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Article in Journal of General Internal Medicine · July 1997

DOI: 10.1007/s11606-006-5088-3 · Source: PubMed

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The Efficacy of Selective Serotonin Reuptake Inhibitors for the Management of Chronic Pain

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OBJECTIVE: **To assess the effectiveness of selective serotonin reuptake inhibitors (SSRIs) in the management of chronic pain.**

METHODS: **Randomized, controlled trials of SSRIs in the management of chronic pain were identified by searching MEDLINE from 1966 to 1997 and by contacting the manufacturers of SSRIs available in the United States.**

MAIN RESULTS: **Nineteen studies were identified, including 10 on the treatment of headache, 3 on diabetic neuropathy, 3 on fibromyalgia, and 3 on mixed-chronic pain. SSRIs were consistently helpful for mixed-chronic pain. Results were conflicting for migraine headache, tension headache, diabetic neuropathy, and fibromyalgia.**

CONCLUSIONS: **SSRIs appear to be beneficial for mixed-chronic pain. It is unclear, from the available evidence, whether SSRIs are beneficial for migraine headaches, tension headaches, diabetic neuropathy, or fibromyalgia. For those patients it may be reasonable to reserve SSRIs for those who fail to respond to other medications or who are intolerant of their side effects.**

KEY WORDS: **chronic pain, management of; selective serotonin reuptake inhibitors.**
J GEN INTERN MED 1997;12:384–389.

The clinical management of chronic pain remains a challenge. Despite advances in pain research and clinical treatment, rates of disability due to chronic pain continue to climb worldwide.[1] Although chronic pain is treated with many medications, such as tricyclic antidepressants, nonsteroidal anti-inflammatory drugs, anticonvulsants, and opioids, none has shown outstanding efficacy. Narcotics are usually avoided because of the risk of developing tolerance, dependence, and functional deterioration.[2] Tricyclic antidepressants have proven efficacy in the treatment of chronic pain conditions such as diabetic neuropathy, fibromyalgia, chronic headaches, and post-herpetic neuralgia.[3] Their ability to relieve pain in these conditions appears to be independent of their antidepressant effect and may be related to their effect on neuronal reuptake of serotonin and norepinephrine. Unfortunately, side effects including dry mouth, constipation, orthostatic hypotension, and urinary retention often limit their use.

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Fluoxetine was introduced as the first selective serotonin reuptake inhibitor (SSRI) in the United States in 1988. Since then, SSRIs have become the most frequently prescribed antidepressant medications owing to their favorable side-effect profile.[4] More than half of antidepressant prescriptions written in the primary care setting are for conditions other than depression.[5] There is considerable interest in the use of SSRIs for the management of chronic pain, although they are not currently approved by the Food and Drug Administration for this purpose. This review summarizes available data on the value of these medications for pain control in several clinical situations.

METHODS

We used the National Library of Medicine search engine to search MEDLINE from 1966 to 1997 using the medical subject heading (MeSH) term "pain," exploding it, and adding the following words in all fields: pain, neuropathy, migraine, and fibromyalgia. We also searched using the MeSH term "serotonin uptake inhibitors" and the following words in all fields: sertraline, paroxetine, fluoxetine, fluvoxamine, femoxetine, zimelidine, and citalopram. We combined results of these two searches with the term "and," and selected for review randomized double-blind, controlled studies published in English and performed on humans. References from studies reviewed provided additional sources of information. We also requested relevant studies from the manufacturers of Prozac (fluoxetine), Zoloft (sertraline), Luvox (fluvoxamine), and Paxil (paroxetine), the four SSRIs available in the United States.

HEADACHE

Ten studies evaluated the efficacy of SSRIs in the treatment of chronic headache (Table 1). Saper et al. compared fluoxetine (20–40 mg/d) with placebo in a randomized, double-blind study of 64 patients with chronic daily headache (headache more than 16 d/mo) and 58 patients with migraine headache (4–12 attacks/mo).[6] After 3 months, patients with chronic daily headache taking fluoxetine showed a 53% mean improvement in self-rated, overall headache status compared with a 17% mean improvement in those receiving placebo ($p = .029$). Of those patients with chronic daily headache taking fluoxetine, 47% also experienced at least a 50% improvement in mood compared with 24% of those in the placebo group ($p = .097$). Patients receiving fluoxetine had a modest decrease in headache frequency but not severity. In contrast to its effect on chronic daily headache, fluoxetine was not effective on any measure of migraine headache with the exception of a modest mood improvement at the end of the third month.

Table 1. Randomized, Double-Blind, Controlled Studies of SSRIs in Headache

Study	Design	Headache Type	*N*	Results
Saper et al.,[6] 1994	Fluoxetine vs placebo	Chronic daily	64	Mean improvement in treated 53% vs 17% with placebo ($p = .029$).
		Migraine	58	Fluoxetine = placebo
Langemark and Olesen,[7] 1994	Paroxetine vs sulpiride, crossover for nonresponders	Chronic tension	50	Both groups improved ($p < .05$) in headache score and analgesic use compared to baseline. Patients testing both drugs showed better relief from sulpiride ($p = .03$).
Manna et al.,[8] 1994	Fluvoxamine vs mianserine	Chronic tension	40	Both groups improved from baseline in headache frequency ($p < .01$), pain severity ($p < .01$), and analgesic consumption ($p < .05$).
Bendtsen et al.,[9] 1996	Threeway crossover of amitriptyline vs citalopram vs placebo	Chronic tension	40	Amitriptyline reduced the area under the headache curve compared to placebo ($p = .002$). Citalopram = placebo ($p = .68$).
Andersson and Petersen,[10] 1981	Femoxetine vs propranolol	Migraine	49	Both groups had fewer migraine attacks and fewer headache days compared to baseline ($p < .001$). There was no difference between treatment groups.
Zeeberg et al.,[11] 1981	Femoxetine vs placebo	Migraine	59	Femoxetine = placebo
Orholm et al.,[12] 1986	Femoxetine vs placebo	Migraine	65	Femoxetine = placebo
Kangsmaniemi et al.,[13] 1983	Crossover of femoxetine vs propranolol	Migraine	29	Compared to baseline, those receiving propranolol had a decrease in attack frequency, headache index, and use of attack relieving drugs ($p < .05$). Femoxetine showed no significant effect.
Adly et al.,[14] 1992	Fluoxetine vs placebo	Migraine	32	Headache scores in the fluoxetine treated group improved compared to placebo group ($p < .05$); 14 patients failed to complete study.
Bánk,[15] 1994	Fluvoxamine vs amitrityline	Migraine	64	Both groups improved over baseline ($p < .02$).

Langemark and Olesen compared paroxetine (20–30 mg/d) with sulpiride (200–400 mg/d), a dopamine antagonist used as a neuroleptic in Europe, in a randomized, double-blind, crossover study of 50 nondepressed patients with chronic tension-type headache.[7] Both treatment groups experienced a significant decrease in headache scores and analgesic use over 8 weeks compared with baseline ($p < .05$). Patients testing both drugs showed significantly better relief from sulpiride ($p = .03$). A placebo arm was not included in the study.

Manna and colleagues enrolled 40 patients in a randomized, double-blind comparison of fluvoxamine (50–100 mg/d) and mianserine (30–60 mg/d), a presynaptic, serotonin receptor antagonist, for the treatment of chronic, tension-type headache.[8] Both treatment groups showed significant improvement in headache frequency ($p < .01$), pain severity ($p < .01$), and analgesic use ($p < .05$). Fluvoxamine was more effective than mianserine in the nondepressed subgroup of patients with more severe headache. Mianserine was more effective in depressed patients with moderate headache.

Bendtsen et al. compared citalopram (20 mg/d), an SSRI not available in the United States, amitriptyline (25–75 mg/d), and placebo in a 32-week, double-blind, threeway crossover study of chronic tension-type headache.[9] Forty nondepressed patients received each of the three drugs for 8 weeks. Treatment periods were separated by 2-week washout periods. Amitriptyline reduced the area under the headache curve (the sum of the daily recordings of headache duration × headache intensity) by 30% compared with placebo ($p = .002$), but citalopram had no significant effect ($p = .68$).

Andersson and Petersen compared femoxetine (400 mg/d), an SSRI not available in the United States, with propranolol (160 mg/d) for the prophylaxis of migraine headache.[10] They randomized 49 patients in a double-blind, crossover trial of 6 months' duration. There was no significant difference between propranolol and femoxetine in the number of headache days or the number of migraine attacks. There was, however, significant improvement in headache parameters with each drug when compared with baseline ($p < .001$).

Zeeberg et al. studied the prophylactic effect on migraine of femoxetine (300 mg/d) in a randomized, double-blind, placebo-controlled study of 59 patients.[11] Headache index as well as number and severity of attacks showed a significant reduction over the 12-week study, but there was no significant difference between the placebo and femoxetine groups.

In a similarly designed follow-up study of 65 patients, femoxetine (200–600 mg/d) and placebo were compared for migraine prophylaxis.[12] The study duration was in-

creased to 16 weeks, and the femoxetine dose was increased to 600 mg/d. No significant difference was found in attack frequency or headache index between groups treated with femoxetine or placebo.

Kangasniemi et al. compared propranolol (160 mg/d) to femoxetine (400 mg/d) for the prophylaxis of migraine headache in a randomized, double-blind, crossover study of 6 months' duration.[13] Attack frequency, headache index, and use of attack-relieving medication were significantly lower during treatment with propranolol ($p < .05$), but not with femoxetine.

Adly et al. compared fluoxetine (20–40 mg/d) with placebo in a randomized, double-blind study of 32 patients with migraine headache.[14] The fluoxetine group had a significant reduction in headache scores after 10 weeks compared with the placebo group ($p < .05$).

Bánk studied the efficacy of fluvoxamine (50 mg/d) and amitriptyline (25 mg/d) for the prophylaxis of migraine headache in a randomized, double-blind study of 64 patients.[15] Both treatment groups had significantly fewer and less severe headaches compared with baseline ($p < .02$). In addition, those treated with fluvoxamine had fewer side effects.

NEUROPATHY

Three placebo-controlled studies on the efficacy of SSRIs in relieving painful diabetic neuropathy came to different conclusions (Table 2). Max et al. compared amitriptyline with desipramine, and fluoxetine with placebo in concurrent, randomized, double-blind, crossover studies.[16] Compared with the placebo group, they found significant and equivalent pain relief in the groups treated with amitriptyline and desipramine ($p < .05$), but no significant improvement in the group receiving fluoxetine ($p = .34$).

Sindrup et al. studied 19 patients with diabetic neuropathy in a randomized, double-blind, crossover comparison of paroxetine (40 mg/d), imipramine (dose adjusted to keep serum imipramine plus desipramine levels between 400 and 600 nM), and placebo.[17] Compared with placebo, paroxetine significantly reduced symptoms of neuropathy ($p < .01$). Compared with paroxetine, imipramine reduced symptoms of neuropathy even more ($p < .01$). In patients with low serum levels of paroxetine, it was less effective than imipramine. Neither drug caused objective changes in peripheral nerve function as measured by vibration, temperature, or evoked potential testing.

In a subsequent dose escalation study of paroxetine, Sindrup and colleagues found that 15 of 19 patients had marked relief of their painful diabetic neuropathy.[18] The therapeutic effect occurred within 1 week, appeared to increase as plasma levels increased, and was maximal at plasma concentrations of 300 to 400 nM.

In another study, Sindrup et al. studied 18 patients with diabetic neuropathy in a randomized, double-blind, placebo-controlled, crossover study of citalopram (40 mg/d), an SSRI not available in the United States.[19] Citalopram relieved the pain associated with neuropathy better than placebo ($p < .02$).

FIBROMYALGIA

Three studies examined the effect of SSRIs on fibromyalgia (Table 3). Wolfe et al. randomized 42 women with fibromyalgia to receive either fluoxetine (20 mg/d) or placebo.[20] After 6 weeks, there was no difference between the fluoxetine and placebo groups. The study was weakened by a high rate of withdrawals (28.6% in the fluoxetine arm and 57.1% in the placebo arm).

In a randomized, double-blind, crossover study of 19 patients, Goldenberg et al. compared the independent and combined efficacy of fluoxetine (20 mg/d) and amitriptyline (25 mg/d) with placebo in the treatment of fibromyalgia.[21] Compared with the placebo group, the fluoxetine group showed significant improvements in scores on the Fibromyalgia Impact Questionnaire ($p = .006$) and on visual analogue scales for pain ($p < .001$), global well-being ($p = .02$), and sleep disturbances ($p = .04$). The amitriptyline group showed similar improvements. When fluoxetine and amitriptyline were used together, there was even greater improvement in these variables. Neither drug alone showed improvement in tender point score, or visual analogue scales for fatigue or feeling refreshed.

Nørregaard and colleagues studied 22 patients with fibromyalgia in a randomized, double-blind, placebo-

Table 2. Randomized, Double-Blind, Controlled Studies of SSRIs in Diabetic Neuropathy

Study	Design	*N*	Results
Max et al.,[16] 1992	Crossover of fluoxetine vs placebo	46	Fluoxetine = placebo ($p = .34$) In a concurrent study, both desipramine and amitriptyline were better than placebo ($p < .05$).
Sindrup et al.,[17] 1990	Crossover of paroxetine vs imiramine vs placebo	19	Compared to placebo, those receiving paroxetine improved ($p < .01$). Compared to placebo or paroxetine, those receiving imipramine improved ($p < .01$).
Sindrup et al.,[19] 1992	Crossover of citalopram vs placebo	18	Compared to placebo, those receiving citalopram had improvements in neuropathy as assessed by physicians ($p = .02$) and by patients themselves ($p = .007$).

Table 3. Randomized, Double-Blind, Controlled Studies of SSRIs in Fibromyalgia

Study	Design	N	Results
Wolfe et al.,[20] 1994	Fluoxetine vs placebo	42	Fluoxetine = placebo
Goldenberg et al.,[21] 1996	Crossover of fluoxetine vs amitriptyline vs placebo	19	Compared to placebo, those receiving fluoxetine showed improvement in their Fibromyalgia Impact Questionnaires ($p = .006$), and their visual analogue scales for pain ($p < .001$), global well-being ($p = .02$), and sleep disturbances ($p = .04$). When amitriptyline and fluoxetine were given together, there was further improvement.
Nørregaard et al.,[22] 1995	Citalopram vs placebo	22	Citalopram = placebo

controlled study of citalopram (20–40 mg/d).[22] After an 8-week treatment period, there were no significant improvements in pain, fatigue, general condition, sleep, tender points, or Beck Depression Scale scores in either group compared with baseline or compared with each other.

CHRONIC PAIN

Three studies found the use of SSRIs in patients with mixed-chronic pain beneficial (Table 4). Johansson and Knorring compared zimelidine (200 mg/d), an SSRI not available in the United States, with placebo in a randomized, double-blind study of 40 patients with chronic pain of either organic or psychogenic origin.[23] Those receiving zimelidine had improved pain relief as assessed by physicians' global rating ($p < .05$) and by patients' self-rating ($p < .05$). They had no significant changes in their common feeling of well-being, analgesic use, or depression ratings.

Gourlay et al. compared zimelidine (300 mg/d) with placebo in a randomized, double-blind, crossover study (6 weeks of each treatment) of 20 patients with chronic pain.[24] They found a significant improvement in pain relief with zimelidine based on global assessment by the doctor's assessment ($p < .05$), but not by the patient's assessment.

Usha Rani et al. compared fluoxetine (20 mg/d), amitriptyline (25 mg/d), and placebo in a randomized, double-blind, 4-week study of 59 patients with chronic rheumatic pain.[25] Twenty-seven patients had low back pain, 16 had osteoarthritis, 8 had fibromyalgia, and 8 had rheumatoid arthritis. After 4 weeks, compared with the placebo group, there was a significant reduction in pain intensity scores and pain relief scores for those treated with amitriptyline ($p < .05$) or fluoxetine ($p < .001$). There was significantly better relief in the fluoxetine group compared with the amitriptyline group ($p < .001$). More side effects occurred in the amitriptyline group than the fluoxetine group.

DISCUSSION

Among the various chronic pain syndromes, randomized, controlled trials have been performed to evaluate the role of SSRIs only in fibromyalgia, diabetic neuropathy, migraine headache, tension-type headache, and mixed-chronic pain.

Patients with chronic tension-type headache improved in one study of paroxetine, one study of fluoxetine, and one study of fluvoxamine, but only one of the studies was placebo-controlled. In one placebo-controlled study of citalopram, there was no improvement. Placebo controls are essential in trials of treatments with uncertain efficacy to control for placebo response, regression to the mean, and the natural history of the illness. Nevertheless, these results suggest that patients with chronic tension-type headache may benefit from SSRIs.

The results of studies on migraine headache are conflicting. Adly et al. found that patients receiving fluoxetine

Table 4. Randomized, Double-Blind, Controlled Studies of SSRIs in Chronic Pain

Study	Design	N	Results
Johansson and Knorring,[23] 1979	Zimelidine vs placebo	40	Compared to placebo, those receiving zimelidine had improved pain relief as assessed by their doctors ($p < .5$) and by the patients themselves ($p < .5$).
Gourlay et al.,[24] 1986	Crossover of zimelidine vs placebo	20	Compared to placebo, those receiving zimelidine had improved pain relief as assessed by their doctors ($p < .5$) but *not* by the patients themselves.
Usha Rani et al.,[25] 1996	Fluoxetine vs amitriptyline vs placebo	59	Compared to placebo, both amitriptyline and fluoxetine groups showed improvement in pain intensity and pain relief scores ($p < .05$). Those receiving fluoxetine improved more than those receiving amiriptyline ($p < .001$).

experienced improvement compared with baseline,[14] while Saper et al. found no benefit of fluoxetine versus placebo.[6] In a separate, multivariate analysis of the data of Adly et al. that took into account the strong placebo effect observed, Saper and colleagues found no significant difference between fluoxetine and placebo.[26] Two placebo-controlled studies of femoxetine found no difference between femoxetine and placebo.[11,12] Andersson and Petersen compared femoxetine to propranolol, a drug with proven efficacy in migraine headache, and found equal improvement with both.[10] In contrast, Kangasniemi et al. compared femoxetine with propranolol and found improvement only in the propranolol group.[13] In Bánk's comparison of fluvoxamine and low-dose amitriptyline, patients experienced similar improvement, but fewer side effects were noted with fluvoxamine.[15] Except Manna et al.,[8] no authors stratified for the presence of major depression or analyzed results separately for depressed and nondepressed groups.

The results of studies on diabetic neuropathy are also inconsistent. Max et al. found that, except in depressed patients, fluoxetine produced no more improvement in pain than placebo.[16] However, Sindrup et al. found a significant improvement in patients treated with either paroxetine or citalopram versus placebo.[17–19] A possible explanation is that serum levels of the treatment drugs were higher in the Sindrup et al. studies. Not enough information is offered in the articles to determine if the depression status of the treatment groups differed significantly.

In patients with fibromyalgia, two studies found no improvement with SSRIs over placebo.[20,22] In contrast, Goldenberg et al. found that patients with fibromyalgia benefitted from fluoxetine, especially when used in combination with amitriptyline.[21]

All three studies of chronic pain of mixed etiologies demonstrated improvement in those treated with SSRIs. However, in the study by Gourlay et al., the improvement was noted only by the physicians, not the patients.[24] The mixture of chronic pain conditions in the study of Usha Rani et al.,[25] and the lack of well-defined pain syndromes in Gourlay et al. and Johansson and Knorring's studies,[23,24] makes the implications of their results unclear.

Whether SSRIs improve chronic pain independent of their effects on coexisting depression remains unsettled. In the treatment of chronic tension-type headache, Saper et al. found improvement of mood and overall headache status was not limited to depressed patients and Beck Depression scores did not predict treatment outcomes.[26] Langemark et al. found improvement with paroxetine in patients who were not depressed at study entry as assessed by the Bech-Rafaelsen Melancholia rating scale.[7] Manna et al. found fluvoxamine was more effective than mianserine in the nondepressed subgroup of patients with more severe headache, while mianserine was more effective in depressed patients with moderate headache.[8] In the management of migraine headaches, Adly et al. found those receiving fluoxetine improved without any concomitant change in their Zung Depression scores.[14]

In the treatment of painful diabetic neuropathy, Sindrup et al. found improvement in patients treated with paroxetine who either were not depressed or did not experience an antidepressant effect as measured by the Beck Depression Inventory.[17,18] In contrast, Max et al. found that fluoxetine was more effective than placebo only in the subgroup of depressed patients.[16] In fibromyalgia, Goldenberg et al. found improvement in the fluoxetine group despite no change in their Beck Depression Inventories.[21] Two studies of chronic pain showed improvement in those treated with zimelidine without significant change in their depression scores.[23,24] All of these studies relied on self-report checklists rather than structured interviews to assess depression.

Of the remaining 10 studies reviewed, 8 did not assess changes in depression status during the studies. Since multiple SSRI depression trials have noted improvements in pain with improvements in depression,[27,28] future treatment trials will need thorough depression assessments to differentiate the SSRI antidepressant effect from any analgesic effect. Another confounding factor is drug dosing. Many trials used SSRIs at antidepressant doses, but tricyclic antidepressants at (lower) analgesic doses.

Overall, SSRIs seem well tolerated. Among patients receiving SSRIs, adverse reactions included headache, nausea, gastrointestinal upset, fatigue, insomnia, anxiety, and depression. In the articles reviewed, adverse reactions occurred in 20% to 84% of patients; however, these reactions were only treatment limiting in 0% to 41%.

Reviews of antidepressant analgesia suggest that antidepressants with both serotonin and norepinephrine reuptake inhibition show the greatest analgesic effect.[3] Trials in neuropathic pain have led some authors to suggest that norepinephrine reuptake inhibition is crucial for relief in diabetic and postherpetic neuralgia.[29] Animal testing has sometimes revealed different pain models to be responsive to different antidepressants. Ardid et al., for example, found SSRIs more effective in the hot plate test and noradrenergic agents more effective in the writhing test.[30] Agents with mixed action, such as amitriptyline, were found to be most effective on both tests. Intrathecal and epidural administration of both adrenergic (α_2)[31] and serotonergic[32] agonists produce analgesia in animal models. Thus, there is reason to believe that both norepinephrine and serotonin reuptake inhibition contribute to relief from chronic pain. Antidepressant agents with mixed action therefore remain the first choice for pain relief. Venlafaxine, a new antidepressant with both serotonergic and noradrenergic reuptake inhibition, lacks the troublesome anticholinergic and antiadrenergic actions of the tricyclic antidepressants. A number of clinical trials testing venlafaxine in chronic pain syndromes are under way, though at present there are only case reports supporting its use in chronic pain.[33]

In conclusion, despite the growing popularity of SSRIs since 1988, there are few controlled studies of their effi-

cacy in managing chronic pain syndromes. Among the studies available, the data are conflicting. The incidence of treatment-limiting adverse effects with SSRIs is low. Whether they provide analgesia independent of their effect on mood is unclear. Further placebo-controlled studies are needed to better elucidate the efficacy of SSRIs for chronic pain.

In three studies, selective serotonin reuptake inhibitors provided less relief than agents with a broader range of reuptake inhibition. Sindrup et al. found that imipramine relieved diabetic neuropathy more effectively than paroxetine.[17] Max and colleagues found a significant improvement in diabetic neuropathy with amitriptyline and desipramine, but not with fluoxetine.[16] Bendtsen et al. found improvement in tension-type headache with amitriptyline, but not citalopram.[9] This suggests that analgesia may be mediated by a combination of serotonin and other neurotransmitters, especially norepinephrine. Given this evidence for the superiority of antidepressants with mixed mechanisms of action and the well-documented efficacy of tricyclic antidepressants in the management of various chronic pain syndromes, it seems reasonable to use tricyclic antidepressants first and reserve SSRIs for patients who do not respond to or are intolerant of the tricyclic antidepressants.

We gratefully acknowledge Douglas Paauw, MD, and Timothy Evans, MD, for assistance in reviewing the manuscript.

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