Antidepressants: Update on New Agents and Indications

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A number of antidepressants have emerged in the U.S. market in the past two decades. Selective serotonin reuptake inhibitors have become the drugs of choice in the treatment of depression, and they are also effective in the treatment of obsessive-compulsive disorder, panic disorder, and social phobia. New indications for selective serotonin reuptake inhibitors include post-traumatic stress disorder, premenstrual dysphoric disorder, and generalized anxiety disorder. Extended-release venlafaxine has recently been approved by the U.S. Food and Drug Administration for the treatment of generalized anxiety disorder. Mirtazapine, which is unrelated to the selective serotonin reuptake inhibitors, is unique in its action—stimulating the release of norepinephrine and serotonin. The choice of antidepressant drug depends on the agent's pharmacologic profile, secondary actions, and tolerability. Sexual dysfunction related to the use of antidepressants may be addressed by reducing the dosage, switching to another agent, or adding another drug to overcome the sexual side effects. Augmentation with lithium or triiodothyronine may be useful in patients who are partially or totally resistant to antidepressant treatment. Finally, tapering antidepressant medication may help to avoid discontinuation syndrome or antidepressant withdrawal. (Am Fam Physician 2003;67:547-54. Copyright© 2003 American Academy of Family Physicians)

See page 441 for definitions of strength-of-evidence levels.

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According to a recent survey[1] of the most common reasons for patient visits to family physicians in the United States, depression and anxiety ranked 11th and 17th, respectively. Ten to 20 percent of adults in the United States experience depression at some point in their lifetime.[2] Many antidepressants have been released in the United States over the past two decades. This article is an update of information about the newer agents for depression and new indications for older antidepressants.

Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) have replaced tricyclic antidepressants as the drugs of choice in the treatment of depressive disorders, mainly because of their improved tolerability and safety if taken in overdose. SSRIs block the reuptake of serotonin (5-HT_{1A}, 5-HT_{2C}, and 5-HT_{3C}) into the presynaptic nerve terminal, thereby enhancing serotonin neurotransmission, which presumably results in their antidepressant effects.

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Although this is the predominant mechanism of action of this class of drugs, each SSRI has a slightly different pharmacologic profile that leads to its distinct clinical activity, side effects, and drug interactions.[3] Six SSRIs are currently marketed in the United States; five of them have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of depression *(Table 1)*.

Numerous double-blind, placebo-controlled trials have demonstrated the efficacy of SSRIs in the treatment of depression. In addition, SSRIs have been proved effective in treating anxiety disorders, including obsessive-compulsive disorder (OCD), panic disorder, and social phobia.[4] Common side effects of SSRIs include transient nausea, diarrhea, insomnia, somnolence, dizziness, akathisia, and long-term orgasmic dysfunction.[5] However, secondary pharmacologic actions may

TABLE 1
Comparison of Selected Antidepressants

Drug	*Availability*	*Cost (generic)**	*Indications†*
SSRIs			
Fluoxetine (Prozac)	Capsules, 10, 20, 40 mg Tablets, 10 mg‡ Oral solution, 20 mg/5 mL	$ 91 (78 to 80) (26 to 78)§ 138 per 120 mL	Depression; OCD; bulimia nervosa
(Prozac Weekly)	Capsules, 90 mg	76	Depression; OCD; bulimia nervosa
(Sarafem)	Capsules, 10, 20 mg	91	PMDD
Sertraline (Zoloft)	Tablets, 25,‡ 50,‡ 100 mg‡ Oral concentrate, 20 mg/mL	75 60 per 60 mL	Depression; OCD; panic disorder; PTSD; PMDD
Paroxetine (Paxil)	Tablets, 10,‡ 20,‡ 30, 40 mg Oral suspension, 10 mg/5 mL	81 131 per 250 mL	Depression; OCD; panic disorder; social phobia; GAD; PTSD
(Paxil CR)	Tablets, 12.5, 25, 37.5 mg	83	Depression; panic disorder
Fluvoxamine (Luvox)	Tablets, 25, 50, 100 mg Tablets, 25, 50,‡ 100 mg‡	88 70 to 81	OCD
Citalopram (Celexa)	Tablets, 10, 20,‡ 40 mg‡ Oral solution, 10 mg/5 mL	65 106 per 240 mL	Depression
Escitalopram (Lexapro)	Tablets, 5, 10,‡ 20 mg‡	63	Depression
Venlafaxine (Effexor)	Tablets, 25,‡ 37.5,‡ 75,‡ 100 mg‡	41	Depression; GAD
(Effexor XR)	Capsules, 37.5, 75, 150 mg	78	Depression; GAD
Mirtazapine (Remeron)	Tablets, 15,‡ 30,‡ 45 mg	83	Depression

SSRIs = selective serotonin reuptake inhibitors; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PTSD = post-traumatic stress disorder; GAD = generalized anxiety disorder.

**—Costs are average wholesale prices for 30 days of the lowest-dose therapy from Red Book. Montvale, N.J.: Medical Economics Data, 2002, rounded to the nearest dollar. Cost to patient will be higher depending on filling fees.*

†—*Approved by the U.S. Food and Drug Administration.*

‡—*Scored tablets.*

§—*Tablet available in generic form only.*

account for differences in efficacy and tolerability and may assist the prescriber in selecting a specific SSRI for an individual patient. As with all antidepressants, care must be taken with SSRIs to screen patients for symptoms of bipolar disorder before prescribing, to avoid precipitating a manic episode.

FLUOXETINE

Fluoxetine (Prozac) was the first SSRI to be FDA-approved for the treatment of depression. Administration usually begins with 20 mg per day, taken in the morning because of its potential for central nervous system activation early in the treatment course. It is the only SSRI that is FDA-approved specifically for the treatment of depression in patients who are 65 years of age or older.[6] A starting dose of 10 mg per day is preferred in elderly patients, with subsequent titration to 20 mg per day or more. Dosages of 20 to 40 mg per day are commonly required for the treatment of depression; 60 to 80 mg per day may be necessary for the treatment of bulimia and OCD[7] *(Table 1)*.

In January 2003, fluoxetine was approved by the FDA for the treatment of depression and OCD in children and adolescents who are seven to 17 years of age.[6] Because fluoxetine has a half-life of two to four days and its active ingredient, norfluoxetine, has a half-life of seven to nine days, it is reasonable to wait four weeks between dose titrations.

Fluoxetine is now available in a special form taken once-weekly for continuation therapy of depression. Prozac

TABLE 2
Selected Antidepressant Drug Interactions

Antidepressant	*Drug interactions*	*Clinical effect*
Fluoxetine (Prozac)	Warfarin (Coumadin) TCAs, carbamazepine (Tegretol), phenytoin (Dilantin)	Possible increase in risk of bleeding Increase in levels, with possible toxicity
Sertraline (Zoloft)	TCAs	Increase in levels, with possible toxicity (high doses only)
Paroxetine (Paxil)	Warfarin (Coumadin) TCAs	Possible increase in risk of bleeding Increase in levels, with possible toxicity
Citalopram (Celexa)	See "All"	
Escitalopram (Lexapro)	See "All"	
Fluvoxamine (Luvox)	Warfarin (Coumadin) TCAs, theophylline	Possible increase in risk of bleeding Increase in levels, with possible toxicity
Venlafaxine (Effexor)	See "All"	
Mirtazapine (Remeron)	Clonidine (Catapres)	One case of hypertensive urgency
All	Any drug that increases serotonin concentrations, including: MAOIs, tramadol (Ultram), sibutramine (Meridia), meperidine (Demerol), sumatriptan (Imitrex), lithium, St. John's wort, ginkgo biloba, and atypical antipsychotic agents	Serotonin syndrome: mental status changes, agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, incoordination, and fever. May be life-threatening.

TCA = tricyclic antidepressants; MAOI = monoamine oxidase inhibitors.

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Weekly is a capsule with pellets containing 90 mg of fluoxetine hydrochloride. The enteric coating prevents dissolution of the pellets until they have passed into the portion of the gastrointestinal tract where the pH exceeds 5.5.[6] In a study[8] of 500 patients with depression, the percentage of patients relapsing during continuation treatment with a 90-mg weekly dose was not significantly different from those taking a 20-mg daily dose. Side effects were similar in both groups. Weekly dosing is recommended to begin seven days after the last daily dose of 20 mg *(Table 1)*.

Fluoxetine (under the trade name Sarafem) is now indicated for the treatment of premenstrual dysphoric disorder (PMDD), also known as late luteal dysphoric disorder or premenstrual syndrome. Improvement in symptoms of tension, irritability, and dysphoria has been demonstrated.[9] [Evidence level A, randomized controlled trial (RCT)] Side effects were comparable with those reported in studies of fluoxetine used for other indications. The usual dosage of the drug is 20 mg orally once daily throughout the month[10] *(Table 1)*.

Administration of fluoxetine during the late luteal phase alone has been investigated in a small study[11] of 24 women with PMDD and no psychiatric history. The drug was taken for 14 days premenstrually for only three menstrual cycles. Seventy-five percent of the women reported significant improvement in premenstrual symptoms. Thus, noncontinuous use of fluoxetine for this indication may be an effective option.

The most common early side effects of fluoxetine are agitation, insomnia, and neuromuscular restlessness resembling akathisia. This may be caused by fluoxetine's relative lack of selectivity over norepinephrine and serotonin-2C receptors (5-HT_{2C}).[3] These side effects are short-lived and may improve with a dose reduction or temporary co-administration of a beta-adrenergic blocker or long-acting benzodiazepine.[7] Clinically important drug interactions are listed in *Table 2*. Because of its long half-life, patients should allow at least five weeks between discontinuation of fluoxetine and commencement of monoamine oxidase inhibitor (MAOI) therapy.[5]

Fluoxetine may be an appropriate antidepressant choice in patients with hypersomnia or psychomotor retardation and should probably be avoided in patients with concomitant anxiety, panic, and agitation.[3]

SERTRALINE

Sertraline (Zoloft) is begun at a dosage of 50 mg per day and titrated to a dosage range of 100 to 200 mg per day in a single daily dose or divided daily doses[12] *(Table 1)*. In elderly patients or patients with concomitant anxiety disorders, a starting dose of 25 mg per day is recommended. The initial dose in children (six to 12 years of age) with OCD is 25 mg; patients who are at least 13 years of age may take adult doses.

Sertraline is also indicated for the treatment of posttraumatic stress disorder (PTSD). In two studies, male and female outpatients with PTSD who were randomized to 12 weeks of treatment with sertraline experienced significantly more relief from symptoms of avoidance/numbing and hyperarousal than did patients treated with placebo.[13,14] [References 13 and 14—Evidence level A, RCTs] Intrusive thoughts/re-experiencing phenomena also improved, although the degree of improvement was not statistically significant for each symptom scale. Whether patients with PTSD will benefit from long-term treatment with sertraline or a combination of the drug and behavior therapy is presently unknown.

The newest indication for sertraline is the treatment of PMDD. Sertraline has been shown to improve quality-of-life scores and psychologic and behavior symptoms in patients with PMDD.[15,16] [Reference 15—Evidence level A, RCT] Its effectiveness has been demonstrated with both continuous dosing throughout the month and luteal-phase dosing. The most common side effects of sertraline are nausea, dry mouth, fatigue, and decreased libido. Treatment with sertraline should be started at 50 mg, either daily throughout the month or daily during the luteal phase of the menstrual cycle. Patients who are not responding to 50 mg per day may benefit from dosage increases up to 150 mg per day continuously or 100 mg per day for luteal-phase treatment. If 100 mg per day has been established for luteal-phase dosing, 50 mg per day for three days is recommended at the beginning of each dosing period.

Sertraline has been associated with more cases of diarrhea than fluoxetine, but with fewer cases of anxiety and insomnia. At high doses, sertraline is an inhibitor of the CYP2D6 enzyme, but clinically significant drug interactions are unusual *(Table 2)*. Nevertheless, a two-week washout period is recommended before initiation of therapy with MAOIs.[12]

PAROXETINE

In the treatment of depression, paroxetine (Paxil) is initiated at a dosage of 20 mg per day *(Table 1);* elderly patients or patients with anxiety disorders may start at a dosage of 10 mg per day.[17] The upper limit of the dosage range is 40 to 60 mg per day. In a small, open-label study[18] of children with depression, 10 mg daily was the preferred initial dose.

Paroxetine was recently approved by the FDA for the treatment of social phobia and generalized anxiety disorder (GAD). Treatment with 12 weeks of paroxetine in patients who had social phobia resulted in significant reductions on the Liebowitz Social Anxiety Scale.[19] [Evidence level A, RCT] In an eight-week placebo-controlled study of 324 patients with GAD, patients treated with paroxetine had significantly greater reduction of GAD symptoms.[20]

Paroxetine was recently approved for the treatment of PTSD. In two 12-week, double-blind, randomized, placebo-controlled trials, patients treated with 20 to 50 mg per day of paroxetine showed improvement in all three symptom clusters associated with PTSD: re-experiencing, avoidance/numbing, and hyperarousal.[21,22] [References 21 and 22—Evidence level A, RCTs] Functional improvement was demonstrated in both studies.

The side effect profile of paroxetine is similar to that of the other SSRIs except that paroxetine tends to be more sedating and constipating, probably because of its anticholinergic activity.[7] The potential for weight gain, drug interactions, and sexual dysfunction tends to be slightly higher with paroxetine than with fluoxetine and sertraline *(Table 2)*. As with all SSRIs, it should not be taken in combination with MAOIs, and there should be a two-week washout period before starting MAOI therapy.[18]

Recently, Paxil CR was brought to market in the United States in an attempt to decrease the gastrointestinal side effects of immediate-release paroxetine.[23] The recommended initial dosage for the treatment of depression is 25 mg per day, with a range of 25 to 62.5 mg per day. Dosage changes should occur at intervals of no less than one week. In patients with panic disorder, a starting dosage of 12.5 mg per day is recommended. Up to 75 mg per day may be used in these patients. Patients should be counseled

that the tablets are to be swallowed whole and not crushed or chewed.

Paroxetine may be useful in patients with anxiety disorder or insomnia.[3] It should probably be avoided in patients in whom the mild anticholinergic activity would be undesirable, such as those with Alzheimer's disease or other cognitive disorders.

Escitalopram (Lexapro) is the newest and most selective of the selective serotonin reuptake inhibitors approved by the FDA for the treatment of depression.

CITALOPRAM

Citalopram (Celexa), which is approved by the FDA for the treatment of depression, has been associated with low rates of insomnia, anxiety, and other activating side effects.[24] Nausea is the most common early side effect, but it should be transient. No clinically significant drug interactions have been documented *(Table 2)*. The dosage range for citalopram is 20 to 60 mg per day *(Table 1);* the higher dose is typically used in the treatment of OCD.[7] Dosage reduction to 10 mg per day may alleviate early nausea. This drug may be appropriate in patients taking multiple medications because of its low potential for drug interactions and in elderly patients because of its tolerability.[3]

Escitalopram (Lexapro) is the newest and most selective of the SSRIs approved by the FDA for the treatment of depression. It is the active isomer of racemic citalopram.[25] Two double-blind studies[26,27] demonstrated its efficacy in the treatment of depression. Escitalopram at a dosage of 10 mg per day was significantly more effective than placebo and as effective as citalopram at a dosage of 40 mg per day. Nausea was reported significantly more often in the escitalopram-treated patients compared with placebo-treated patients. Frequency of side effects such as nausea and diarrhea were similar in escitalopram-treated and citalopram-treated patients. The recommended dosage of escitalopram is 10 mg per day *(Table 1)*. There is no greater benefit from 20 mg per day. No dosage adjustments are needed in patients with hepatic impairment or mild to moderate renal impairment. As with citalopram, the potential for drug interactions is low.

FLUVOXAMINE

Fluvoxamine (Luvox) is FDA-approved only for the treatment of OCD in patients who are at least eight years of age and older,[28] although its spectrum of activity is likely to be similar to that of other SSRIs. The initial dosage in adults is 50 mg daily, titrating up to 150 to 250 mg per day divided into two doses *(Table 1)*. Children can be started at a dosage of 25 mg at bedtime, increasing every week to a maximum of 200 mg per day in divided doses. The most common side effects are nausea, vomiting, and headache. Clinically important drug interactions with fluvoxamine are listed in *Table 2*.

Venlafaxine

Venlafaxine (Effexor) is a structurally novel compound first approved by the FDA for the treatment of major depression in 1993.[29] It is a bicyclic antidepressant that produces strong inhibition of norepinephrine and serotonin reuptake.[7] Venlafaxine was first released in an immediate-release (IR) form that is taken two or three times daily. In 1997, an extended-release form (Effexor XR) was approved by the FDA, allowing for once-daily administration. The recommended venlafaxine XR starting dosage is 37.5 mg to 75 mg per day *(Table 1)*. The dosage may be increased in increments of up to 75 mg every four to seven days, to a maximum daily dosage of 225 mg.

Venlafaxine is the first antidepressant that is proved effective in treating patients with GAD, with or without depression.[30] The dosage range is the same for GAD as for the treatment of depression. Because some patients can experience jitteriness with the usual starting dose of 75 mg per day, beginning treatment at a dose of 37.5 mg per day for the first week is advisable.

The side effect profile is comparable to that of the SSRIs and lower than that of the tricyclic antidepressants. The most common side effects include nausea, dizziness, insomnia, somnolence, and dry mouth.[29] Anticholinergic side effects are significantly less severe than those encountered with other antidepressants. Sexual side effects are similar to side effects caused by SSRIs.

There were initial reports of significant elevations in diastolic blood pressure; however, subsequent analyses show that this phenomenon is significant only above a dosage of 300 mg daily.[31] No clinically significant drug interactions have been documented *(Table 2)*. A troublesome discontinuation syndrome may occur with abrupt discontinuation. To avoid this syndrome, venlafaxine XR

should be tapered by reducing the daily dose by 75 mg at one-week intervals.

Mirtazapine

Mirtazapine (Remeron) is a tetracyclic antidepressant unrelated to tricyclic antidepressants and SSRIs. It is unique in its action among the currently available antidepressants.[32] Mirtazapine is a presynaptic alpha$_2$-adrenergic receptor antagonist plus a potent antagonist of postsynaptic 5-HT$_2$ and 5-HT$_3$ receptors. The net outcome of these effects is stimulation of the release of norepinephrine and serotonin.

Current evidence suggests that mirtazapine is effective in the treatment of depressive illness at all levels of severity. In addition, analyses of placebo-controlled trials in moderate and severe depression have shown mirtazapine to be effective in subgroups of depressed patients, particularly those with anxiety, sleep disturbance, and agitation, as well as mentally retarded patients.[33]

Mirtazapine has an onset of efficacy of two to four weeks, although sleep disturbances and anxiety symptoms may improve in the first week of treatment.[32] In a review[34] of multiple double-blind studies comparing mirtazapine with SSRIs, the proportion of responders with onset of persistent improvement in week 1 was twice as great with mirtazapine (13 percent versus 6 percent).

Because of its unique pharmacologic profile, mirtazapine is virtually devoid of anticholinergic, adrenergic, and serotonin-related side effects. The most frequently reported adverse events were fatigue, dizziness, transient sedation, and weight gain.[35] Sexual dysfunction is not a side effect of this agent. Drug interactions with mirtazapine have not been studied systematically *(Table 2)*. The recommended starting dosage is 15 mg at bedtime, which may be titrated up to 45 mg daily, if needed *(Table 1)*.

Nefazodone

In January 2002, the FDA and the manufacturer of nefazodone (Serzone) added a black box warning to the prescribing information concerning rare cases of liver failure.[36] The reported rate is one per 250,000 to 300,000 patient-years. Physicians should counsel patients who are taking nefazodone to be alert for signs and symptoms of liver failure, including jaundice, anorexia, gastrointestinal problems, and malaise. Nefazodone therapy should be avoided in patients with active liver disease or elevated serum transaminase levels, and discontinued in patients whose alanine aminotransferase or aspartate aminotransferase levels are three times the upper limit of normal or more. There is no recommendation, however, for periodic testing of liver function.

Antidepressant-Induced Sexual Dysfunction

Sexual dysfunction, usually delayed ejaculation or anorgasmia, may occur in both men and women who are taking SSRIs and venlafaxine. These patients have several options: reducing the dosage, switching to another agent, or adding another agent to overcome the sexual side effects.[37] Sexual dysfunction typically reverses within one to three days after discontinuation of the antidepressant and returns on reintroduction. Recovery after withdrawal from fluoxetine may occur within one to three weeks. Uncontrolled studies and case reports[37] suggest that the addition of bupropion (Wellbutrin), cyproheptadine (Periactin), nefazodone, or mirtazapine may decrease sexual side effects. In patients with antidepressant-induced erectile dysfunction, sildenafil (Viagra) may be useful if the patient has no history of angina and is not taking nitrates.[37]

Treatment Resistance: Augmentation and Switching

Ten to 30 percent of patients taking antidepressants are partially or totally resistant to the treatment.[38] Some patients also may experience breakthrough or recurrence of depression while taking the medication. Strategies for dealing with these problems include optimizing the

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dosage, switching medications, and adding combination or augmentation therapy, or electroconvulsive therapy.[39]

An adequate trial of antidepressant therapy is commonly defined as four to six weeks. If the patient has a partial response, another four to six weeks of treatment and dosage titration should allow for a more complete response.

Patients who are unresponsive to treatment with antidepressants may become responsive by switching (45 percent) or augmentation (56 percent).[40] Nonresponders are likely to respond if switched to an antidepressant with a different mechanism of action. Because SSRIs are structurally diverse, switching within the class of SSRIs may be useful. Patients must taper off of one agent before starting another to avoid the possibility of drug interactions, particularly serotonin syndrome.[41]

Combination therapy involves the addition of a second antidepressant in patients who exhibit a partial response to one agent. This approach is frequently used to boost the response to initial treatment; however, no double-blind, placebo-controlled studies confirm the usefulness of this practice. In addition, it may lead to significant adverse effects or drug-drug interactions.

Augmentation, or the addition of another drug to an antidepressant, is a useful strategy in patients with a partial response. The second drug is usually not an antidepressant. The best documented options are lithium and triiodothyronine (T_3).[42] Lithium is administered in the usual dosages, keeping the lithium blood levels to the lower end of the range (0.4 to 0.8 mEq per L). The augmentation dosage of T_3 is 25 mcg per day.

Case reports and open studies indicate that augmentation with buspirone (Buspar, in a dosage of 15 to 30 mg per day), the psychostimulant methylphenidate (Ritalin, in a dosage of 10 to 15 mg per day), or pindolol (Visken, in a dosage of 2.5 to 7.5 mg per day with SSRIs) can be effective and tends to cause minimal adverse effects.[43]

Electroconvulsive therapy is the most effective treatment in patients with severe resistance to medical antidepressant therapy or those with psychotic depression. Electroconvulsive therapy is safe under medically monitored conditions.

Discontinuation Syndrome

Discontinuation symptoms (withdrawal) are recognized with tricyclic antidepressants, MAOIs, SSRIs, and various other antidepressants, including venlafaxine and mirtazapine.[44] The symptoms—physical, psychologic, and psychomotor—are usually mild, start within a week of treatment cessation, and should resolve by the end of three weeks. The most common symptoms associated with discontinuation of SSRIs include dizziness, nausea, lethargy, and headache. Other symptoms can include flu-like feelings, panic attacks, numbness, agitation, and insomnia.

All antidepressants do not have the same type or severity of withdrawal symptoms. In studies comparing fluoxetine, sertraline, paroxetine, and citalopram, withdrawal from paroxetine was shown to cause more severe symptoms that may occur more quickly, even after the second missed dose. Because of its long half-life, fluoxetine may have the least severe symptoms.[44,45] Strategies to prevent antidepressant discontinuation syndrome include tapering the drug and educating the patient to avoid sudden cessation of the medication. Reinstatement of the medication will usually reverse severe symptoms within 24 hours.[44]

The authors indicate that they do not have any conflicts of interest. Sources of funding: none reported.

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