Off-Label Applications for SSRIs

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Selective serotonin reuptake inhibitors (SSRIs) are widely used because of their safety, tolerability, and demonstrated efficacy across a broad range of clinical conditions. Medical literature supports the use of SSRIs for the treatment of many conditions outside of the indications approved by the U.S. Food and Drug Administration. SSRIs offer a reasonable alternative to traditional therapy for generalized anxiety disorder. A side effect of SSRIs coincidentally provides therapy for premature ejaculation. SSRIs may reduce the frequency and severity of migraine headaches and are possibly effective in reducing the pain of diabetic neuropathy. When taken in combination with tricyclic antidepressants, SSRIs offer more potent therapy for fibromyalgia than either agent alone. SSRIs appear to be effective in some patients with neurocardiogenic syncope that is refractory to standard therapies. Clinical experience supported by ongoing research continues to expand on the broad array of therapeutic applications for this class of medication. (Am Fam Physician 2003;68:498-504.

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Selective serotonin reuptake inhibitors (SSRIs) were initially developed to relieve depression and have become the most commonly prescribed class of antidepressants.[1] SSRIs block the reuptake of serotonin at the presynaptic neuron, with minimal or no effect on norepinephrine or dopamine. This narrow mechanism of action confers similarity of efficacy and tolerability with few side effects.[1]

The following five SSRIs have been approved by the U.S. Food and Drug Administration (FDA) for use in the United States: citalopram (Celexa), fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), and sertraline (Zoloft). Although the FDA has approved these SSRIs for treatment of a variety of conditions, the medical literature supports their use for a number of "off-label" indications. Off-label use does not imply improper or illegal use.[2] The FDA cannot give approval for further indications until it has reviewed new efficacy and safety data provided by the pharmaceutical companies.

The use of a well-documented therapy that lacks a specific "labeling" should not be precluded. The decision to prescribe a given medication should be based on the available evidence and a careful consideration of the potential risks and benefits in the context of the individual patient.

See page 406 for definitions of strength-of-evidence levels.

See editorial on page 425.

This article reviews the use of SSRIs for six conditions commonly managed by family physicians: generalized anxiety disorder, premature ejaculation, migraine headache, diabetic neuropathy, fibromyalgia, and neurocardiogenic syncope *(Table 1)*.[3-20]

Generalized Anxiety Disorder

Generalized anxiety disorder (GAD) is one of the most prevalent psychiatric disorders. Benzodiazepines such as diazepam (Valium), alprazolam (Xanax), and clonazepam (Klonopin), which are used to treat GAD, can cause sedation, difficulty concentrating, and other bothersome side effects. Dependence can develop, leading to withdrawal symptoms on discontinuation of these agents. Buspirone (BuSpar), a nonbenzodiazepine anxiolytic that does not lead to dependence, is an effective alternative, but it must be taken three times daily.[21]

SSRIs have been prescribed safely and effectively for mixed anxiety and depression syndromes, as well as for social anxiety.[22] Paroxetine may be effective for GAD treatment.[5] [Evidence level A, randomized controlled trial (RCT)]

TABLE 1
Off-Label Applications of SSRIs

Condition	*Medication and recommended dosages*	*Efficacy/recommendations*	*Level of evidence*
Generalized anxiety disorder	Fluvoxamine (Luvox), 50 to 300 mg daily[3,4]	Effective; may be a good long-term alternative to benzodiazepines or other anxiolytics	A: RCT
	Paroxetine (Paxil), 20 to 60 mg daily (generalized anxiety disorder is not an off-label use)[5]	—	A: RCT
Premature ejaculation	Paroxetine, 20 mg daily or as needed a few hours before anticipated sexual activity[6,7]	Effective; consider as first-line treatment	A: RCT
	Sertraline (Zoloft), 25 to 50 mg daily or as needed a few hours before anticipated sexual activity[6,8,9]		
	Fluoxetine (Prozac), 20 mg daily[6]		
Migraine headaches (prophylaxis)	Fluoxetine, 20 to 40 mg daily[10-12]	May be useful if patient cannot use standard prophylactic agents or if other agents fail; good choice if patient has concomitant depression or other illness treatable with SSRI	A: RCT
Diabetic neuropathy	Paroxetine, 40 mg daily[13]	Possibly effective; other drugs should be considered first. One meta-analysis found no difference between placebo and SSRIs.	B: lower quality RCT
Fibromyalgia	Fluoxetine, 20 mg daily[14,15]	Possibly effective, particularly when combined with amitriptyline (Elavil)	B: lower quality RCT
	Citalopram (Celexa), 20 to 40 mg daily[16,17]	Studies on citalopram showed no significance	B: lower quality RCT
Neurocardiogenic syncope	Paroxetine, 20 mg daily[18]	May be useful if standard treatments fail	A: RCT
	Sertraline, 50 mg daily[19]	Has been studied in children	B: nonrandomized, small, prospective trial
	Fluoxetine, 20 mg daily[20]	—	B: nonrandomized, small, prospective trial

SSRIs = selective serotonin reuptake inhibitors; RCT = randomized controlled trial.

Information from references 3 through 20.

Delayed or inhibited ejaculation, a known side effect of SSRIs, has made SSRIs potentially useful in the management of premature ejaculation.

In the trial,[5] 81 patients were randomized to treatment with paroxetine (20 mg daily), imipramine (Tofranil), or the benzodiazepine 2'chlordesmethyldiazepam. The patients had a diagnosis of GAD according to criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed (DSM-IV), a score of at least 18 on the Hamilton Rating Scale for Anxiety (HRSA), and no comorbid psychiatric conditions. The patients ranged from 18 to 65 years of age. Demographics were similar in each group. Sixty-three patients (77.7 percent) completed the study. Using the HRSA to measure response, 68 percent of the patients in the paroxetine group, 72 percent in the imipramine group, and 55 percent in the 2'chlordesmethyldiazepam group had at least a 50 percent decrease in HRSA score by the end of the eight-week study. Paroxetine was recently approved by the FDA for GAD treatment.

SSRIs may be particularly useful in the treatment of GAD in pediatric patients.[3] [Evidence level A, RCT] In a multicenter, double-blind trial, 128 children six to 17 years of age with social phobia, separation anxiety disorder, or GAD (as defined by DSM-IV) were randomized to treatment with fluvoxamine or placebo.[3] All had received three weeks of psychotherapy without showing improvement. Fluvoxamine was chosen because it was the only SSRI approved by the FDA for use in children in 1996 when the study was designed. Fluvoxamine therapy (at a maximum dosage of 300 mg daily) resulted in a statistically significant decrease in scores on the Pediatric Anxiety Rating Scale compared with placebo. Although this trial was not specific to GAD, it was noted that anxiety disorders in children typically occur together, thereby making it difficult to isolate one disorder for study.

SSRIs seem particularly suited for use in older patients with anxiety disorders.[4] [Evidence level B, nonrandomized trial] In a small, open-label trial, patients more than 50 years of age with GAD, panic disorder, or obsessive-compulsive disorder were treated with fluvoxamine (median dose, 200 mg daily).[4] Twelve of 19 patients (63 percent) completed the 21-week study, with eight of the 12 (66.6 percent) achieving a 50 percent reduction in symptoms as measured by standardized scales. The existence of comorbid depression, as well as the confounding variable of therapy combined with benzodiazepines, were two further limitations of this trial. The authors conclude that randomized, placebo-controlled trials are warranted to study the use of SSRIs for treatment of anxiety disorders in the older population.

Premature Ejaculation

Though premature ejaculation has been overshadowed by recent attention given to erectile dysfunction, it is the most prevalent form of male sexual dysfunction.[23] Delayed or inhibited ejaculation, a known side effect of SSRIs, has made SSRIs potentially useful in the treatment of this disorder. The ejaculation-delaying effect was analyzed in a double-

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blind, placebo-controlled trial completed by 51 men.[6] Fluoxetine, sertraline, and paroxetine have been found to increase the latent period of intravaginal ejaculation and therefore to be beneficial in patients who prematurely ejaculate.[6] [Evidence level A, RCT] Fluvoxamine had the least effect in increasing ejaculatory latency, a difference that was not statistically significant compared with placebo. Citalopram was not studied.

It was demonstrated in a second study[6] that SSRI-induced ejaculation delay is probably an effect independent of the baseline ejaculatory latency time.

In a study of 46 men 22 to 63 years of age who prematurely ejaculate (with a baseline mean ejaculatory interval of less than one minute), sertraline increased the ejaculatory interval in a dose-dependent fashion.[8] At 25 mg daily, sertraline increased the mean ejaculatory interval to 7.6 minutes with the fewest side effects and with no men experiencing anejaculation. At 50 mg daily, the mean ejaculatory interval increased to 13.1 minutes with four men experiencing anejaculation and two men experiencing minor side effects (drowsiness, anorexia, dyspepsia). At 100 mg daily, the mean ejaculatory interval increased to 16.4 minutes, but 10 men experienced anejaculation and two men experienced erectile dysfunction and decreased libido.

Studies also show that SSRIs, particularly sertraline[9] and paroxetine,[7] can probably be used on an as-needed basis and taken a few hours before anticipated sexual activity. [Reference 9—Evidence level B, nonrandomized trial; Reference 7—Evidence level B, randomized crossover trial]

Migraine Headache Prophylaxis

There is fair support for the effectiveness of SSRIs in migraine prophylaxis. Prophylactic treatments for migraine headaches have included tricyclic antidepressants, beta-adrenergic blockers, and calcium channel blockers. These medications are frequently associated with an unfavorable side effect profile and may not be well tolerated by a significant number of patients with migraines. Because most theories of migraine pathophysiology focus on altered serotonergic metabolism, and given the favorable tolerability of SSRIs, the use of SSRIs in migraine prophylaxis has been studied.[10-12,24] While published results are promising, most authors acknowledge that these studies are only preliminary.

Three randomized, double-blind, placebo-controlled studies showed a decrease in the frequency and severity of migraine headaches with fluoxetine therapy.

Most studies used fluoxetine. Of these, at least four were randomized, double-blind, placebo-controlled studies.[10-12,24] Three of these four studies showed a significant decrease ($P < .05$) in the frequency and severity of headaches.[10-12] [References 10, 11, and 12—Evidence level A, RCT] The patients ranged from 18 to 65 years of age, and the minimum frequency of migraines ranged from more than one per month to more than one per week. Daily dosages of fluoxetine ranged from 20 to 40 mg in these studies.

Evidence is limited regarding the use of the other SSRIs in migraine headache treatment. One randomized comparison study of fluvoxamine and amitriptyline (Elavil) showed that fluvoxamine decreased the number of migraine attacks as effectively as amitriptyline.[25] [Evidence level B, double-blind comparison]

Diabetic Neuropathy

Tricyclic antidepressants are well established as effective therapy for the symptoms of diabetic neuropathy.[26,27] Although mexiletine (Mexitil), capsaicin (Zostrix), carbamazepine (Tegretol), and gabapentin (Neurontin) are among other therapies that have been shown to be effective in treating neuropathic pain, no single medication has proved to be consistently effective.[28-31] SSRIs should not be considered as first-line therapy for diabetic neuropathy; the

SSRIs should not be considered as first-line therapy for diabetic neuropathy, because the evidence for their use for this purpose is limited.

evidence for their use is fair and indicates that SSRIs may be only possibly effective.

A randomized, double-blind, crossover study of 29 patients found both imipramine (50 to 75 mg daily) and paroxetine (40 mg daily) to be superior to placebo.[13] [Evidence level B, lower quality RCT] Imipramine, however, was significantly better than paroxetine for relieving nearly all symptoms, including pain and sleep disturbance.

However, one study did not find SSRIs to be superior to placebo in relieving painful neuropathy.[32] [Evidence level A, meta-analysis] The meta-analysis of RCTs compared the efficacy and adverse effects of antidepressants and anticonvulsants in treating neuropathic pain, including diabetic neuropathy. Overall, for every three patients treated with a tricyclic antidepressant or an anticonvulsant, one experienced a 50 percent reduction in pain (number needed to treat [NNT] of three). While the authors noted the lack of statistically significant improvement using the pooled data of SSRIs, they thought the data insufficient to "draw a robust conclusion."[32]

Another review of RCTs found SSRIs to be helpful in treating diabetic neuropathy but confirmed that they are not as efficacious as other therapies.[33] [Evidence level B, nonquantitative systematic review] An NNT of 1.4 was calculated for imipramine, compared with the NNT of 2.4 calculated from other studies of tricyclic antidepressants. The NNT was 1.9 for dextromethorphan (Delsym), 3.3 for carbamazepine, 3.4 for tramadol (Ultram) and levodopa (Larodopa), 3.7 for gabapentin, 5.9 for capsaicin, 6.7 for SSRIs, and 10.0 for mexiletine. It was cautioned that, with the exception of the tricyclic antidepressants, these numbers were calculated on the basis of few trials or small total patient numbers per drug.

Fibromyalgia

Fibromyalgia is the most common rheumatic cause of chronic pain.[34] Medications most commonly prescribed are tricyclic antidepressants, SSRIs, muscle relaxants, simple analgesics, and nonsteroidal anti-inflammatory drugs.[35] Pharmacologic therapies have shown only modest benefit at best. A meta-analysis of 49 studies found exercise and cognitive behavior therapy to be more efficacious than pharmacologic treatment alone.[36] [Evidence level A, meta-analysis] The results of the few RCTs involving SSRIs have been mixed.

Two small trials of citalopram (20 to 40 mg daily) failed to reach significance, although there were subtle trends toward improvements in sleep, pain, and functioning.[16,17] [References 16 and 17—Evidence level B, lower quality RCTs] A trial of fluoxetine (20 mg daily) did not show significant improvement after six weeks of therapy, but the study was limited by a 43 percent dropout rate from an initially small sample of 42 patients.[14] [Evidence level B, lower quality RCT]

Conversely, a crossover, placebo-controlled trial comparing fluoxetine (20 mg daily) and amitriptyline (25 mg daily) demonstrated significant improvement in global well-being, pain, and sleep for each medication alone, and further improved efficacy when the two were used in combination.[15] [Evidence level B, lower quality RCT] Nineteen of 31 initial participants (61 percent) completed each of four six-week trials separated by two-week washout periods. Significant improvement was noted by 63 percent of those taking the combination compared with 32 percent and 24 percent of patients taking a single agent. The effects were independent of coexistent depression. The study was limited by the dropout rate and has not been duplicated.

Although the Cochrane Musculoskeletal Group is performing a systematic review to

assess the efficacy of SSRIs versus placebo and other antidepressants, it is clear that further study is necessary.[37] Currently, SSRIs, with or without tricyclic antidepressants, can be viewed as only possibly effective in patients with unsatisfactory responses to nonpharmacologic therapy.

Neurocardiogenic Syncope

SSRIs appear to be an effective treatment in neurocardiogenic syncope refractory to standard therapies. Neurocardiogenic syncope, or vasovagal syncope, is a common disorder of transient autonomic nervous system dysfunction.[38] Although no definitive treatment for neurocardiogenic syncope exists, standard therapies such as atenolol (Tenormin) and midodrine (ProAmatine) have demonstrated efficacy. Fludrocortisone (Florinef) and increased salt and fluid intake are commonly used as well.[38]

One randomized, double-blind, placebo-controlled study involved the use of paroxetine in the treatment of neurocardiogenic syncope refractory to standard therapies.[18] [Evidence level A, RCT] Paroxetine (20 mg daily) was found to significantly improve symptoms in patients refractory to or intolerant of standard treatments. Of the 68 patients in the study, all of whom had a documented positive head-up tilt test initially, 61.8 percent in the paroxetine group versus 38.2 percent in the placebo group had negative tilt table tests after one month. During the approximately two-year follow-up period, spontaneous syncope occurred in 17.6 percent in the paroxetine group compared with 52.9 percent in the placebo group. Paroxetine was generally well tolerated.

Smaller, nonrandomized, prospective studies (two involving pediatric patients) involved the use of sertraline and fluoxetine in the treatment of refractory neurocardiogenic syncope.[19,20,39] Each of these agents showed promising results, with most patients having a negative repeat tilt test or remaining symptom-free for at least six months.

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