The American Psychiatric Publishing Textbook of Psychiatry

FIFTH EDITION

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American Psychiatric Publishing, Inc.

Washington, DC
London, England

Rash. As with other medications, some patients taking an SSRI may experience a rash during the course of treatment. Severe rashes warrant treatment medication discontinuation.

Syndrome of inappropriate secretion of antidiuretic hormone. Some patients taking SSRIs may develop the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), although the incidence of SIADH in the context of SSRI treatment is not known. Symptoms include lethargy, headache, hyponatremia, increased urinary sodium excretion, and hyperosmotic urine. Acute treatment of this syndrome should consist of discontinuation of the drug as well as restriction of fluid intake. Patients experiencing severe confusion, convulsions, or coma should receive intravenous sodium chloride.

Apathy syndrome. We and others have noted an apathy syndrome in some patients after months or years of successful treatment with SSRIs. The syndrome is characterized by a loss of motivation, increased passivity, and feelings of lethargy and "flatness." However, sadness, tearfulness, emotional angst, decreased concentration, feelings of hopelessness or worthlessness, and thoughts of suicide are not associated with this syndrome. If specifically asked, patients often remark that the symptoms are not experientially similar to their original depressive symptoms. This syndrome has not been adequately studied, and the pathophysiology is not known. However, there is speculation that subchronic stimulation of central serotonin attenuates dopamine functioning in several areas of the brain, including the frontal cortex. The apathy syndrome appears to be dose dependent and reversible.

It is important to distinguish the apathy syndrome from a relapse or recurrence of depressive symptoms because treatment approaches for these two scenarios are different. For instance, if an apathy syndrome is mistaken for a depressive relapse, the clinician may increase the dose of the antidepressant, thereby potentially leading to a worsening of symptoms. If dosage reduction is not effective, adding a stimulant may be beneficial. Other agents that increase dopamine also may be effective. Olanzapine, which increases frontal lobe dopamine, also has been reported to be effective in the treatment of apathy in patients taking SSRIs (Marangell et al. 2002).

Serotonin syndrome. The serotonin syndrome results from excess serotonergic stimulation and can range in severity from mild to life-threatening. The most common symptoms are confusion, flushing, diaphoresis, tremor, and myoclonic jerks. The patient may have symptoms of the serotonin syndrome in the context of monotherapy with a serotonergic medication, but this scenario is less common than symptoms resulting from use of two or more serotonergic drugs simultaneously. Discontinuation of the serotonergic medications is the first step in treatment, followed by emergency medical treatment. The serotonin type 2A ($5\text{-}HT_{2A}$) receptor antagonist cyproheptadine can be used if further treatment is warranted, beginning with an oral dose of 12 mg and then administering 2 mg every 2 hours. Although cyproheptadine is available only in oral form, tablets may be crushed, mixed in a suspension, and administered via a nasogastric tube. However, efficacy for this presumed antidote has not been established.

Discontinuation syndrome. Some patients may experience a series of symptoms after discontinuation or dose reduction of serotonergic antidepressant medications, including dizziness, headache, paresthesia, nausea, diarrhea, insomnia, and irritability. These symptoms also may be seen when a patient misses doses of a serotonergic antidepressant. A prospective double-blind, placebo-substitution study confirmed that discontinuation symptoms are most common with short-half-life antidepressants, such as paroxetine (Rosenbaum et al. 1998). To avoid a discontinuation syndrome, clinicians should slowly taper antidepressant medications on discontinuation of the drug, particularly medications with short half-lives.

Teratogenicity

Managing major depression, or any psychiatric disorder, in the context of pregnancy is challenging. Although minimizing the risk to the fetus is a clear goal, many patients, families, and even some practitioners need to be reminded that the illness of depression can have adverse effects on the fetus and neonate. Each woman who is facing pregnancy and related psychiatric treatment decisions needs to be approached and advised in the context of her unique circumstances. Some data indicate that the incidence of congenital abnormalities associated with the SSRIs is comparable to that associated with placebo, but other reports note an increased risk of congenital abnormalities, including septal heart defects, with first-trimester exposure and that this risk may be greater with paroxetine and clomipramine (Källén et al. 2006). These data have resulted in a new FDA Category D pregnancy classification for paroxetine. Other data indicate that antidepressants may increase the risk of pulmonary