking just one (Sayar et al., 2003; Bradley et al., 2003).

The second study, a randomized, double-blinded, placebo-controlled, multicenter trial on Duloxetine in the treatment of fibromyalgia, provided evidence suggesting that patients treated with Duloxetine had significant improvement of symptoms compared with those treated with placebo (Arnold et al., 2004). In this investigation, female subjects demonstrated greater improvement than male patients. In fact, male participants failed to improve significantly on any efficacy measure. The trial determined that Duloxetine was well tolerated and an effective and safe treatment (Arnold et al., 2004). It was also noted that the effect of Duloxetine on the reduction of pain was independent of its effect on mood (Arnold et al., 2004).

In the third study examined, Milnacipran, another serotonin norepinephrine reuptake inhibitor was investigated in the treatment of fibromyalgia. This drug is currently approved in many countries outside of the United States (Littlejohn, 2004). The study evaluated milnacipran in the treatment of pain and associated symptoms (fatigue, depressed mood, and sleep). Seventy five percent of milnacipran-treated patients reported overall improvement, compared with 38% in the placebo group and 84% were able to take the highest dose of 200 mg/day with no tolerance issues. The results of the study suggest that milnacipran may have potential to relieve pain, as well as other symptoms associated with fibromyalgia (Vitton, 2004).

Figure 1

Table 1: Studies of serotonin norepinephrine reuptake inhibitors for treatment of fibromyalgia

Study	Sample Size	Drug Employed	Study Design	Primary Outcome	Secondary Outcome	Results
Sayer et al., 2003	N=15 (females)	Venlafaxine (75mg)	12 week pre/ post within subjects design	Fibromyalgia Impact Questionnaire	Pain Inventory	Significant improvement in the mean intensity of pain and the disability Independent of anxiolytic and antidepressant properties
Arnold et al., 2004	N=207 89% females	Duloxetine (60 mg BID)	12 week pre/ post within subjects design	Fibromyalgia Impact Questionnaire total score Fibromyalgia Impact Questionnaire pain score	Various Standards of measure	Significant improvement of symptoms compared with the placebo Females > improvement than males
Vitton et al., (2004)	N=125	Milnacipran (up to 200mg)	12 week pre/ post within subjects design	Patient Daily Electronic Diary	NA	75% patients reported overall improvement 84% tolerated the highest dose

DISCUSSION AND CONCLUSION

The purpose of this paper is to provide the physician assistant with the newest information on the treatment of fibromyalgia and its associated symptoms through pharmacological mechanisms. The results of the above studies suggest that using a pharmacological regimen that blocks the reuptake of serotonin and norepinephrine rather than just one of the neurotransmitters may provide added benefit to patients with fibromyalgia. This combination of therapy may also help the pain associated with fibromyalgia

as well as the common comorbid condition of depression.

Adherence to medications has historically been problematic in the management of fibromyalgia. Many of the treatments offered have unwanted side effects that result in cessation of medication and relapse of symptoms. In contrast to other commonly used pharmacological agents, serotonin norepinephrine reuptake inhibitors may increase adherence because of their favorable side effect profile. Though there is no standard of treatment, tricyclic antidepressants have been evaluated and used most often (Goldenberg, 1999). Due to the lack of tricyclic antidepressant postsynaptic action on muscarinic and alpha-adrenergic receptors, the side effect profile of serotonin norepinephrine reuptake inhibitors is more favorable compared to tricyclic antidepressants (Bradley et al., 2003).

Additionally, there is no cure for fibromyalgia and the treatment of fibromyalgia is a multimodal approach with the goal of controlling symptoms (Sierpina & Carter 1999). Physician assistants have the opportunity as a physician extender to participate in the education and extended treatment of stable patients with the diagnosis of fibromyalgia. Because many patients will need to adjust their medications several times before finding a combination at the right dose that is successful for them, a physician assistant can provide adequate time and education to these patients at a reasonable cost. They can also work with the patient to create a regimen of non-pharmacological treatments, in addition to pharmacological treatment, to increase the patient's chance of improvement with fibromyalgia symptoms.

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