

Frequently Asked Questions From Clinical Practice

Q

Are serotonin uptake inhibitors useful in chronic pain syndromes such as fibromyalgia or diabetic neuropathy?

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Clinicians often use older tricyclic antidepressants to treat chronic pain syndromes such as fibromyalgia or diabetic neuropathy. These medications are moderately effective in treating these conditions but can cause serious side effects.¹⁻⁴ The selective serotonin reuptake inhibitors (SSRIs) are a newer class of antidepressants that are effective in treating major depression. They are better tolerated and much less dangerous if taken in large doses than are tricyclic antidepressants. Blocking the reuptake of serotonin has been hypothesized to effect the pain modulating systems in the brainstem. Several studies have examined the use of SSRIs in pain syndromes. Most of these involved patients with fibromyalgia or diabetic neuropathy.

Fibromyalgia is a syndrome of widespread chronic musculoskeletal pain with increased tenderness at specific anatomic sites. There have been case reports of patients with fibromyalgia who have responded to fluoxetine therapy.⁵ These reports prompted several randomized controlled trials. The first, by Wolfe et al,⁶ compared 20 mg/d of fluoxetine to placebo in 42 women during a 6-week period. There was no difference between the fluoxetine and placebo groups in pain scores, or global severity of disease. Unfortunately 28% of the active treatment and 57% of the placebo patients withdrew from the study before its completion. The low number of patients severely limited the power of this study to detect meaningful improvements due to fluoxetine therapy. In a more recent study Goldenberg et al⁷ compared fluoxetine, 20 mg/d, and amitriptyline, 25 mg/d, with placebo in a randomized, double-blind, crossover study. Nineteen patients were randomized in a crossover fashion to fluoxetine vs placebo, fluoxetine and amitriptyline vs placebo or amitriptyline vs placebo. Individually, patients receiving both fluoxetine and amitriptyline had improvement in pain compared with placebo, global well-being, and sleep disturbance scores. The combination of fluoxetine and amitriptyline was more effective than either alone. Another study of SSRIs for fibromyalgia used citalopram which is not licensed in the United States.⁸ In this double-blind, placebo-controlled

study in 22 patients Norregaard et al⁶ found no improvement in pain scores or global functioning.

Diabetic sensory neuropathy is a symmetric, usually distal neuropathy, associated with diabetes mellitus. The sensory symptoms often include burning or throbbing extremity pain. A few studies have examined whether SSRIs are valuable in relieving the pain of diabetic neuropathy. In a randomized, double-blind, crossover study of 20 patients, Sindrup et al⁹ compared paroxetine, 40 mg/d, with dose adjusted imipramine, median 200 mg/d. Paroxetine reduced neuropathy pain more than placebo but less than imipramine.⁹ In a similar study, Sindrup et al¹⁰ also found that citalopram, a SSRI not licensed in the United States, had a small effect in relieving diabetic neuropathy pain. In the largest study of 46 patients, Max et al¹¹ compared amitriptyline with desipramine and fluoxetine with placebo in a randomized, double-blind, crossover trial with each treatment period lasting 6 weeks. The dosages were titrated for each patient with mean daily dosages of: amitriptyline, 105 mg; desipramine, 111 mg; and fluoxetine, 40 mg. The end points evaluated were daily pain scores and global pain relief at the end of treatment. Fluoxetine was no better than placebo except in the subset of depressed patients. Amitriptyline and desipramine were equally effective.

Selective serotonin reuptake inhibitors have been studied in several other chronic pain conditions. In a double-blind, crossover study of chronic nonmalignant pain, Gourlay¹² found that zimelidine, an SSRI not licensed in the United States, was ineffective in decreasing patient pain ratings or changing daily activity levels. In another study, Rani¹³ compared daily fluoxetine, 20 mg, amitriptyline, 25 mg, and placebo in a randomized controlled trial of 59 Indian patients with chronic musculoskeletal pain of multiple etiologies. He found that fluoxetine was superior to both amitriptyline and placebo. The enrollment criteria for patients in this study were poorly described and therefore its findings should be interpreted with some caution.

In patients with fibromyalgia or diabetic neuropathy traditional antidepressants such as amitriptyline have been well studied and are effective. These medications should be used first if patients can tolerate them. The dosages should be titrated slowly based on the patients symptoms.

There is fair evidence that fluoxetine, 20 mg/d, is effective in reducing pain and improving global well-being in patients with fibromyalgia. The combination of amitriptyline, 25 mg/d, and fluoxetine, 20 mg/d, may offer more benefit than either alone.

For patients with diabetic neuropathy the best current study found no benefit from fluoxetine therapy except in a subset of depressed patients. One small study did find that paroxetine, 40 mg/d, decreased pain and paresthesias.

In patients with chronic pain due to other conditions there is insufficient evidence to recommend for or against using SSRIs.

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Clinical Pearl

Coronary Artery Bypass Graft Surgery vs Angioplasty

In patients with multivessel coronary artery disease, coronary artery bypass graft surgery vs angioplasty was associated with a better quality of life for 3 years after the surgery at a generally similar monetary cost. (*N Engl J Med.* 1997;336:92-99.)