delayed ejaculation, anorgasmia) can occur with SSRIs in adolescents. Because seizures have been observed in the context of SSRI use, SSRIs should be used cautiously in patients with a history of a seizure disorder. Abnormal bleeding, especially with concomitant administration of aspirin or nonsteroidal anti-inflammatory drugs, can occur with SSRIs and can cause surgical risk; rare bleeding events include ecchymosis, hematoma, epistaxis, petechiae, and hemorrhage.

Serotonin syndrome,[174] caused by elevated brain serotonin levels, can be triggered when multiple serotonergic medications are prescribed concomitantly. Symptoms can arise within 24 to 48 hours after combining medications and are characterized by mental status changes (confusion, agitation, anxiety); neuromuscular hyperactivity (tremors, clonus, hyperreflexia, muscle rigidity); and autonomic hyperactivity (hypertension, tachycardia, arrhythmias, tachypnea, diaphoresis, shivering, vomiting, diarrhea). Advanced symptoms include fever, seizures, arrhythmias, and unconsciousness, which can lead to fatalities. Treatment is hospital based and includes discontinuation of all serotonergic agents and supportive care with continuous cardiac monitoring. Monoamine oxidase inhibitors (MAOIs) play a role in most cases of serotonin syndrome and should be avoided in combination with any other serotonergic drug, including another MAOI. Moreover, caution should be exercised when combining 2 or more non-MAOI serotonergic drugs, including antidepressants, opioids and other pain medications, stimulants, cough/cold/allergy medications, and other over-the-counter products. Caution entails starting the second non-MAOI serotonergic drug at a low dose, increasing the dose slowly, and monitoring for symptoms, especially in the first 24 to 48 hours after dosage changes. Adolescents should be informed that certain recreational drugs (eg, dextromethorphan, "ecstasy") are highly serotonergic and can cause serious interactions with antidepressants.

Each SSRI has special prescribing considerations. Paroxetine, fluvoxamine, and sertraline have been associated with discontinuation syndrome[175] (see below for syndrome description). As noted below, fluvoxamine may have greater potential for drug−drug interactions. Citalopram may cause QT prolongation associated with Torsade de Pointes, ventricular tachycardia, and sudden death at daily doses exceeding 40 mg per day and should be avoided in patients with long QT syndrome. Paroxetine has been associated with increased risk of suicidal thinking or behavior compared to other SSRIs.

SSRIs vary in their potential for drug−drug interactions.[176] Concomitant administration of any of the SSRIs with any of the MAOIs is contraindicated because of increased risk of serotonin syndrome. SSRIs (especially citalopram) also may interact with drugs that prolong the QT interval; fluoxetine, paroxetine, and sertraline may interact with drugs metabolized by CYP2D6; and fluvoxamine may interact with drugs metabolized by CYP1A2, CYP2C19, CYP2C9, CYP3A4, and CYP2D6. Citalopram/escitalopram may have the least effect on CYP450 isoenzymes compared with other SSRIs and, as such, may have a lower propensity for drug interactions.

Medical education, training, and experience are necessary to safely and effectively prescribe antidepressant medications. Antidepressant treatment has been organized into 3 phases: *acute*, *continuation*, and *maintenance*. The goal of the acute phase is to achieve response and ultimately remission, whereas the goals of the continuation and maintenance phases are to prevent relapse and recurrence. Treatment goals have been defined in some research settings as follows: *response*: a significant (eg, >50%) reduction in symptoms for at least 2 weeks; *remission*: a period of at least 2 weeks but less than 2 months with few or no symptoms; *recovery*: absence of significant symptoms for 2 months or greater; *relapse*: a new episode of depression during the period of remission; and *recurrence*: a new episode of depression during recovery.[8]

An illustrative medication trial for mild-to-moderate depression presentations entails prescribing the recommended therapeutic dose (adjusted for age in some cases), monitoring weekly for adverse effects, and assessing for response (ideally with both clinical interview and standardized symptom rating scale) in 4 to 6 weeks (acute phase). Minimal data support an association between higher dosing and higher efficacy, and higher doses typically result in more adverse effects.[177] Accordingly, if the 4- to 6-week assessments show minimal response, a trial of a second SSRI could be considered (although, in some situations, dose increase of the initial SSRI may be warranted). In the Treatment of Resistant Depression in Adolescents (TORDIA) study, 55% of adolescents with MDD who were nonresponders to an initial SSRI demonstrated a significant response when prescribed a second SSRI or an SNRI with CBT.[178] Little rigorous evidence is currently available regarding other approaches to treatment-resistant depression.

Treatment resistance can arise from many factors, which should be thoroughly explored and remedied; these include inadequate medication dose or duration, misdiagnosis, untreated comorbidities, discontinuation because of adverse medication effects, exposure to significant environmental stressors, inadequate fit with or skill level of treating practitioners, and nonadherence to the medication regimen. Determinants of nonadherence are multi-determined,