

# Pharmacology Rounds

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## Drug Interactions with SSRIs

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Selective serotonin reuptake inhibitors (SSRIs) are first-line agents for the treatment of major depression and other disorders. Currently, five SSRIs have been approved for use in the United States: citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. When SSRIs are used in combination with certain drugs, multiple pharmacodynamic and pharmacokinetic interactions can result in a broad spectrum of symptoms, ranging from mild toxicity to death.<sup>1,2</sup>

Venlafaxine is not, strictly speaking, an SSRI; it inhibits the reuptake of serotonin as well as norepinephrine and (to a lesser extent) dopamine. However, it is often used as an SSRI, and it shares similar pharmacodynamic and pharmacokinetic drug interactions.

**Serotonin syndrome:** SSRIs prolong serotonin exposure at the neuronal synapses by inhibiting sero-

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**Table 1. Serotonergic agents**

Coadministration of an SSRI and one of the following agents may result in the serotonin syndrome:

**Amphetamines**

Methylphenidate

**Anorexiants**

Fenfluramine

**Antidepressants**

Monoamine oxidase inhibitors

Phenelzine

Tranylcypromine

Tricyclics

Amitriptyline

Clomipramine

Imipramine

Other antidepressants

Nefazodone

Saint-John's-wort

Trazodone

**Antiparkinsonians**

Selegiline

**Narcotics**

Cocaine

Dextromethorphan

Meperidine

**Other agents**

Buspirone

Dihydroergotamine

Lithium

Sumatriptan

SSRI, selective serotonin reuptake inhibitor.

Data extracted from Finley PR. *Ann Pharmacother.* 1994<sup>1</sup>; Lane R, Baldwin D. *J Clin Psychopharmacol.* 1997<sup>2</sup>; Sporer KA. *Drug Saf.* 1995.<sup>3</sup>

tonin reuptake. When any two serotonergic agents are combined, the excessive serotonin exposure in the central nervous system can result in the serotonin syndrome. This constellation of symptoms includes confusion, agitation, diarrhea, fever, diaphoresis, nausea, blood pressure changes, myoclonus, hyperreflexia, and tremor.<sup>2</sup> The serotonin syndrome can vary in severity from mild to fatal.

Thus, the combination of an SSRI and any of the serotonergic agents listed in Table 1 should be avoided or used with extreme caution.<sup>3</sup> Treatment of the serotonin syndrome involves withdrawal of the inciting agents and supportive care.

**Hepatic enzyme interactions:**


The SSRIs interact with the cytochrome P-450 (CYP) enzyme system; thus, when they are used with other agents metabolized by CYP isozymes, serious drug interactions may occur. Both fluoxetine and paroxetine are potent inhibitors of the isozyme CYP 2D6; furthermore, these SSRIs are metabolized by CYP 2D6 and thus inhibit their own metabolism.<sup>4</sup> Sertraline, citalopram, and venlafaxine are weak inhibitors of CYP 2D6. Serious drug reactions may occur in persons with reduced CYP 2D6 activity.

Clinically significant drug interactions also can develop when any of these agents are combined with other inhibitors of the CYP 2D6 pathway, such as amitriptyline.

Fluvoxamine is a potent inhibitor of the CYP 1A2 isozyme<sup>5</sup> and may increase serum concentrations of agents metabolized by this enzyme, such as propranolol, theophylline, and warfarin. When using one of these agents in combination with fluvoxamine, clinicians should monitor patients for signs of drug toxicities. Fluvoxamine also inhibits the CYP 3A3/4 isozymes, as do fluoxetine and sertraline; therefore, caution should be used when coadministering these SSRIs with cisapride and astemizole.<sup>6</sup>

*Other important interactions:*

Clinicians should also be aware of other important interactions with SSRIs. Patients who smoke should be warned that smoking increases the metabolism of fluvoxamine.<sup>7</sup> Paroxetine and sertraline are highly protein bound; these agents should be used cautiously when combined with other highly protein-bound drugs (eg, warfarin and phenytoin).<sup>7</sup>

Table 2 lists agents that may cause clinically significant drug interactions when used with SSRIs. Blood concentrations of these drugs should be measured (when indicated). In addition, patients should be monitored carefully for signs of toxicity. Adjustment in dosage of one or both agents may be necessary. 

**REFERENCES**

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**Table 2. Monitoring for SSRI drug interactions**

<p>Monitor patients for signs of adverse reactions or drug toxicity when using an SSRI with any drug or any agent of the drug classes listed below:</p> <ul style="list-style-type: none"> <li>Benzodiazepines</li> <li>Caffeine*</li> <li>Cisapride</li> <li>Clozapine</li> <li>Codeine</li> <li>Cyclobenzaprine</li> <li>Haloperidol</li> <li>Nonsedating antihistamines</li> <li>Propafenone</li> <li>Propranolol*</li> <li>Tricyclic antidepressants</li> </ul> <p>Monitor drug concentrations and watch for signs of adverse reactions or drug toxicity when using an SSRI with any drug listed below:</p> <ul style="list-style-type: none"> <li>Carbamazepine</li> <li>Phenytoin</li> <li>Theophylline*</li> <li>Valproic Acid</li> <li>Warfarin</li> </ul> <p>SSRI, selective serotonin reuptake inhibitor.</p> <p>* Interactions have been reported only with fluvoxamine.</p> <p>Data extracted from Finley PR. <i>Ann Pharmacother.</i> 1994<sup>1</sup>; Harvey AT, Preskorn SH. <i>J Clin Psychopharmacol.</i> 1996<sup>4</sup>; Sproule BA, et al. <i>Clin Pharmacokinet.</i> 1997<sup>6</sup>; Ereshefsky L, et al. <i>Clin Pharmacokinet.</i> 1995.<sup>8</sup></p>
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