

Answers to your questions about SSRIs

Which SSRI is best? What drug interactions should you be most concerned about? The authors provide evidence-based answers to 7 frequently asked questions.

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PRACTICE RECOMMENDATIONS

- *Avoid prescribing a highly activating SSRI, such as fluoxetine, for patients for whom agitation is a presenting symptom. **B***
- *Consider citalopram and escitalopram, which have less potential for drug interactions and less complex dose titration compared with other SSRIs, as first-line agents for depressed patients with complex medication profiles. **C***
- *For patients with sexual side effects caused by SSRIs, consider augmentation therapy with bupropion or mirtazapine; for male sexual dysfunction, a trial of a phosphodiesterase inhibitor is another alternative. **B***

Strength of recommendation (SOR)

- A** Good-quality patient-oriented evidence
- B** Inconsistent or limited-quality patient-oriented evidence
- C** Consensus, usual practice, opinion, disease-oriented evidence, case series

Shortly after the US Food and Drug Administration (FDA) approved fluoxetine for the treatment of major depression nearly a quarter of a century ago, Prozac became a household name. And, as a handful of additional selective serotonin reuptake inhibitors (SSRIs) were approved, the popularity of this category of antidepressant continued to grow.¹ In 2008, 5 of the 6 SSRIs on the US market (fluvoxamine was the exception) were among the 200 most frequently dispensed prescription drugs.²

While much has been written about the properties of SSRIs, uncertainty about many features of particular agents and what should be considered in selecting an antidepressant for a particular patient remains. To help clear up the confusion, we've addressed 7 questions about SSRIs that we are often asked. Although there are no simple answers, the evidence presented, both in the answers and in the tables that follow, will help primary care physicians make more informed choices for patients who require antidepressant therapy.

1 Which is the best SSRI to start a patient on?

A recent meta-analysis of 117 head-to-head studies assessed the efficacy and acceptability of 12 newer antidepressants, including all 6 SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline).³ The researchers found 2 SSRIs, sertraline and escitalopram, to be superior to the other medications studied on both counts. A choice between sertraline or escitalopram may be a reasonable starting point in many cases, but it is impossible to recommend 1 or 2 SSRIs that are effective for all patients. There are several reasons for this.

The first is addressed by the Cipriani meta-analysis. The researchers assessed the efficacy of initial antidepressant therapy at 8 weeks, so the results cannot be extrapolated to long-term response rates or acceptability. (For a detailed review of the

TABLE 1
SSRIs: Neurotransmitter affinity and side effects⁹

Neurotransmitter/ enzyme	SSRIs with most potent affinity*	Likely side effects
Serotonin	Paroxetine Sertraline Fluoxetine Citalopram Fluvoxamine	Sexual dysfunction, including anorgasmia; GI disturbance; activation
Dopamine	Sertraline Paroxetine Fluoxetine Fluvoxamine Citalopram	Extrapyramidal
Norepinephrine	Paroxetine Fluoxetine Sertraline Fluvoxamine Citalopram	Tremor; tachycardia; elevated BP
Muscarinic receptors	Paroxetine Sertraline Fluoxetine Citalopram Fluvoxamine	Anticholinergic (blurred vision, constipation, dry mouth)

*SSRIs listed in order of potency; escitalopram would be expected to have effects comparable to citalopram.

BP, blood pressure; GI, gastrointestinal; SSRI, selective serotonin reuptake inhibitors.

meta-analysis, see “Try these 2 drugs first for depression,” *J Fam Pract.* 2009;58:365-369.)

A second reason is the substantial publication bias associated with studies of antidepressants. Turner et al assessed 74 studies registered with the FDA, determined whether the results were positive or negative, and categorized the studies based on publication status.⁴ Their conclusions: 97% of studies with positive findings (n=38) were published.

The majority of the remaining studies, all of which were determined to have negative findings, were either not published or published in a manner that suggested a positive outcome. When these additional studies are taken into account, the percentage of published studies with a positive response drops to 51%.⁴ In addition, the effect size of each agent is reduced when all the studies are included.

There are many confounding variables associated with publication, so Turner and his colleagues were unable to definitively determine the reason for the disparity. Nonethe-

less, their evaluation raises questions about the reported effectiveness, not only of SSRIs, but of antidepressants in general.

A recent Cochrane review of SSRIs for treatment of depression in children and adolescents (a topic covered in greater detail in the answer to Question 6) raised similar concerns. The reviewers cited study methodology and recruitment methods as potential sources of the conflicting results they found.⁵

Finally, individual differences, such as age, comorbidities, and medication history, require an individualized approach to SSRI treatment.

2 Which side effects are common to all SSRIs, and which can be resolved by switching agents?

As a class, SSRIs are well tolerated, but they do have some common adverse effects, most notably gastrointestinal (GI) problems, sexual dysfunction, and sleep disturbances. There are also considerable differences in SSRI profiles and a few adverse effects that a switch to another SSRI may alleviate or resolve.

Compared with other SSRIs, for example, sertraline has a higher risk of diarrhea, but this adverse event does not usually lead to medication discontinuation. If it is bothersome to the patient or does not resolve with continued therapy, a change to another agent might eliminate this adverse effect.

Weight gain has been found to be more significant with paroxetine than with fluoxetine or sertraline, which may be due to the anticholinergic action of the drug.⁶ For someone who is particularly concerned about extra weight, avoiding paroxetine in the first place, or changing a patient who's already taking it to fluoxetine or sertraline, might be an effective treatment strategy.

Overall, paroxetine has more anticholinergic side effects than other SSRIs, the likely result of its higher affinity for muscarinic receptors (TABLE 1). Its potential sedating effect,⁷ which can be extremely disturbing to some patients, may be a desired feature for others. A patient with insomnia, for example, might benefit from taking paroxetine at bedtime or switching to a less activating SSRI, such as citalopram or escitalopram. Excessive activation, such as significant insomnia, may also be a warning sign

of undiagnosed bipolar disorder. Thus, careful screening is needed prior to switching medications or adding a hypnotic agent. (See “Treating depression in primary care: Tips from a psychiatrist” on page 22.)

A switch to another SSRI is not the only way to alleviate a troublesome side effect, of course. Insomnia can also be managed by adding a short course of trazodone to the drug regimen or by switching the patient to mirtazapine or a tricyclic antidepressant (TCA).⁸

Augmentation with either bupropion or mirtazapine may alleviate sexual side effects and should be tried prior to switching the patient to a different antidepressant; however, the positive effects of augmentation should be balanced with any additional adverse events either agent may cause. For male sexual dysfunction, a trial of a phosphodiesterase inhibitor such as sildenafil is another alternative.

3 What drug interactions with SSRIs should I be most concerned about?

Like other psychotropic medications, SSRIs interact with drugs in a number of ways. There are interactions that occur at the cytochrome (CYP) 450 level and can result in toxicity or loss of effect, interactions that increase the likelihood of bleeding, and interactions that can lead to serotonin syndrome.

■ CYP 450 interactions. Depending on the CYP substrates that the SSRI and the other medication act upon, the result could be an increased concentration of the other agent and increased or decreased concentrations of the SSRI. The additive toxicity that could result has the potential to result in rare SSRI-associated adverse events, such as seizures and syndrome of inappropriate antidiuretic hormone (SIADH). Three exceptions to the increased concentration interaction are codeine, tamoxifen, and clopidogrel. Codeine, which relies on CYP metabolism to morphine, may have less analgesic effect if given with a CYP inhibitor. Tamoxifen may not be converted to endoxifen if given with a CYP inhibitor, resulting in a potentially lower therapeutic effect. Theoretically, a similar interaction could occur with clopidogrel when a CYP inhibitor is administered concurrently.

Fluoxetine, fluvoxamine, and paroxetine are the SSRIs with the greatest likelihood

TABLE 2

CYP 450 interactions: Beware of these drug pairings^{9,10,13-17}

SSRI*	Other medications
Fluoxetine	Aripiprazole Clopidogrel Codeine Dextromethorphan Diazepam Duloxetine Haloperidol Metoprolol Phenobarbital Phenytoin PPIs Risperidone Tamoxifen TCAs Tramadol Venlafaxine
Fluvoxamine	Amitriptyline Clopidogrel Clozapine Cyclobenzaprine Diazepam Imipramine Naproxen Phenobarbital Phenytoin PPIs Theophylline
Paroxetine	Aripiprazole Codeine Dextromethorphan Duloxetine Haloperidol Metoprolol Risperidone TCAs Tramadol Venlafaxine

*Sertraline is a modest CYP 2D6 inhibitor.

CYP, cytochrome; PPIs, proton pump inhibitors; SSRI, selective serotonin reuptake inhibitor; TCAs, tricyclic antidepressants.

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of having a significant CYP 450 interaction by inhibiting the metabolism of medications mediated by CYP 2D6, CYP 1A2, and CYP 2C19.^{9,10} (A partial list of medications and drug classes mediated by these substrates appears in TABLE 2.)

■ **Risk of bleeding.** Combining any SSRI with a nonsteroidal anti-inflammatory drug (NSAID) without the addition of an acid-suppressing agent would cause 1 in 250 patients to experience an upper GI bleed, a recent study found.¹¹ One in 500 patients treated with an SSRI and an antiplatelet agent developed an upper GI bleed. If a patient taking an SSRI requires antiplatelet or anticoagulant therapy, it is crucial to

alert him or her to the risk and to carefully review signs and symptoms of bleeding. Hepatitis C, cirrhosis, hepatic failure, and portal hypertension are independent causes of coagulopathy, so patients with any of these conditions face an elevated risk of bleeding and would need to be monitored more closely.¹¹ Avoid prescribing fluoxetine for patients with severe liver disease; an SSRI with a shorter half-life would be a more appropriate choice.

■ **Serotonin syndrome.** Combining an SSRI with a drug that affects serotonin (venlafaxine, mirtazapine, and serotonin receptor agonists such as sumatriptan, TCAs, St. John's wort, meperidine, and tryptophan) or a drug that exhibits monoamine oxidase inhibition properties (isocarboxazid, linezolid, phenelzine, phentermine, selegiline, and tranylcypromine) may lead to serotonin syndrome. This toxidrome is identified by autonomic instability, neuromuscular changes, and altered mental status in a patient who has ingested a substance that could elevate serotonin levels, but typically resolves within 24 hours after the serotonergic agent is discontinued.¹²

Because of the high risk of serotonin syndrome when a monoamine oxidase inhibitor (MAOI) is combined with an SSRI, do not prescribe a drug in this class until the patient has been off the SSRI for at least 2 weeks. Fluoxetine has a longer half-life, so a patient should be off of it for 5 weeks before taking an MAOI.¹³

Treating depression in primary care: Tips from a psychiatrist

- Use a validated instrument for depression screening and monitoring treatment success—preferably the PHQ-9 (<http://www.depression-primarycare.org/clinicians/toolkits>), which is validated for primary care practice. Use it at subsequent visits to track treatment response. The goal is not just response to treatment but remission of depressive symptoms, both of which are correlated with a decrease in the PHQ-9 total score.
- Take a careful history of bipolar symptoms and family history before starting a new patient on an SSRI. The DIGFAST mnemonic (<http://www.usmle-forums.com/usmle-step-1-mnemonics/793-dig-fast-mnemonic-mania-symptoms.html>) can help. Failure to respond to an SSRI or exacerbation of symptoms such as restlessness or insomnia once treatment has started should prompt you to consider a missed diagnosis.
- Consider augmentation strategies for patients who show partial improvement on an SSRI, rather than throwing out the gain with a wholesale switch to another drug. If a patient is only 30% better on the first agent you prescribe, try adding a second agent, which may significantly boost the response rate. Suggestions for SSRI augmentation include lithium, thyroid hormone, bupropion, and aripiprazole.
- Make sure the patient has been on a therapeutic dose for a sufficient period of time—at least 4 weeks—before chalking up a lack of response to an SSRI failure. Very often a patient is started on, say, 50 mg of sertraline and never titrated up. Many patients will not respond to the starting dose; those who don't should be tried on higher doses of a single agent until tolerability factors predominate, maximum approved dose is reached, or remission of symptoms is obtained.

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4 What precautions are necessary when starting a patient on an SSRI or modifying therapy?

Dosing is the initial concern, with adjustments made based on specific patient factors. Elderly patients should be started on a low dose and titrated up more slowly than younger patients, for example. Low starting doses are also recommended for patients with hepatic dysfunction.¹⁴⁻¹⁷

“Start low and go slow” is a good rule to follow when prescribing an SSRI to anyone whom you suspect may be intolerant to common side effects—a patient with GI symptoms associated with depression, for example.

Patient comorbidities affect choice of agent as well as dose. For a patient with a creatinine clearance <20 mL/min, citalopram

and escitalopram should be used with caution.^{14,15} Paroxetine should be initiated at lower doses for patients with a creatinine clearance <30 mL/min. While citalopram and escitalopram may not be ideal SSRIs for patients with renal impairment because of the potential for accumulation, they lack the substantial drug interactions and marked discontinuation syndrome seen with SSRIs such as paroxetine.

Two key concerns when changing from an SSRI to another class of antidepressant, or vice versa, are the increased risk of adverse events and a reduction in symptom control. A cross-titration strategy is appropriate for most such changes, provided the other drug is not an MAOI.

Discontinuation syndrome, which can be remembered by the mnemonic FINISH (Flu-like symptoms, Insomnia, Imbalance, Sensory disturbances, and Hyperarousal),¹⁸ is also a concern when antidepressant therapy is modified. The likelihood that a patient will develop discontinuation syndrome appears to be related to dose and agent, but not to the duration of treatment.¹⁹

While discontinuation syndrome is self-limiting, it is prudent to taper SSRI therapy whenever possible to minimize the risk of this adverse event, especially with paroxetine. A sample taper would be to reduce paroxetine by 10 mg per day every 5 to 7 days until the dose is down to 5 to 10 mg daily, then to discontinue the drug completely.²⁰ Cross-titration to a different medication will also prevent withdrawal symptoms and minimize the risk that a patient who was taking the maximum dose of an SSRI will develop serotonin syndrome.²¹ Because of the long half-life of fluoxetine and its metabolite, nor-fluoxetine, fluoxetine is less likely than other SSRIs to cause discontinuation syndrome. Basically, it self-tapers.

5 What should I tell pregnant patients about the risks of SSRIs?

Be upfront with them that depression in pregnancy presents a dilemma.

Tell them that on the one hand, untreated depression has been found to increase the risk of preterm labor, low birth weight, decreased fetal growth, preeclampsia, and a

worsening psychiatric condition after childbirth.^{22,23} In a 2006 study of 201 pregnant women with a previous diagnosis of depression, 43% relapsed during pregnancy. Those who were not taking antidepressants were 2.6 times more likely to relapse than women being treated for depression.²⁴

Patients also need to be informed that antidepressant therapy during pregnancy carries its own set of risks. Five SSRIs are pregnancy category C,²⁵ indicating either animal studies have found the drug to be harmful to fetuses *and* there are no well-done studies in pregnant women *or* that no animal studies *and* no human studies have tested its safety during pregnancy (the data were gathered after pregnancy). The sole exception is paroxetine, which has a D rating.²⁵ Studies have linked paroxetine to an increased risk of cardiovascular malformations in babies who were exposed to it during the first trimester.²⁶ These ratings may change shortly, however, as they are under FDA review. In May 2008, a new classification system for medication use in pregnancy was proposed.²⁷ While this system would have great clinical utility, no target date for its release has been identified.

Use of SSRIs during the second and third trimester increases the risk of neonatal pulmonary hypertension. One study found that exposed newborns were 6 times more likely to experience persistent pulmonary hypertension, compared with newborns who were not exposed to SSRIs in the second and third trimesters.²⁸

In addition, a derivative of the discontinuation syndrome is associated with neonatal withdrawal after in utero exposure, especially during the third trimester. Up to 30% of infants exposed to an SSRI may experience withdrawal symptoms, including increased or decreased muscle tone, jitteriness, feeding problems, irritability, sleep disturbance, and respiratory distress.²⁹

Under the circumstances, the best you can do is to provide the patient with as much information as possible about the benefits and risks of each strategy. In any case, pregnant women suffering from depression should receive frequent follow-up and a referral to a mental health professional. Emphasize the importance of discussing their



Use a cross-titration strategy when switching a patient from an SSRI to another antidepressant to prevent discontinuation syndrome.

current medications and symptoms of depression with their obstetrician and psychiatrist or psychotherapist.

6 What can I tell adolescents and their parents about SSRI safety?

Explain that 4 SSRIs—escitalopram, fluoxetine, fluvoxamine, and sertraline—are approved for use in this age group, for specific indications. Fluoxetine and escitalopram are approved for the treatment of depression in children ≥ 8 and ≥ 12 years of age, respectively. Fluvoxamine, fluoxetine, and sertraline are approved for obsessive-compulsive disorder in children ≥ 8 , ≥ 7 , and ≥ 6 years, respectively.

You can also tell patients and parents that adolescents typically fare better when they receive a combination of medication and psychotherapy, compared with medications or therapy alone.

The FDA issued an initial warning about antidepressant use in pediatric and adolescent patients in 2003, based on data from 23 randomized controlled trials submitted by 8 different drug manufacturers.³⁰ Most of the studies reported roughly twice the risk for suicidal ideation in adolescents taking SSRIs, compared with placebo. It is noteworthy, however, that there were no reports of completed suicides in the submitted trials.³⁰ In fact, data suggest that despite some increased suicidal ideation when SSRIs are initiated, these antidepressants result in improved symptom control. In 2007, after a data review, the FDA issued an advisory warning physicians about increased suicidality in young patients.³¹

The FDA has recommended increased monitoring of adolescents taking SSRIs, with office visits once a week for the first month of treatment and every 2 weeks for the second

month, followed by 1 visit every 3 months. This stringent schedule has proven difficult to adhere to. One study showed that only 5% of adolescent patients received this level of attention.³² The American Academy of Child and Adolescent Psychiatry and the American Psychiatric Association advocate an individualized treatment plan instead.³³

If you prescribe SSRIs for depressed adolescents, educate patients and parents about the atypical presentation of depression that is common in patients of this age group. Advise them to watch closely for, and promptly report, increases in agitation, anxiety, impulsiveness, and restlessness, and symptoms of mania or hypomania.³³

7 When should I refer a patient to a mental health professional?

Refer patients to a mental health specialist when the optimal treatment calls for a combination of psychotherapy and medication, as is the case with depressed adolescents. Referral is recommended, too, for any complex patients. Examples include elderly individuals who are taking multiple medications or have comorbidities that can interfere with optimal treatment, and pregnant women who need additional help weighing the benefits and risks of antidepressant therapy vs nonpharmacologic treatments.

Finally, referral is critical for any patient who does not respond to treatment, even after dose adjustments, for patients who need cross-tapering that may be better handled by a specialist, and certainly for any patient who you suspect may have suicidal ideation. **JFP**

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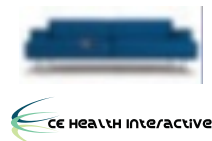
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