Risk of suicidality; importance of patients, family, and caregivers being alert to and immediately reporting emergence of suicidality, worsening depression, or unusual changes in behavior, especially during the first few months of therapy or during periods of dosage adjustment. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

Importance of informing patients of potential risk of serotonin syndrome and neuroleptic malignant syndrome (NMS)-like reactions, particularly with concurrent use of escitalopram and 5-HT_1 receptor agonists (also called triptans), tramadol, tryptophan, other serotonergic agents, or antipsychotic agents. Importance of immediately contacting clinician if signs and symptoms of these syndromes develop (e.g., restlessness, hallucinations, loss of coordination, fast heart beat, increased body temperature, muscle stiffness, labile blood pressure, diarrhea, coma, nausea, vomiting, confusion).

Risk of psychomotor impairment; importance of exercising caution while operating hazardous machinery, including driving a motor vehicle, until the drug's effects on the individual are known.

Importance of patients being aware that withdrawal effects may occur when stopping escitalopram, especially with abrupt discontinuance of the drug.

Risks associated with concomitant use of escitalopram with alcohol or racemic citalopram.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs or herbal supplements, as well as any concomitant illnesses (e.g., bipolar disorder) or personal or family history of suicidality or bipolar disorder. Risk of bleeding associated with concomitant use of escitalopram with aspirin or other nonsteroidal anti-inflammatory agents, warfarin, or other drugs that affect coagulation.

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.

Importance of advising patients that, although they may notice improvement with escitalopram therapy within 1–4 weeks, they should continue therapy as directed.

Importance of informing patients of other important precautionary information. (See Cautions.)

Overview[a] (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Escitalopram Oxalate

Oral		
Solution	5 mg (of escitalopram) per 5 mL	**Lexapro**®, Forest
Tablets, film-coated	5 mg (of escitalopram)	**Lexapro**®, Forest
	10 mg (of escitalopram)	**Lexapro**® (scored), Forest
	20 mg (of escitalopram)	**Lexapro**® (scored), Forest

Fluoxetine Hydrochloride

■ Fluoxetine, a selective serotonin-reuptake inhibitor (SSRI), is an antidepressant.

Uses

Fluoxetine is used in the treatment of major depressive disorder, obsessive-compulsive disorder, premenstrual dysphoric disorder, and bulimia nervosa. In addition, fluoxetine has been used for the treatment of depression associated with bipolar disorder†; obesity†; anorexia nervosa†; panic disorder† with or without agoraphobia; myoclonus†; cataplexy†; alcohol dependence†; and premature ejaculation†.

■ **Major Depressive Disorder** Fluoxetine is used in the treatment of major depressive disorder. The efficacy of fluoxetine for long-term use (i.e., longer than 5–6 weeks) as an antidepressant has not been established by controlled studies, but the drug has been used in some patients for substantially longer periods (e.g., up to 4 years or longer) without apparent loss of clinical effect or increased toxicity. If fluoxetine is used for extended periods, the need for continued therapy should be reassessed periodically.

A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks). According to DSM-IV criteria, a major depressive episode includes at least 5 of the following 9 symptoms (with at least one of the symptoms being either depressed mood or loss of interest or pleasure): depressed mood most of the day as indicated by subjective report (e.g., feels sad or empty) or observation made by others; markedly diminished interest or pleasure in all, or almost all, activities most of the day; significant weight loss (when not dieting) or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite; insomnia or hypersomnia; psychomotor agitation or retardation (observable by others, not merely subjective feelings of restlessness or being slowed down); fatigue or loss of energy; feelings of worthlessness or excessive or inappropriate guilt (not merely self-reproach or guilt about being sick); diminished ability to think or concentrate or indecisiveness (either by subjective account or as observed by others); and recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide.

Treatment of major depressive disorder generally consists of an acute phase (to induce remission), a continuation phase (to preserve remission), and a maintenance phase (to prevent recurrence). Various interventions (e.g., psychotherapy, antidepressant drug therapy, electroconvulsive therapy [ECT]) are used alone or in combination to treat major depressive episodes. Treatment should be individualized and the most appropriate strategy for a particular patient is determined by clinical factors such as severity of depression (e.g., mild, moderate, severe), presence or absence of certain psychiatric features (e.g., suicide risk, catatonia, psychotic or atypical features, alcohol or substance abuse or dependence, panic or other anxiety disorder, cognitive dysfunction, dysthymia, personality disorder, seasonal affective disorder), and concurrent illness (e.g., asthma, cardiac disease, dementia, seizure disorder, glaucoma, hypertension). Demographic and psychosocial factors as well as patient preference also are used to determine the most effective treatment strategy.

While use of psychotherapy alone may be considered as an initial treatment strategy for patients with mild to moderate major depressive disorder (based on patient preference and presence of clinical features such as psychosocial stressors), combined use of antidepressant drug therapy and psychotherapy may be useful for initial treatment of patients with moderate to severe major depressive disorder with psychosocial issues, interpersonal problems, or a comorbid axis II disorder. In addition, combined use of antidepressant drug therapy and psychotherapy may be beneficial in patients who have a history of poor compliance or only partial response to adequate trials of either antidepressant drug therapy or psychotherapy alone.

Antidepressant drug therapy can be used alone for initial treatment of patients with mild major depressive disorder (if preferred by the patient) and usually is indicated alone or in combination with psychotherapy for initial treatment of patients with moderate to severe major depressive disorder (unless ECT is planned). ECT is not generally used for initial treatment of uncomplicated major depression, but is recommended as first-line treatment for severe major depressive disorder when it is coupled with psychotic features, catatonic stupor, severe suicidality, food refusal leading to nutritional compromise, or other situations when a rapid antidepressant response is required. ECT also is recommended for patients who have previously shown a positive response or a preference for this treatment modality and can be considered for patients with moderate or severe depression who have not responded to or cannot receive antidepressant drug therapy. In certain situations involving depressed patients unresponsive to adequate trials of several individual antidepressant agents, adjunctive therapy with another agent (e.g., buspirone, lithium) or concomitant use of a second antidepressant agent (e.g., bupropion) has been used; however, such combination therapy is associated with an increased risk of adverse reactions, may require dosage adjustments, and (if not contraindicated) should be undertaken only after careful consideration of the relative risks and benefits. (See Drug Interactions: Serotonergic Drugs, see Drug Interactions: Tricyclic and Other Antidepressants, and see Drug Interactions: Lithium.)

Efficacy of fluoxetine for the management of major depression has been established principally in outpatient settings; the drug's antidepressant efficacy in hospital or institutional settings has not been adequately studied to date. Most patients evaluated in clinical studies with fluoxetine had major depressive episodes of at least moderate severity, had no evidence of bipolar disorder, and had experienced either single or recurrent episodes of depressive illness. Limited evidence suggests that mildly depressed patients may respond less well to fluoxetine than moderately depressed patients. There also is some evidence that patients with atypical depression (which usually is characterized by atypical signs and symptoms such as hypersomnia and hyperphagia), a history of poor response to prior antidepressant therapy, chronic depressive symptomatology with or without episodic worsening of depressive symptoms, a longer duration of depression in the current episode, and/or a younger age of onset of depression may be more likely to respond to fluoxetine than to tricyclic antidepressant therapy.

Considerations in Choosing Antidepressants A variety of antidepressant drugs are available for the treatment of major depressive disorder, including selective serotonin-reuptake inhibitors (SSRIs; e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline), selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs; e.g., desvenlafaxine, duloxetine, venlafaxine), tricyclic antidepressants (e.g., amitriptyline, amoxapine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine), monoamine oxidase (MAO) inhibitors (e.g., phenelzine, tranylcypromine), and other antidepressants (e.g., bupropion, maprotiline, nefazodone, trazodone). Most clinical studies have shown that the antidepressant effect of usual dosages of fluoxetine in patients with moderate to severe depression is greater than that of placebo and comparable to that of usual dosages of tricyclic antidepressants, maprotiline, other selective serotonin-reuptake inhibitors (e.g., paroxetine, sertraline), and other antidepressants (e.g., trazodone). Fluoxetine appears to be

as effective as tricyclic antidepressants in reducing most of the signs and symptoms associated with major depressive disorder, including depression, anxiety, cognitive disturbances, and somatic symptoms. However, in some studies, the drug did not appear to be as effective as tricyclic antidepressants or trazodone in reducing sleep disturbances associated with depression. In geriatric patients with major depressive disorder, fluoxetine appears to be as effective as and to cause fewer overall adverse effects than doxepin. The onset of action of fluoxetine appears to be comparable to that of tricyclic antidepressants, although the onset of action has been variably reported to be somewhat faster or slower than that of tricyclic antidepressants in some studies.

Because response rates in patients with major depression are similar for most currently available antidepressants, the choice of antidepressant agent for a given patient depends principally on other factors such as potential adverse effects, safety or tolerability of these adverse effects in the individual patient, psychiatric and medical history, patient or family history of response to specific therapies, patient preference, quantity and quality of available clinical data, cost, and relative acute overdose safety. No single antidepressant can be recommended as optimal for all patients because of substantial heterogeneity in individual responses and in the nature, likelihood, and severity of adverse effects. In addition, patients vary in the degree to which certain adverse effects and other inconveniences of drug therapy (e.g., cost, dietary restrictions) affect their preferences.

In the large-scale Sequenced Treatment Alternatives to Relieve Depression (STAR*D) effectiveness trial, patients with major depressive disorder who did not respond to or could not tolerate therapy with one SSRI (citalopram) were randomized to switch to extended-release ("sustained-release") bupropion, sertraline, or extended-release venlafaxine as a second step of treatment (level 2). Remission rates as assessed by the 17-item Hamilton Rating Scale for Depression (HRSD-17) and the Quick Inventory of Depressive Symptomatology—Self Report (QIDS-SR-16) were approximately 21 and 26% for extended-release bupropion, 18 and 27% for sertraline, and 25 and 25% for extended-release venlafaxine therapy, respectively; response rates as assessed by the QIDS-SR-16 were 26, 27, and 28% for extended-release bupropion, sertraline, and extended-release venlafaxine therapy, respectively. These results suggest that after unsuccessful initial treatment of depressed patients with an SSRI, approximately 25% of patients will achieve remission after therapy is switched to another antidepressant, and either another SSRI (e.g., sertraline) or an agent from another class (e.g., bupropion, venlafaxine) may be reasonable alternative antidepressants in patients not responding to initial SSRI therapy.

Patient Tolerance Considerations. Because of differences in the adverse effect profile between selective serotonin-reuptake inhibitors and tricyclic antidepressants, particularly less frequent anticholinergic effects, cardiovascular effects, and weight gain with selective serotonin-reuptake inhibitors, these drugs may be preferred in patients in whom such effects are not tolerated or are of potential concern. The decreased incidence of anticholinergic effects associated with fluoxetine and other selective serotonin-reuptake inhibitors compared with tricyclic antidepressants is a potential advantage, since such effects may result in discontinuance of the drug early during therapy in unusually sensitive patients. In addition, some anticholinergic effects may become troublesome during long-term tricyclic antidepressant therapy (e.g., persistent dry mouth may result in tooth decay). Although selective serotonin-reuptake inhibitors share the same overall tolerability profile, certain patients may tolerate one drug in this class better than another. In an open study, most patients who had discontinued fluoxetine therapy because of adverse effects subsequently tolerated sertraline therapy. Antidepressants other than selective serotonin-reuptake inhibitors may be preferred in patients in whom certain adverse GI effects (e.g., nausea, anorexia) or nervous system effects (e.g., anxiety, nervousness, insomnia, weight loss) are not tolerated or are of concern, since such effects appear to occur more frequently with fluoxetine and other drugs in this class.

Pediatric Considerations. The clinical presentation of depression in children and adolescents can differ from that in adults and generally varies with the age and developmental stages of the child. Younger children may exhibit behavioral problems such as social withdrawal, aggressive behavior, apathy, sleep disruption, and weight loss; adolescents may present with somatic complaints, self esteem problems, rebelliousness, poor performance in school, or a pattern of engaging in risky or aggressive behavior.

Data from controlled clinical studies evaluating various antidepressant agents in children and adolescents are less extensive than with adults, and many of these studies have methodologic limitations (e.g., nonrandomized or uncontrolled, small sample size, short duration, nonspecific inclusion criteria). However, there is some evidence that the response to antidepressants in pediatric patients may differ from that seen in adults, and caution should be used in extrapolating data from adult studies when making treatment decisions for pediatric patients. Results of several studies evaluating tricyclic antidepressants (e.g., amitriptyline, desipramine, imipramine, nortriptyline) in preadolescent and adolescent patients with major depression indicate a lack of overall efficacy in this age group.

Based on the lack of efficacy data regarding use of tricyclic antidepressants and MAO inhibitors in pediatric patients and because of the potential for life-threatening adverse effects associated with the use of these drugs, many experts consider selective serotonin-reuptake inhibitors, including fluoxetine, the drugs of choice when antidepressant therapy is indicated for the treatment of major depressive disorder in children and adolescents. However, the US Food and Drug Administration (FDA) states that, while efficacy of fluoxetine has been established in pediatric patients, efficacy of other newer antidepressants (i.e., citalopram, desvenlafaxine, duloxetine, escitalopram, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, venlafaxine) was not conclusively established in clinical trials in pediatric patients with major depressive disorder. In addition, FDA now warns that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder and other psychiatric disorders. (See Cautions: Pediatric Precautions.) FDA currently states that anyone considering using an antidepressant in a child or adolescent for any clinical use must balance the potential risk of therapy with the clinical need. (See Cautions: Precautions and Contraindications.)

Geriatric Considerations. The response to antidepressants in depressed geriatric patients without dementia is similar to that reported in younger adults, but depression in geriatric patients often is not recognized and is not treated. In geriatric patients with major depressive disorder, SSRIs appear to be as effective as tricyclic antidepressants (e.g., amitriptyline) but may cause fewer overall adverse effects than these other agents. Geriatric patients appear to be especially sensitive to anticholinergic (e.g., dry mouth, constipation, vision disturbance), cardiovascular, orthostatic hypotensive, and sedative effects of tricyclic antidepressants. The low incidence of anticholinergic effects associated with fluoxetine and other SSRIs compared with tricyclic antidepressants is a potential advantage in geriatric patients, since such effects (e.g., constipation, dry mouth, confusion, memory impairment) may be particularly troublesome in these patients. However, SSRI therapy may be associated with other troublesome adverse effects (e.g., nausea and vomiting, agitation and akathisia, parkinsonian adverse effects, sexual dysfunction, weight loss, hyponatremia). Some clinicians state that SSRIs including fluoxetine may be preferred for treating depression in geriatric patients in whom the orthostatic hypotension associated with many antidepressants (e.g., tricyclics) potentially may result in injuries (such as severe falls). However, despite the fewer cardiovascular and anticholinergic effects associated with SSRIs, these drugs did not show any advantage over tricyclic antidepressants with regard to hip fracture in a case-control study. In addition, there was little difference in the rates of falls between nursing home residents receiving SSRIs and those receiving tricyclic antidepressants in a retrospective study. Therefore, all geriatric individuals receiving either type of antidepressant should be considered at increased risk of falls and appropriate measures should be taken. In addition, clinicians prescribing SSRIs in geriatric patients should be aware of the many possible drug interactions associated with these drugs, including those involving metabolism of the drugs through the cytochrome P-450 system. (See Drug Interactions.)

Patients with dementia of the Alzheimer's type (Alzheimer's disease, presenile or senile dementia) often present with depressive symptoms, such as depressed mood, appetite loss, insomnia, fatigue, irritability, and agitation. Most experts recommend that patients with dementia of the Alzheimer's type who present with clinically important and persistent depressive symptoms be considered as candidates for pharmacotherapy even if they fail to meet the criteria for a major depressive syndrome. The goals of such therapy are to improve mood, functional status (e.g., cognition), and quality of life. Treatment of depression also may reduce other neuropsychiatric symptoms associated with depression in patients with dementia, including aggression, anxiety, apathy, and psychosis. Although patients may present with depressed mood alone, the possibility of more extensive depressive symptomatology should be considered. Therefore, patients should be evaluated and monitored carefully for indices of major depression, suicidal ideation, and neurovegetative signs since safety measures (e.g., hospitalization for suicidality) and more vigorous and aggressive therapy (e.g., relatively high dosages, multiple drug trials) may be needed in some patients.

Although placebo-controlled trials of antidepressants in depressed patients with concurrent dementia have shown mixed results, the available evidence and experience with the use of antidepressants in patients with dementia of the Alzheimer's type and associated depressive manifestations indicate that depressive symptoms (including depressed mood alone and with neurovegetative changes) in such patients are responsive to antidepressant therapy. In some patients, cognitive deficits may partially or fully resolve during antidepressant therapy, but the extent of response will be limited to the degree of cognitive impairment that is directly related to depression. SSRIs such as fluoxetine, citalopram, escitalopram, paroxetine, or sertraline are generally considered as first-line agents in the treatment of depressed patients with dementia since they are usually better tolerated than some other antidepressants (e.g., tricyclic antidepressants, monoamine oxidase inhibitors). Some possible alternative agents to SSRIs include bupropion, mirtazapine, and venlafaxine. Some geriatric patients with dementia and depression may be unable to tolerate the antidepressant dosages needed to achieve full remission. When a rapid antidepressant response is not critical, some experts therefore recommend a very gradual dosage increase to increase the likelihood that a therapeutic dosage of the SSRI or other antidepressant will be reached and tolerated. In a randomized, double-blind study comparing fluoxetine and amitriptyline in a limited number of patients with major depression complicating Alzheimer's disease, fluoxetine and amitriptyline were found to be equally effective; however, fluoxetine was better tolerated.

Cardiovascular Considerations. The relatively low incidence of adverse cardiovascular effects, including orthostatic hypotension and conduction disturbances, associated with fluoxetine and other selective serotonin-reuptake inhibitors may be advantageous in patients in whom cardiovascular effects associated with tricyclic antidepressants may be hazardous. However, most

clinical studies of fluoxetine for the management of depression did not include individuals with cardiovascular disease (e.g., those with a recent history of myocardial infarction or unstable heart disease), and further experience in such patients is necessary to confirm the reported relative lack of cardiotoxicity with the drug. (See Cautions: Precautions and Contraindications.)

Sedative Considerations. Because fluoxetine and other SSRIs generally are less sedating than some other antidepressants (e.g., tricyclics), some clinicians state that these drugs may be preferable in patients who do not require the sedative effects associated with many antidepressant agents; however, an antidepressant with more prominent sedative effects (e.g., trazodone) may be preferable in some patients (e.g., those with insomnia).

Suicidal Risk Considerations. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. However, there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidal thinking and behavior (suicidality) in certain patients during the early phases of treatment. FDA states that antidepressants increased the risk of suicidality in short-term studies in children, adolescents, and young adults (18–24 years of age) with major depressive disorder and other psychiatric disorders. (See Cautions: Pediatric Precautions.) It currently is unknown whether the suicidality risk extends to longer-term antidepressant use (i.e., beyond several months); however, there is substantial evidence from placebo-controlled maintenance trials in adults with major depressive disorder that antidepressants can delay the recurrence of depression. Because the risk of suicidality in depressed patients may persist until substantial remission of depression occurs, appropriate monitoring and close observation of patients of all ages who are receiving antidepressant therapy are recommended. (See Cautions: Precautions and Contraindications.)

Dosing Interval Considerations. Fluoxetine can be administered once weekly as delayed-release capsules for continuing management of major depressive disorder. Whether the weekly regimen is equivalent to daily therapy with conventional preparations for preventing relapse has not been established. In a double-blind study in adults who responded to daily fluoxetine therapy for major depressive disorder, the relapse rate for continuing therapy with fluoxetine 20-mg conventional capsules administered daily, fluoxetine 90-mg delayed-release capsules administered once weekly, or placebo was 26, 37, or 50%, respectively.

Other Considerations. Fluoxetine has been effective for the treatment of depression in adults with human immunodeficiency virus (HIV) infection. In one randomized, placebo-controlled study, analysis of patients who completed the study showed a statistically significant benefit in patients receiving fluoxetine compared with those receiving placebo. However, results of intent-to-treat analysis did not show a statistically significant benefit in those receiving the antidepressant, possibly because of a high attrition rate and substantial placebo response. There was no evidence that the degree of immunosuppression affected the response to antidepressant therapy.

Fluoxetine has been effective when used in combination with lithium in a limited number of patients with refractory depression who had not responded to prior therapy (including tricyclic antidepressants and MAO inhibitors administered alone or in combination with lithium), suggesting that lithium may potentiate the antidepressant activity of fluoxetine. (See Drug Interactions: Lithium.) In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) level 2 trial, patients with major depressive disorder who did not respond to or could not tolerate therapy with citalopram (another SSRI) were randomized to receive either extended-release ("sustained-release") bupropion or buspirone therapy in addition to citalopram. Although both extended-release bupropion and buspirone were found to produce similar remission rates, extended-release bupropion produced a greater reduction in the number and severity of symptoms and a lower rate of drug discontinuance than buspirone in this large-scale, effectiveness trial. These results suggest that augmentation of SSRI therapy with extended-release bupropion may be useful in some patients with refractory depression.

Fluoxetine has been used safely for the management of depression in at least one patient with established susceptibility to malignant hyperthermia, suggesting that the drug may be useful in depressed patients susceptible to malignant hyperthermia and in whom tricyclics and MAO inhibitors are potentially hazardous; however, additional experience is necessary to confirm this preliminary finding.

Because fluoxetine possesses anorectic and weight-reducing properties, some clinicians state that the drug may be preferred in obese patients and/or patients in whom the increase in appetite, carbohydrate craving, and weight gain associated with tricyclic antidepressant therapy may be undesirable (e.g., potentially hazardous to the patient's health; result in possible discontinuance of or noncompliance with therapy). However, the possibility that some patients with concurrent eating disorders or those who may desire to lose weight may misuse fluoxetine for its anorectic and weight-reducing effects should be considered. (See Uses: Eating Disorders and also see Chronic Toxicity.)

■ **Obsessive-Compulsive Disorder** Fluoxetine is used in the treatment of obsessive-compulsive disorder in adults and pediatric patients 7 years of age and older when the obsessions or compulsions cause marked distress, are time consuming, or interfere substantially with social or occupational functioning. Obsessions are recurrent and persistent ideas, thoughts, impulses, or images that, at some time during the disturbance, are experienced as intrusive and inappropriate (i.e., "ego dystonic") and that cause marked anxiety or distress but that are not simply excessive worries about real-life problems. Compulsions are repetitive, intentional behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) performed in response to an obsession or according to rules that must be applied rigidly (e.g., in a stereotyped fashion). Although the behaviors or acts are aimed at preventing or reducing distress or preventing some dreaded event or situation, they either are not connected in a realistic manner with what they are designed to neutralize or prevent or are clearly excessive. At some time during the course of the disturbance, the patient, if an adult, recognizes that the obsessions or compulsions are excessive or unreasonable; children may not make such a recognition.

The efficacy of fluoxetine for the management of obsessive-compulsive disorder has been established in several multicenter, placebo-controlled studies, including 2 studies of 13 weeks' duration in adults and one study of 13 weeks' duration in children and adolescents 7–17 years of age. Patients in these studies had moderate to severe obsessive-compulsive disorder with average baseline total scores on the Yale-Brown Obsessive-Compulsive Scale (YBOCS) of 22–26 in adults and 25–26 in children and adolescents (measured on the Children's Yale-Brown Obsessive-Compulsive Scale [CY-BOCS]).

In 2 fixed-dose studies of 13 weeks' duration, adults receiving fluoxetine dosages of 20, 40 and 60 mg daily experienced substantially greater reductions in the YBOCS total score than those receiving placebo. Mean reductions in total scores on the YBOCS in fluoxetine-treated patients were approximately 4–6 units in one study and 4–9 units in the other study compared with a 1-unit reduction in patients receiving placebo. In these 2 studies, a positive clinical response (much or very much improved on the Clinical Global Impressions improvement scale) occurred in 36–47 or 11% of patients receiving fluoxetine or placebo, respectively. While there was no indication of a dose-response relationship for effectiveness in one study, a dose-response relationship was observed in the other study, with numerically better responses in patients receiving 40 or 60 mg of fluoxetine daily compared with those receiving 20 mg of the drug daily. No age- or gender-related differences in outcome were noted in either of these studies.

In another randomized, placebo-controlled study of 13 weeks' duration, children and adolescents 7–17 years of age with obsessive-compulsive disorder who received mean fluoxetine dosages of approximately 25 mg daily (range: 10–60 mg daily) demonstrated substantially greater reductions in the CY-BOCS total score than those receiving placebo. In this study, a positive clinical response (much or very much improved on the Clinical Global Impressions improvement scale) occurred in approximately 55–58 or 9–19% of patients receiving fluoxetine or placebo, respectively. In addition, 49% of patients who received fluoxetine were classified as responders (i.e., patients with a 40% or greater reduction in their CY-BOCS total score from baseline) compared with 25% of those who received placebo. Subgroup analyses on outcome did not suggest any differential responsiveness on the basis of age or gender.

Results from comparative studies to date suggest fluoxetine and other selective serotonin-reuptake inhibitors (SSRIs; e.g., fluvoxamine, paroxetine, sertraline) are as effective or somewhat less effective than clomipramine in the management of obsessive-compulsive disorder. In a pooled analysis of separate short-term (10–13 weeks) studies comparing clomipramine, fluoxetine, fluvoxamine, or sertraline with placebo, clomipramine was calculated as being more effective (as determined by measures on the YBOC scale) than SSRIs, although all drugs were superior to placebo.

Many clinicians consider an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) or clomipramine to be the drugs of choice for the pharmacologic treatment of obsessive-compulsive disorder. The decision whether to initiate therapy with an SSRI or clomipramine often is made based on the adverse effect profile of these drugs. For example, some clinicians prefer clomipramine in patients who may not tolerate the adverse effect profile of SSRIs (nausea, headache, overstimulation, sleep disturbances) while SSRIs may be useful alternatives in patients unable to tolerate the adverse effects associated with clomipramine therapy (anticholinergic effects, cardiovascular effects, sedation). Consideration of individual patient characteristics (age, concurrent medical conditions), pharmacokinetics of the drug, potential drug interactions, and cost of therapy may also influence decisions regarding use of SSRIs or clomipramine as first-line therapy in patients with obsessive-compulsive disorder. Although not clearly established, it has been suggested that the mechanism of action of fluoxetine and other drugs (e.g., clomipramine) used in the management of obsessive-compulsive disorder may be related to their serotonergic activity.

Other Disorders with an Obsessive-Compulsive Component

Experience in a limited number of patients suggests that fluoxetine also reduces obsessive-compulsive symptoms associated with Tourette's disorder† (Gilles de la Tourette's syndrome); however, the drug did not appear to be effective in suppressing motor and vocal tics associated with the condition.

Trichotillomania† (an urge to pull out one's hair) has some features in common with those of obsessive-compulsive disorder and some studies have suggested that antiobsessional agents such as SSRIs and clomipramine may be useful in treating this condition. Successful treatment with fluoxetine has been reported in some patients with trichotillomania, including in 2 short-term, open studies in which dosages of up to 80 mg daily were given. However, fluoxetine's efficacy in the management of this disorder was not demonstrated in 2 double-blind, placebo-controlled, crossover studies. In addition, behavioral therapy was found to be more effective than fluoxetine in treating trichotillomania in a short-term, controlled study. Further studies are needed to more

clearly determine the role of fluoxetine and other serotonin-reuptake blockers in the management of this condition.

■ **Premenstrual Dysphoric Disorder** Fluoxetine is used in the treatment of premenstrual dysphoric disorder (previously late luteal phase dysphoric disorder). DSM-IV criteria for premenstrual dysphoric disorder (PMDD) require that in most menstrual cycles of the previous year at least 5 of the following 11 symptoms must have been present for most of the time during the last week of the luteal phase (with at least one of the symptoms being the first 4 listed): marked depressed mood, feelings of hopelessness, or self-deprecating thoughts; marked anxiety, tension, feelings of being "keyed up" or on "edge"; marked affective lability (e.g., feeling suddenly sad or tearful or increased sensitivity to rejection); persistent and marked anger or irritability or increased interpersonal conflicts; decreased interest in usual activities (e.g., work, school, friends, hobbies); a subjective sense of difficulty in concentrating; lethargy, easy fatigability, or marked lack of energy; marked change in appetite, overeating, or specific food cravings; hypersomnia or insomnia; a subjective sense of being overwhelmed or out of control; and other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, or a sensation of "bloating" or weight gain. Such symptoms should begin to remit within a few days of the onset of menses (follicular phase) and are always absent in the week following menses. The presence of this cyclical pattern of symptoms must be confirmed by at least 2 consecutive months of prospective daily symptom ratings. PMDD should be distinguished from the more common premenstrual syndrome (PMS) by prospective daily ratings and the strict criteria listed above.

There is some evidence that serotonergic agents (e.g., fluoxetine, paroxetine) have greater efficacy compared with non-serotonergic agents (e.g., bupropion, maprotiline) in relieving the physical and/or emotional symptoms of PMDD. In published studies, the response rates to fluoxetine therapy in women with PMDD appear to be similar to those described in patients with depression, panic disorder, and obsessive-compulsive disorder. However, unlike the onset of action of fluoxetine in other psychiatric conditions (6–8 weeks), some clinicians have observed a rapid onset of response to fluoxetine (approximately 2–4 weeks) in women with PMDD, suggesting that the mechanism of action of these agents in PMDD is not mediated by the drug's antidepressant or anti-obsessive effects. In addition, use of fluoxetine in the treatment of PMDD does not appear to produce the sustained remission typically seen in the treatment of major depressive disorder. PMDD symptoms recur soon after discontinuance of fluoxetine therapy (e.g., within 2 menstrual cycles), even in women who have received the drug for more than 1 year. It has been suggested that a past history of major depression may be associated with a partial or absent response to lower dosages of fluoxetine therapy. Because patients on oral contraceptives were excluded from most clinical studies to date, efficacy of fluoxetine used in conjunction with oral contraceptives for the treatment of PMDD has not been determined.

The efficacy of fluoxetine for the management of PMDD has been established in 3 randomized, placebo-controlled (1 intermittent- and 2 continuous-dosing) studies of 3 or 6 months' duration in adult women who met DSM-III-R or DSM-IV criteria for PMDD. One study involved over 300 women (20–40 years of age) who were randomized to receive either fluoxetine (at fixed dosages of 20 or 60 mg daily) or placebo continuously throughout the full menstrual cycle, beginning on the first day of their cycle. In this study, fixed doses of fluoxetine were shown to be substantially more effective than placebo in decreasing the mean total of 3 visual analog scale scores (tension, irritability, dysphoria); total scores decreased by 36–39% on 20 or 60 mg of fluoxetine and 7% on placebo. However, marked (greater than 50% reduction from baseline) improvement in total luteal phase visual analog scale scores occurred only in 18% of patients receiving 60 mg of fluoxetine and in 6 or 4% of those receiving 20 mg of fluoxetine or placebo, respectively. Fluoxetine therapy appeared to be well tolerated in patients receiving dosages of 20 mg daily, but approximately 33% of women receiving 60 mg daily discontinued the drug because of adverse reactions and 86% of those receiving this dosage who remained in the study reported one or more adverse effects attributable to the drug.

In a second double-blind, placebo-controlled, crossover study, women with PMDD who received flexible doses of fluoxetine (20–60 mg daily; mean dosage of 27 mg daily) throughout the menstrual cycle for a total of 3 cycles had an average visual analog scale total score (follicular to luteal phase increase) that was 3.8 times lower than that of patients receiving placebo. However, results of another double-blind, parallel study indicated that the response rate in women receiving fluoxetine 20 mg daily or bupropion 300 mg daily continuously for 2 cycles was not substantially superior to placebo on the Clinical Global Impressions scale.

The efficacy of intermittent dosing (defined as initiation of daily dosage 14 days prior to the anticipated onset of menstruation and continuing through the first full day of menses) was established in a double-blind, parallel group study of 3 months' duration. In this study, women receiving intermittent dosing of 20 mg daily dosages of fluoxetine had substantially greater improvements on the Daily Record of Severity of Problems, a patient-rated instrument that mirrors the diagnostic criteria for PMDD as identified in the DSM-IV, than those receiving placebo. Further studies are needed to evaluate the comparative efficacy of continuous and intermittent dosing regimens.

■ **Eating Disorders** Fluoxetine is used in the treatment of bulimia nervosa; the drug also has been used in a limited number of patients with other eating disorders (e.g., anorexia nervosa).

Although DSM-IV criteria provide guidelines for establishing a diagnosis of a specific eating disorder, the symptoms frequently occur along a continuum between those of anorexia nervosa and bulimia nervosa. The primary features in both anorexia nervosa and bulimia nervosa are weight preoccupation and excessive self-evaluation (i.e., disturbed perception) of body weight and shape, and many patients exhibit a mixture of both anorexic and bulimic behaviors.

The American Psychiatric Association (APA) states that psychiatric management forms the foundation of treatment for patients with eating disorders and should be instituted for all patients in combination with other specific treatment modalities (e.g., nutritional rehabilitation and pharmacotherapy). Because patients with eating disorders often exhibit comorbid conditions and/or associated psychiatric features that may compromise clinical outcome, treatment programs should identify and address all comorbid conditions before initiating therapy. Clinicians should recognize that patients with concurrent diabetes mellitus often underdose their insulin in order to lose weight, and that pregnant patients with disturbed eating behaviors (e.g., inadequate nutritional intake, binge eating, purging, abuse of teratogenic medications) may be at high risk for fetal or maternal complications. Results from several studies indicate that patients with associated psychiatric features such as substance abuse/dependence or personality disorder may require longer-term therapy than those without these comorbid conditions. Although the presence of depression at initial presentation has no predictive value for treatment outcome, many clinicians suggest that severe depression can impair the patient's involvement in and/or response to psychotherapy, and such patients should receive initial pharmacologic therapy to improve mood symptoms.

Bulimia Nervosa Fluoxetine is used in the management of binge-eating and self-induced vomiting behaviors in patients with moderate to severe bulimia nervosa (e.g., at least 3 bulimic episodes per week for 6 months).

According to DSM-IV, bulimia nervosa is characterized by recurrent episodes of binge eating and recurrent inappropriate compensatory behaviors to prevent weight gain (e.g., self-induced vomiting; misuse of laxatives, diuretics, enemas, or other medications; fasting; excessive exercise) and binge eating and compensatory behaviors both occur at least twice a week for 3 months.

Treatment strategies for bulimia nervosa include psychosocial interventions, nutritional counseling and rehabilitation, and pharmacotherapy. The primary goals in treating bulimia nervosa are to reduce binge eating and purging. Although antidepressants initially were used only in bulimic patients who were clinically depressed, evidence from recent studies indicates that nondepressed patients also respond to these agents, and that the presence of depression is not predictive of therapeutic response. Therefore, antidepressants are included as one component of initial treatment regimens for patients with bulimia nervosa. Because selective serotonin-reuptake inhibitors have a more favorable adverse effects profile, these drugs usually are preferred and may be especially useful for patients with symptoms of depression, anxiety, obsessions, or certain impulse disorder symptoms or for those who previously failed to achieve optimal response to psychosocial therapy. Other antidepressants also may be used to reduce the symptoms of binge eating and purging and help prevent relapse. However, the APA cautions against the use of tricyclic antidepressants in patients who are suicidal and cautions against use of MAO inhibitors in those with chaotic binge eating and purging.

The APA states that in patients who fail to respond to initial antidepressant therapy, it may be necessary to assess whether the patient has taken the drug shortly before vomiting or to determine whether effective drug concentrations have been achieved. Although only limited data are available regarding use of antidepressants for maintenance therapy, there appears to be a high rate of relapse during the treatment phase and an even higher rate following discontinuance of therapy. However, limited data indicate that the rate of relapse appears to correlate with the time at which drug therapy is initiated. In one small, open-label study, patients who received drug treatment within 13 weeks of diagnosis were more likely to exhibit sustained recovery during the first year than those who did not receive pharmacotherapy. Furthermore, continuing cognitive behavior therapy following discontinuance of drug therapy appears to prevent relapse in patients with bulimia nervosa. Additional study is needed to determine the effects of sequential use of psychotherapy and pharmacotherapy in the treatment of bulimia nervosa.

The efficacy of fluoxetine for the management of bulimia nervosa has been established in several multicenter, placebo-controlled studies, including 2 studies of 8 weeks' duration (using fluoxetine dosages of 20 or 60 mg daily) and one study of 16 weeks' duration (using fluoxetine dosages of 60 mg once daily) in patients with moderate to severe bulimia nervosa with median binge eating and self-induced vomiting of 7–10 and 5–9 times a week, respectively. In these studies, fluoxetine given in dosages of 60 mg daily (but not in dosages of 20 mg daily) was substantially more effective than placebo in reducing the number of binge-eating and self-induced vomiting episodes weekly. The superiority of fluoxetine compared with placebo was evident as early as within 1 week of therapy and persisted throughout each study period. The drug-related reduction in bulimic episodes appeared to be independent of baseline depression as assessed by the Hamilton Depression Rating Scale. The beneficial effect of fluoxetine therapy (compared with placebo), as measured by median reductions in the frequency of bulimic behaviors at the end of therapy compared with baseline, ranged from 1–2 and 2–4 episodes per week for binge eating and self-induced vomiting, respectively. The magnitude of clinical effect was related to baseline frequency of bulimic behaviors since greater reductions in such behaviors were observed in patients with higher baseline frequencies. Although binge eating and purging resolved completely in some patients who received

fluoxetine therapy, the majority of fluoxetine-treated patients only experienced a partial reduction in the frequency of bulimic behaviors.

In an uncontrolled study in patients with bulimia nervosa, fluoxetine substantially reduced the frequency of binge eating and self-induced vomiting but did not affect bodily dissatisfaction in patients receiving 60–80 mg of the drug for 4 weeks; in several patients, therapeutic effects of the drug appeared to be maintained during chronic therapy. In another uncontrolled study, fluoxetine reduced the frequency of binge eating and self-induced vomiting in several patients with bulimia nervosa who were unresponsive to previous therapy with imipramine. The drug also reportedly improved bulimic symptoms, expanded food preferences, and resulted in weight gain in one underweight patient with anorexia nervosa and bulimia who was unresponsive to or unable to tolerate previous therapy for her eating disorder (including tricyclic antidepressants, monoamine oxidase inhibitors, bupropion, nomifensine, or lithium). In addition, fluoxetine used in combination with lithium was effective in improving bulimic symptoms in a patient with major depression and bulimia who was unresponsive to prior therapy.

The efficacy of fluoxetine for long-term use in the treatment of bulimia nervosa has been established in a placebo-controlled study of up to 52 weeks' duration in patients who responded to an initial single-blind, 8-week acute treatment phase with fluoxetine 60 mg daily for bulimia nervosa. In this study, fluoxetine decreased the likelihood of relapse and improved the clinical outcome. However, symptoms of bulimia gradually worsened over time in patients in both the fluoxetine and placebo groups in this study, suggesting that fluoxetine alone may not be an adequate maintenance treatment after acute response in some patients with bulimia nervosa. Additional management strategies, such as psychotherapy, may be required to augment or to sustain initial improvement in this condition.

Pending further accumulation of data, most clinicians recommend that antidepressant therapy, including fluoxetine, be continued for at least 6–12 months in patients with bulimia nervosa before attempting to discontinue therapy. If fluoxetine is used for extended periods, the need for continued therapy with the drug should be reassessed periodically.

Anorexia Nervosa Fluoxetine has been used in a limited number of patients with anorexia nervosa†. According to DSM-IV, anorexia nervosa is characterized by refusal to maintain body weight at or above a minimally normal weight for age and height (e.g., weight loss leading to maintenance of body weight less than 85% of that expected or failure to make expected weight gain during periods of growth, leading to body weight less than 85% of that expected); intense fear of gaining weight or becoming fat (even though underweight); disturbance in the perception of body weight and shape, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight; and amenorrhea in postmenarchal females (i.e., absence of at least 3 consecutive menstrual cycles). Patients with anorexia nervosa often exhibit depressive (e.g., depressed mood, social withdrawal, irritability, insomnia, and diminished interest in sex) and obsessive-compulsive symptoms that may be associated with or exacerbated by undernutrition.

The APA recommends that a program of nutritional rehabilitation, including vitamin (e.g., potassium and phosphorus) supplementation, be established for all patients who are significantly underweight. The APA states that pharmacologic measures (e.g., antidepressants) may be considered in patients with anorexia nervosa to maintain weight and normal eating behaviors; to treat psychiatric symptoms associated with the disorder (e.g., depression, anxiety, or obsessive-compulsive symptoms); and to prevent relapse. However, such therapy should not be used as the sole or primary treatment for anorexia nervosa. Because associated psychiatric symptoms of anorexia nervosa (e.g., depression) often improve with weight gain, the APA states that the decision to initiate antidepressant therapy should be deferred until weight gain has been restored, and that the choice of an antidepressant agent depends on the remaining symptoms. According to the APA, selective serotonin-reuptake inhibitors commonly are considered in patients with anorexia nervosa whose depressive, obsessive, or compulsive symptoms persist in spite of or in the absence of weight gain.

Although there are few well-controlled, clinical studies of antidepressants for the treatment of anorexia nervosa, data from one study indicate that weight-restored patients with anorexia nervosa who received fluoxetine (40 mg daily) after hospital discharge had less weight loss, depression, and fewer rehospitalizations for anorexia nervosa during the subsequent year than those who received placebo. However, it should be noted that fluoxetine has been misused for its anorectic and weight-reducing effects in a patient with a history of chronic depression, anorexia nervosa, and laxative abuse who was receiving the drug for the treatment of depression; therefore, the misuse potential of fluoxetine in depressed patients with concurrent eating disorders or in other patients who may desire to lose weight should be considered. (See Chronic Toxicity.)

■ **Panic Disorder** Fluoxetine is used in the treatment of panic disorder with or without agoraphobia. Panic disorder is characterized by the occurrence of unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a clinically important change in behavior related to the attacks.

According to DSM-IV, panic disorder is characterized by recurrent unexpected panic attacks, which consist of a discrete period of intense fear or discomfort in which 4 (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: palpitations, pounding heart, or accelerated heart rate; sweating; trembling or shaking; sensations of shortness of breath or smothering; feeling of choking; chest pain or discomfort; nausea or abdominal distress; feeling dizzy, unsteady, lightheaded, or faint; derealization (feelings of unreality) or depersonalization (being detached from oneself); fear of losing control; fear of dying; paresthesias (numbness or tingling sensations); and chills or hot flushes.

The efficacy of fluoxetine for the management of panic disorder with or without agoraphobia has been established by 2 randomized, double-blind, placebo-controlled studies in adult outpatients who met DSM-IV criteria for panic disorder with or without agoraphobia. These studies were of 12 weeks' duration and used a flexible dosing schedule. Fluoxetine therapy in both studies was initiated in a dosage of 10 mg daily for the first week and then the dosage was escalated to 20–60 mg daily depending on clinical response and tolerability. In these studies, 42–62% of patients receiving fluoxetine were free from panic attacks at week 12 compared with 28–44% of those receiving placebo. The mean fluoxetine dosage in one of these studies was approximately 30 mg daily.

The optimum duration of fluoxetine therapy required to prevent recurrence of panic disorder has not been established to date. The manufacturer states that the efficacy of fluoxetine for long-term use (i.e., longer than 12 weeks) has not been demonstrated in controlled studies. However, in a 10-week, placebo-controlled, fixed-dose study, patients responding to fluoxetine 10 or 20 mg daily were randomized to receive continued therapy with their previous fluoxetine dosage or placebo during a 6-month continuation phase. The patients who received an additional 6 months of fluoxetine therapy in this study demonstrated continued clinical improvement. The manufacturer and some clinicians state that panic disorder is a chronic condition and requires several months or longer of sustained therapy. Therefore, it is reasonable to continue therapy in responding patients. The manufacturer recommends, however, that patients be reassessed periodically to determine the need for continued therapy.

Panic disorder can be treated with cognitive and behavioral psychotherapy and/or pharmacologic therapy. There are several classes of drugs that appear to be effective in the pharmacologic management of panic disorder, including tricyclic antidepressants (e.g., imipramine, clomipramine), monamine oxidase (MAO) inhibitors (e.g., phenelzine), selective serotonin-reuptake inhibitors (SSRIs), and benzodiazepines (e.g., alprazolam, clonazepam). When choosing among the available drugs, clinicians should consider their acceptance and tolerability by patients; their ability to reduce or eliminate panic attacks, reduce clinically important anxiety and disability secondary to phobic avoidance, and ameliorate other common comorbid conditions (such as depression); and their ability to prevent relapse during long-term therapy. Because of their better tolerability when compared with other agents (such as the tricyclic antidepressants and benzodiazepines), the lack of physical dependence problems commonly associated with benzodiazepines, and efficacy in panic disorder with comorbid conditions (e.g., depression, other anxiety disorders such as obsessive-compulsive disorder, alcoholism), many clinicians prefer SSRIs as first-line therapy in the management of panic disorder. If SSRI therapy is ineffective or is not tolerated, use of a tricyclic antidepressant or a benzodiazepine is recommended.

■ **Bipolar Disorder** Fluoxetine has been used for the short-term treatment of acute depressive episodes† in a limited number of patients with bipolar depression† (bipolar disorder, depressed). In one poorly controlled study, fluoxetine was more effective than imipramine, and each drug was more effective than placebo in the management of depression in patients with bipolar disorder; fluoxetine appeared to be particularly effective in reducing anxiety and somatic symptoms in these patients. However, because the drug has been reported to cause manic reactions in some patients, the possibility that hypomanic or manic attacks may be precipitated in patients with bipolar disorder must be considered. In addition, some experts have reported an association between use of antidepressants and the development of rapid cycling and mixed affective states in patients with bipolar disorder, suggesting that such use may worsen the overall course of bipolar disorder in these patients. Consequently, the American Psychiatric Association (APA) does not recommend use of antidepressant monotherapy in patients with bipolar disorder. Initiation or optimization of dosages of maintenance agents (i.e., lithium, lamotrigine) are considered first-line therapies for the management of acute episodes of depression in patients with bipolar disorder. While the addition of either lamotrigine, bupropion, or paroxetine currently is recommended as the next step for patients who fail to respond to optimum dosages of maintenance agents, the APA states that other SSRIs (e.g., fluoxetine) can be used as an alternative to these agents. For further information on the management of bipolar disorder, see Uses: Bipolar Disorder, in Lithium Salts 28:28.

Fluoxetine also is used in combination with olanzapine for the treatment of acute depressive episodes in patients with bipolar disorder. In 2 randomized, double-blind studies of 8 weeks' duration comparing a fixed combination of fluoxetine and olanzapine (Symbyax®) with olanzapine monotherapy and placebo, the fixed combination (flexible daily dosages of 6 mg olanzapine and 25 or 50 mg of fluoxetine or of 12 mg of olanzapine and 50 mg of fluoxetine) was more effective than olanzapine monotherapy (5–20 mg daily) or placebo in improvement in depressive symptoms as assessed by the Montgomery-Asberg Depression Rating Scale (MADRS). Although the manufacturer states that efficacy beyond 8 weeks' duration remains to be established, patients have received the fixed combination for up to 24 weeks in clinical trials. Clinicians who elect to extend therapy beyond 8 weeks should reevaluate the risks and benefits of continued therapy periodically.

■ **Obesity** Fluoxetine has been used in a limited number of patients for the short-term management of exogenous obesity†. In a controlled study, obese

(i.e., more than 20% overweight), nondepressed individuals receiving fluoxetine (average dosage: 64.9 mg daily), benzphetamine hydrochloride (average dosage: 97 mg daily), or placebo concurrently with reduced food intake and increased exercise for 8 weeks lost an average of about 4.8, 4, and 1.7 kg, respectively. Fluoxetine-treated patients who usually experienced carbohydrate cravings reportedly lost more weight during this study than those who did not experience such cravings. (See Pharmacology: Effects on Appetite and Body Weight.)

In a study evaluating the safety of fluoxetine therapy in the management of exogenous obesity, the drug was generally well tolerated. The adverse effect profile of the drug in nondepressed obese patients appeared to differ somewhat from that in depressed patients receiving similar dosages of the drug; obese patients reportedly had a higher incidence of fatigue and a lower incidence of nausea, anxiety, and tremor. Unlike amphetamines, the potential for addiction to or abuse of fluoxetine appears to be minimal (see Chronic Toxicity), and tolerance to the drug's anorectic and weight-reducing effects has not been reported to date following short-term administration. However, long-term studies are necessary to fully determine whether tolerance develops during chronic fluoxetine therapy and to fully establish the relative efficacy and safety of fluoxetine in the management of exogenous obesity.

■ **Cataplexy** Fluoxetine has been used for the symptomatic management of cataplexy† in a limited number of patients with cataplexy and associated narcolepsy. In one study, the drug appeared to be as effective as clomipramine in reducing the number of cataplexy attacks in patients concurrently receiving CNS stimulants (e.g., dextroamphetamine) for the symptomatic management of associated narcolepsy.

■ **Alcohol Dependence** Like some other selective serotonin-reuptake inhibitors (SSRIs; e.g., citalopram, zimeldine [not commercially available in the US]), fluoxetine has been used in the management of alcohol dependence†. However, studies of SSRIs have generally shown modest effects on alcohol consumption. In a limited number of early-stage problem drinkers (who drank an average of about 8 drinks daily prior to therapy), alcohol consumption was reduced by an average of 17% in patients receiving 60 mg of fluoxetine daily; however, response showed considerable interindividual variability, and alcohol consumption was not altered substantially in problem drinkers receiving 40 mg of the drug daily. It has been suggested that the clinical effects of SSRIs in the management of alcohol dependence may only be transient. In patients with mild to moderate alcohol dependence, alcohol consumption is substantially decreased for only the first 1–4 weeks of fluoxetine therapy or first 12 weeks of citalopram therapy. Additional study is required to fully determine the safety and efficacy of fluoxetine in the management of alcohol dependence. (See Pharmacology: Effects on Alcohol Intake and also see Drug Interactions: Alcohol.)

■ **Myoclonus** Fluoxetine has been used for the management of intention myoclonus†, including postanoxic action myoclonus† and progressive action myoclonus†, in a limited number of patients. Although fluoxetine alone was not effective in improving myoclonus, speech abnormalities, gait abnormalities, or overall performance on neurological examination in such patients, the drug did appear to potentiate the therapeutic effects of combined oxitriptan (l-5-hydroxytryptophan, l-5HTP) and carbidopa therapy in some patients. In addition, fluoxetine reportedly reduced the dosage requirement of oxitriptan and the incidence of adverse GI effects (e.g., diarrhea, abdominal cramps) associated with such therapy. Fluoxetine used in combination with oxitriptan also has exhibited antimyoclonic activity in animals. (See Pharmacology: Other Effects.) However, because toxic effects have been reported in some patients concurrently receiving fluoxetine and tryptophan, a serotonergic agent that is structurally similar to oxitriptan (see Tryptophan and Other Serotonin Precursors under Drug Interactions: Serotonergic Drugs), further study and experience are needed to fully determine the safety and efficacy of combined therapy with fluoxetine and oxitriptan-carbidopa in the management of intention myoclonus.

■ **Premature Ejaculation** Like some other SSRIs, fluoxetine has been used with some success in the treatment of premature ejaculation†. In a placebo-controlled study, fluoxetine produced substantial improvements compared with placebo in time to ejaculation and was well tolerated in most patients. However, in a comparative study, patients receiving either clomipramine or sertraline reported a greater increase in mean intravaginal ejaculation latency time and a greater patient sexual satisfaction rating than those receiving either fluoxetine or placebo. Although the mechanism of action of SSRIs in delaying ejaculation is unclear, it has been suggested that these drugs may be particularly useful in patients who fail or refuse behavioral or psychotherapeutic treatment or when partners are unwilling to cooperate with such therapy.

Dosage and Administration

■ **Administration** Fluoxetine hydrochloride is administered orally without regard to meals.

Fluoxetine hydrochloride conventional capsules, tablets, and solution are administered once or twice daily; the delayed-release capsules are administered once weekly. For the initial management of depression, obsessive-compulsive disorder, premenstrual dysphoric disorder, or bulimia nervosa, the drug generally is administered once daily in the morning. If the dosage exceeds 20 mg daily, the manufacturer and some clinicians state that fluoxetine should be administered in 2 divided doses daily (preferably in the morning and at noon). However, limited evidence suggests that no clinically important differences in either the efficacy or incidence of adverse effects exist with once-daily (in the morning) versus twice-daily (in the morning and at noon) administration of the drug. If sedation occurs during fluoxetine therapy, administering the second dose at bedtime rather than at noon may be useful. Because fluoxetine and its principal active metabolite have relatively long half-lives, the drug has been administered less frequently than once daily (e.g., every 2–7 days), particularly during maintenance therapy. Fluoxetine delayed-release capsules are administered once weekly as maintenance therapy in the management of major depressive disorder in patients who have responded to daily administration of the drug. Some clinicians have suggested that conventional fluoxetine preparations administered less frequently than once daily (i.e., three 20-mg capsules once weekly) may also be effective as maintenance therapy in the management of major depressive disorder, but such dosing regimens should be considered investigational at this time and require additional study to confirm their safety and efficacy.

Because of the prolonged elimination of fluoxetine and its active metabolite from the body, missing a dose of the drug once steady-state concentrations have been achieved is unlikely to result in substantial alterations in plasma fluoxetine or norfluoxetine concentrations.

■ **Dosage** Dosage of fluoxetine hydrochloride is expressed in terms of fluoxetine.

In titrating dosage of or discontinuing fluoxetine therapy, the prolonged elimination half-life of fluoxetine and norfluoxetine should be considered. Several weeks will be required before the full effect of such alterations is realized.

The manufacturers and some clinicians recommend that an interval of at least 5 weeks elapse between discontinuance of fluoxetine therapy and initiation of monoamine oxidase (MAO) inhibitor therapy, and that at least 2 weeks elapse following discontinuance of an MAO inhibitor prior to initiation of fluoxetine therapy. For additional information on potentially serious drug interactions that may occur between fluoxetine and MAO inhibitors or other serotonergic agents, see Cautions: Precautions and Contraindications and see also Drug Interactions: Serotonergic Drugs.

Withdrawal symptoms, including dysphoric mood, irritability, agitation, dizziness, anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, and sensory disturbances (e.g., paresthesias such as electric shock sensations), have been reported following discontinuance of fluoxetine and other selective serotonin-reuptake inhibitors (SSRIs), particularly upon abrupt discontinuance. While these events are generally self-limiting, there have been reports of serious discontinuance symptoms. If fluoxetine is to be discontinued, the manufacturer recommends that the dosage be tapered gradually and the patient closely monitored for these manifestations. Abrupt discontinuance should be avoided whenever possible. If intolerable symptoms occur following a decrease in the dosage or upon discontinuance of therapy, fluoxetine therapy may be reinstituted at the previously prescribed dosage. Subsequently, the clinician may continue decreasing the dosage but at a more gradual rate. Plasma concentrations of fluoxetine and norfluoxetine (the principal metabolite) decline gradually after cessation of therapy, which may minimize the risk of withdrawal symptoms.

Patients receiving fluoxetine should be monitored for possible worsening of depression, suicidality, or unusual changes in behavior, especially at the beginning of therapy or during periods of dosage adjustment. (See Cautions: Precautions and Contraindications.)

Major Depressive Disorder Adult Dosage. For the management of major depression, the recommended initial dosage of fluoxetine in adults is 20 mg daily. However, some clinicians suggest that fluoxetine therapy be initiated with lower dosages (e.g., 5 mg daily or 20 mg every 2 or 3 days). Although symptomatic relief may be apparent within the first 1–3 weeks of fluoxetine therapy, optimum antidepressant effect usually requires at least 4 weeks or more of therapy with the drug. If insufficient clinical improvement is apparent after several weeks of fluoxetine therapy at 20 mg daily, an increase in dosage may be considered. Efficacy of fluoxetine for major depression was demonstrated in clinical trials employing 10–80 mg daily. Studies comparing fluoxetine 20, 40, and 60 mg daily to placebo indicate that a dosage of 20 mg daily is sufficient to obtain a satisfactory response in most adults with major depression. Fluoxetine dosages up to 80 mg daily have been administered in some patients, and dosages as low as 5 mg daily may be effective in some patients with depression. In addition, in a study in moderately depressed patients, increasing the dosage of fluoxetine from 20 mg to 40 or 60 mg daily did not result in substantial improvement in depression but was associated with an increase in certain adverse effects (e.g., nausea, anxiety, diarrhea, dry mouth, weight loss). The manufacturer states that the maximum dosage of fluoxetine in adults with major depression should not exceed 80 mg daily; however, somewhat higher dosages (e.g., 100–120 mg daily) occasionally have been used in patients who did not respond adequately to lower dosages.

When fluoxetine hydrochloride delayed-release capsules are used for the continuing management of major depressive disorder, the recommended dosage of fluoxetine is 90 mg once weekly beginning 7 days after the last dose of fluoxetine 20 mg daily. If a satisfactory response is not maintained with once weekly administration, consideration may be given to reestablishing a daily dosage schedule.

As with the use of fluoxetine for other indications, lower dosages or less frequent dosing regimens should be considered for geriatric patients, patients with concurrent disease, and patients receiving multiple concomitant drug therapies.

Pediatric Dosage. For the management of major depressive disorder in children and adolescents 8–18 years of age, the recommended initial dosage of fluoxetine is 10 or 20 mg daily. If therapy is initiated at 10 mg daily, it can be increased after 1 week to 20 mg daily. Because higher plasma fluoxetine concentrations occur in lower weight children, the manufacturer states that both the initial and target dosage in lower weight children may be 10 mg daily. An increase in dosage to 20 mg daily may be considered after several weeks in lower weight children if insufficient clinical improvement is observed. Because a rare but serious drug interaction may occur in depressed children and adolescents with comorbid attention-deficit hyperactivity disorder (ADHD) who receive stimulants and selective serotonin-reuptake inhibitors concomitantly, some experts recommend a maximum fluoxetine dosage of 20 mg daily in such patients. (See Tramadol and Other Serotonergic Drugs under Drug Interactions: Serotonergic Drugs.)

Duration of Therapy. The optimum duration of fluoxetine therapy required to prevent recurrence of depressive symptoms has not been established to date. However, many experts state that acute depressive episodes require several months or longer of sustained antidepressant therapy. Systematic evaluation of fluoxetine has shown that its antidepressant efficacy is maintained for periods of up to approximately 9 months following 3 months of open-label acute treatment (12 months total) in adults receiving 20 mg daily as conventional fluoxetine capsules or for periods of up to approximately 6 months with once-weekly dosing of the 90 mg delayed-release fluoxetine capsules following 3 months of open-label treatment with 20 mg once daily as conventional fluoxetine capsules. However, the therapeutic equivalence of once-weekly administration of the 90-mg delayed-release capsules with that of once-daily administration of the 20-mg conventional preparations for delaying time to relapse has not been established. In addition, it has not been determined to date whether the dosage of the antidepressant necessary to treat acute symptoms of depression is the same as the dosage necessary to prevent recurrence of such symptoms. If therapy with the drug is prolonged, the lowest possible dosage should be employed and the need for continued therapy reassessed periodically.

Switching To or From Other Antidepressants. Because concurrent use of fluoxetine and a tricyclic antidepressant may result in greater than two- to 10-fold elevations in plasma tricyclic antidepressant concentrations, dosage of the tricyclic antidepressant may need to be reduced and plasma tricyclic concentrations may need to be monitored temporarily when fluoxetine is administered concurrently or has been recently discontinued. (See Drug Interactions: Tricyclic and Other Antidepressants.)

Because of the potential risk of serotonin syndrome, the manufacturer recommends that an interval of at least 2 weeks elapse when switching a patient from a monoamine oxidase (MAO) inhibitor to fluoxetine. Because both fluoxetine and its principal metabolite have relatively long half-lives, the manufacturers and some clinicians recommend that at least 5 weeks elapse between discontinuance of fluoxetine therapy and initiation of MAO inhibitor therapy. (See Drug Interactions: Serotonergic Drugs.)

Obsessive-Compulsive Disorder **Adult Dosage.** For the management of obsessive-compulsive disorder, the recommended initial dosage of fluoxetine in adults is 20 mg once daily. Because a possible dose-response relationship for effectiveness was suggested in one clinical study, an increase in dosage may be considered following several weeks of therapy if insufficient clinical improvement is observed. The manufacturer recommends fluoxetine dosages of 20–60 mg daily for the treatment of obsessive-compulsive disorder; dosages up to 80 mg daily have been well tolerated in clinical studies evaluating the drug in adults with obsessive-compulsive disorder. The manufacturer states that fluoxetine dosage should not exceed 80 mg daily. Like fluoxetine's antidepressant effect, the full therapeutic effect of the drug in patients with obsessive-compulsive disorder may be delayed until 5 weeks of fluoxetine therapy or longer.

Pediatric Dosage. For the management of obsessive-compulsive disorder, the recommended initial dosage of fluoxetine in children and adolescents 7–17 years of age is 10 mg once daily. In adolescents and higher weight children, the dosage should be increased to 20 mg daily after 2 weeks; additional dosage increases may be considered after several more weeks if insufficient clinical improvement is observed. In lower weight children, dosage increases may be considered after several weeks if insufficient clinical improvement is observed. The manufacturer recommends fluoxetine dosages of 20–60 mg daily for adolescents and higher weight children and fluoxetine dosages of 20–30 mg daily for lower weight children for the treatment of obsessive-compulsive disorder. In lower weight children, the manufacturer states that clinical experience with fluoxetine dosages exceeding 20 mg daily is minimal and that there is no experience with dosages exceeding 60 mg daily in such patients.

Duration of Therapy. Although the efficacy of fluoxetine for long-term use (i.e., longer than 13 weeks) has not been demonstrated in controlled studies, patients have been continued on the drug under double-blind conditions for up to an additional 6 months without loss of benefit. The manufacturer and many experts state that obsessive-compulsive disorder is chronic and requires several months or longer of sustained therapy. Therefore, it is reasonable to continue therapy in responding patients. If fluoxetine is used for extended periods, dosage should be adjusted so that the patient is maintained on the lowest effective dosage, and the need for continued therapy with the drug should be reassessed periodically.

Premenstrual Dysphoric Disorder For the management of premenstrual dysphoric disorder (previously late luteal phase dysphoric disorder), the recommended dosage of fluoxetine is 20 mg once daily given continuously throughout the menstrual cycle or intermittently (i.e., only during the luteal phase, starting 14 days prior to the anticipated onset of menstruation and continuing through the first full day of menses). The intermittent dosing regimen is then repeated with each new menstrual cycle. Decisions regarding which dosing regimen to use should be individualized. In a clinical study evaluating continuous dosing of fluoxetine dosages of 20 or 60 mg once daily for the treatment of premenstrual dysphoric disorder (PMDD), both dosages were effective but there was no evidence that the higher dosage provided any additional benefit. The manufacturer states that dosages exceeding 60 mg daily have not been systematically studied in patients with PMDD and that 80 mg daily is the maximum dosage of fluoxetine for the management of PMDD.

Clinical studies using fluoxetine dosages of 20 mg daily given intermittently or continuously have shown that the efficacy of the drug in the treatment of PMDD is maintained for up to 3 or 6 months, respectively. Patients should be periodically reassessed to determine the need for continued treatment. Discontinuance of the drug (even after more than 1 year of therapy) has resulted in relapse of PMDD within approximately 2 menstrual cycles.

Eating Disorders **Bulimia Nervosa.** For the management of bulimia nervosa in adults, the recommended dosage of fluoxetine is 60 mg daily, administered as a single dose in the morning. The manufacturer states that in some patients, oral dosage of the drug may be carefully titrated up to the recommended initial dosage over a period of several days. However, since 60-mg doses of fluoxetine were found to be well tolerated, the APA states that many clinicians initiate treatment for bulimia nervosa at the higher dosage, titrating downward as necessary to minimize adverse effects. Fluoxetine dosages exceeding 60 mg daily have not been evaluated in patients with bulimia.

Systematic evaluation of fluoxetine has demonstrated that its efficacy in the treatment of bulimia nervosa is maintained for periods of up to 12 months following 2 months of acute treatment in patients receiving 60 mg daily as conventional fluoxetine capsules. Pending further accumulation of data, most clinicians recommend that antidepressant therapy, including fluoxetine, be continued for at least 6–12 months in patients with bulimia nervosa before attempting to discontinue therapy. If fluoxetine is used for extended periods, the manufacturer states that the need for continued therapy should be reassessed periodically.

Anorexia Nervosa. Although safety and efficacy of fluoxetine for the management of anorexia nervosa† and optimal dosage of the drug for this disorder have not been established, fluoxetine has been given in a dosage of 40 mg daily in weight-restored patients with anorexia nervosa.

Panic Disorder For the management of panic disorder, the recommended initial dosage of fluoxetine in adults is 10 mg daily. After 1 week, the dosage should be increased to 20 mg once daily. If no clinical improvement is apparent after several weeks of fluoxetine therapy at 20 mg daily, an increase in dosage may be considered. Efficacy of the drug was demonstrated in clinical trials employing 10–60 mg daily. However, the most frequently administered dosage in flexible-dose clinical studies was 20 mg daily. As with the use of fluoxetine for other indications, lower dosages or less frequent dosing regimens should be considered for geriatric patients and patients with concurrent disease or those receiving multiple concomitant drug therapies. The manufacturer states that fluoxetine dosages exceeding 60 mg daily have not been systematically evaluated in patients with panic disorder.

The optimum duration of fluoxetine therapy required to prevent recurrence of panic disorder has not been established to date. The manufacturer states that the efficacy of fluoxetine beyond 12 weeks of therapy has not been demonstrated in controlled studies. However, the manufacturer and some clinicians state that panic disorder is chronic and requires several months or longer of sustained therapy. Therefore, it is reasonable to continue therapy in responding patients. The manufacturer recommends, however, that patients be reassessed periodically to determine the need for continued therapy.

Bipolar Disorder **Monotherapy.** For the short-term treatment of acute depressive episodes in patients with bipolar disorder†, fluoxetine has been given in a dosage of 20–60 mg daily. Because of the risk of developing manic episodes associated with antidepressant therapy in patients with bipolar disorder, many clinicians recommend using the lowest effective dosage of fluoxetine for the shortest time necessary using the antidepressant in conjunction with a mood-stabilizing agent (e.g., lithium).

Combination Therapy. When used in fixed combination with olanzapine for acute depressive episodes in patients with bipolar disorder, fluoxetine is administered once daily in the evening, usually initiating therapy with a dose of 6 mg of olanzapine and 25 mg of fluoxetine (Symbyax® 6/25). This dosage generally should be used as initial and maintenance therapy in patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or those with factors that may slow metabolism of the drugs(s) (e.g., female gender, geriatric age, nonsmoking status); when indicated, dosage should be escalated with caution. In other patients, dosage can be increased according to patient response and tolerance as indicated. In clinical trials, antidepressive efficacy was demonstrated at olanzapine dosages ranging from 6–12 mg daily and fluoxetine dosages ranging from 25–50 mg daily. Dosages exceeding 18 mg of olanzapine and 75 mg of fluoxetine have not been evaluated in clinical studies.

Cataplexy For the management of cataplexy†, fluoxetine has been given in a dosage of 20 mg once or twice daily in conjunction with CNS stimulant therapy (e.g., methylphenidate, dextroamphetamine).

Alcohol Dependence For the management of alcohol dependence†, fluoxetine has been given in a dosage of 60 mg daily. Studies have shown that reductions in alcohol intake occur only with dosages of selective serotonin-reuptake inhibitors that are higher than the average therapeutic dosages used in depression. Alcohol intake in patients receiving lower dosages of fluoxetine (40 mg daily) was comparable to that of patients receiving placebo.

■ **Dosage in Renal and Hepatic Impairment** The need for modification of fluoxetine dosage in patients with renal impairment has not been fully determined to date, and the drug should be used with caution in such patients. Although the elimination of fluoxetine and norfluoxetine following single-dose administration does not appear to be altered substantially in patients with renal impairment, multiple-dose studies are needed to determine whether accumulation of the parent drug and/or its metabolites occurs during long-term fluoxetine therapy in patients with severe renal impairment. (See Pharmacokinetics.) The manufacturer and some clinicians state that a reduction in dose and/or frequency of administration of fluoxetine should be considered in patients with renal impairment, particularly those with severe renal impairment. Supplemental doses of fluoxetine during hemodialysis do not appear to be necessary since the drug and its active metabolite norfluoxetine are not removed substantially by hemodialysis.

Since fluoxetine is extensively metabolized in the liver, elimination may be prolonged in patients with hepatic impairment. Therefore, the manufacturer and some clinicians recommend a reduction in dose and/or frequency of administration of fluoxetine in patients with hepatic impairment. Some clinicians recommend a 50% reduction in initial fluoxetine dosage for patients with well-compensated cirrhosis; however, patients with more substantial hepatic impairment, particularly those with severe disease, will require careful individualization of dosage. Subsequent dosage adjustment based on the tolerance and therapeutic response of the patient has been recommended in patients with hepatic impairment.

■ **Treatment of Pregnant Women during the Third Trimester** Because some neonates exposed to fluoxetine and other SSRIs or selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) late in the third trimester of pregnancy have developed severe complications, consideration may be given to cautiously tapering fluoxetine therapy in the third trimester prior to delivery if the drug is administered during pregnancy. (See Pregnancy under Cautions: Pregnancy, Fertility, and Lactation.)

Cautions

The adverse effect profile of fluoxetine is similar to that of other selective serotonin-reuptake inhibitors (SSRIs; e.g., citalopram, escitalopram, fluvoxamine, paroxetine, sertraline). Because fluoxetine is a highly selective serotonin-reuptake inhibitor with little or no effect on other neurotransmitters, the incidence of some adverse effects commonly associated with tricyclic antidepressants, such as anticholinergic effects (dry mouth, dizziness, constipation), adverse cardiovascular effects, drowsiness, and weight gain, is lower in patients receiving fluoxetine. However, certain adverse GI (e.g., nausea) and nervous system (e.g., anxiety, nervousness, insomnia) effects appear to occur more frequently during fluoxetine therapy than during therapy with tricyclic antidepressants.

In controlled studies, the most common adverse reactions occurring more frequently in adults receiving fluoxetine than in those receiving placebo included nervous system effects such as anxiety, nervousness, insomnia, drowsiness, fatigue or asthenia, tremor, and dizziness or lightheadedness; GI effects such as anorexia, nausea, and diarrhea; vasodilation; dry mouth; abnormal vision; decreased libido; abnormal ejaculation; rash; and sweating. Discontinuance of fluoxetine therapy was required in about 15% of adults, principally because of adverse psychiatric (e.g., nervousness, anxiety, insomnia), other nervous system (e.g., dizziness, asthenia, headache), GI (e.g., nausea), and dermatologic (e.g., rash, pruritus) effects. Because of the relatively long elimination half-lives of fluoxetine and its principal metabolite norfluoxetine, the possibility that some adverse effects may resolve slowly following discontinuance of the drug should be considered.

In controlled clinical trials, adverse effects reported in adults with weekly administration of fluoxetine delayed-release capsules were similar to those reported with daily administration of conventional capsules. Diarrhea and cognitive problems occurred more frequently with the delayed-release formulation compared with the conventional capsules.

Common adverse effects associated with fluoxetine therapy for major depressive disorder or obsessive-compulsive disorder in children and adolescents 7 years of age and older are generally similar to those observed in adults and include nausea, tiredness, nervousness, dizziness, and difficulty concentrating. However, manic reactions, including mania and hypomania, were the most common adverse events associated with discontinuance of the drug in 3 pivotal, pediatric, placebo-controlled studies. These reactions occurred in 2.6% of pediatric patients receiving fluoxetine compared with 0% of those receiving placebo and resulted in the discontinuance of fluoxetine in 1.8% of the patients during the acute phases of the studies combined. Consequently, regular monitoring for the occurrence of mania and hypomania is recommended by the manufacturer.

The usual cautions and precautions of olanzapine should be observed when fluoxetine is used in fixed combination with the antipsychotic.

■ **Nervous System Effects** Headache has occurred in approximately 20% of patients receiving fluoxetine and has required discontinuance of therapy in less than 1.5% of patients. Nervousness and anxiety have occurred in about 15 and 9% of patients, respectively, and insomnia has occurred in about 14% of patients receiving the drug; such effects appear to be dose-related and have required discontinuance of therapy in approximately 5% of fluoxetine-treated patients. However, because insomnia is a symptom also associated with depression, relief of insomnia and improvement in sleep patterns may occur when clinical improvement in depression becomes apparent during antidepressant therapy. The manufacturer and some clinicians state that a sedative (e.g., a short-acting benzodiazepine, chloral hydrate) may be administered to patients who experience insomnia or nervousness early in therapy; however, the possibility that fluoxetine may interact with some benzodiazepines (e.g., diazepam) should be considered. (See Drug Interactions: Benzodiazepines.)

Drowsiness and fatigue or asthenia reportedly occur in about 12 and 4%, respectively, of patients receiving fluoxetine therapy. Tremor and dizziness have occurred in about 8 and 6% of patients, respectively; the incidence of dizziness may be dose-related. Adverse nervous system effects reportedly occurring in approximately 1–2% of patients include sedation, sensation disturbance, lightheadedness, confusion, myoclonus, agitation, amnesia, and decreased concentration. Abnormal dreams and agitation have been reported in more than 1% of patients receiving fluoxetine therapy.

Hypomania, mania, and manic reaction have been reported in 1% or less of patients receiving fluoxetine, including those with depression or obsessive-compulsive disorder. In addition, mania reportedly occurred following administration of a higher than recommended dosage (140 mg daily) in a patient with major depression refractory to conventional antidepressant therapy; this patient subsequently responded to a fluoxetine dosage of 60 mg daily without apparent adverse effects. Such reactions have occurred in patients receiving other antidepressant agents and may be caused by antidepressant-induced functional increases in catecholamine activity within the CNS, resulting in a "switch" from depressive to manic behavior. There is some evidence that patients with bipolar disorder may be more likely to experience antidepressant-induced hypomanic or manic reactions than patients without evidence of this disorder. In addition, limited evidence suggests that such reactions may occur more frequently in bipolar depressed patients receiving tricyclics and tetracyclics (e.g., maprotiline, mianserin [not commercially available in the US]) than in those receiving SSRIs (e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline). However, further studies are needed to confirm these findings.

Extrapyramidal reactions, including acute dystonic reactions, torticollis, buccolingual syndrome, and akathisia, have occurred rarely in patients receiving fluoxetine. An extrapyramidal reaction consisting of torticollis, jaw rigidity, cogwheel rigidity, and loss of fluid motion in gait reportedly occurred in one patient several days after initiation of fluoxetine therapy, but responded rapidly to an anticholinergic antiparkinsonian agent (i.e., trihexyphenidyl) and did not recur despite continued fluoxetine therapy. Serum prolactin concentrations were increased and CSF 3-methoxy-4-hydroxyphenylacetic acid (homovanillic acid, HVA) concentrations were decreased in this patient, suggesting that a decrease in dopaminergic activity (possibly as a result of enhanced serotonergic neurotransmission) may have contributed to the reaction.

Although a causal relationship to the drug has not been established, serotonin syndrome and neuroleptic malignant syndrome (NMS)-like reactions also have been reported rarely in patients receiving fluoxetine, other SSRIs, and selective serotonin- and norepinephrine-reuptake inhibitors. (See Cautions: Precautions and Contraindications and see also Drug Interactions: Serotonergic Drugs.)

The incidence of seizures during fluoxetine therapy appears to be similar to that observed during therapy with most other currently available antidepressants. Seizures or events that were described as possible seizures have been reported in approximately 0.2% of patients receiving fluoxetine therapy to date. (See Cautions: Precautions and Contraindications.) In addition, seizures have occurred following acute overdosage of the drug (see Acute Toxicity) and in at least one patient undergoing electroconvulsive therapy (ECT) concomitantly.

Adverse nervous system effects occurring in less than 1% of fluoxetine-treated patients include ataxia, abnormal gait, incoordination, hyperkinesia, hypoesthesia, neuropathy, neuralgia, and hydrocephalus; however, a causal relationship to the drug has not been established. Migraine, acute brain syndrome, amnesia, CNS stimulation, vertigo, emotional lability, hostility, depersonalization, apathy, malaise, hangover effect, and euphoria also have been reported in less than 1% of patients receiving the drug. Psychosis, paranoid reaction, delusions, and hallucinations have been reported in less than 1% of patients, although these adverse effects have not been definitely attributed to fluoxetine. Rarely reported adverse nervous system effects for which a causal relationship has not been established include antisocial reaction, violent behavior, chronic brain syndrome, confusion, circumoral paresthesia, precipitation or worsening of depression, stupor, coma, EEG abnormalities, dysarthria, hypertonia, hysteria, myoclonus, dyskinesia, nystagmus, paralysis, exacerbation of multiple sclerosis, and decreased reflexes. Interference with facial nerve conduction, manifesting as ocular tics and impaired hearing, also has been reported. In some patients developing movement disorders with fluoxetine, there were underlying risk factors such as predisposing drug therapy and/or the disorder was an exacerbation of a preexisting disorder.

Suicidality The US Food and Drug Administration (FDA) has determined that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (18–24 years of age) with major depressive disorder and other psychiatric disorders. Suicidal ideation, which can manifest as persistent, obsessive, and violent suicidal thoughts,

has emerged occasionally in adults receiving fluoxetine. In a report of several fluoxetine-associated cases, severe suicidal ideation developed within 2–7 weeks after initiation of fluoxetine therapy and resolved within several days to months after discontinuance of the drug; however, the patients were unresponsive to fluoxetine and had received monoamine oxidase inhibitor therapy previously, and most had a history of suicidal ideation, were receiving relatively high dosages (60–80 mg daily) of fluoxetine, and were receiving other psychotropic therapy concomitantly. Suicidal ideation also has been reported in patients who reportedly had no history of such ideation, but the drug also has been used without recurrence of suicidal ideation in a few patients in whom such ideation emerged during tricyclic antidepressant therapy. Because of the possibility of suicidality, patients should be appropriately monitored and closely observed for clinical worsening, suicidality, and unusual changes in behavior, particularly during initiation of fluoxetine therapy (i.e., the first few months) and during periods of dosage adjustments. (See Cautions: Precautions and Contraindications and see Cautions: Pediatric Precautions and see Acute Toxicity.)

■ **GI Effects** The most frequent adverse effect associated with fluoxetine therapy is nausea, which occurs in about 21% of patients. Nausea generally is mild, occurs early in therapy, and usually subsides after a few weeks of continued therapy with the drug. Limited evidence suggests that the incidence of nausea may be dose-related, but additional experience with the drug is necessary to confirm this finding. Adverse GI effects, principally nausea, have required discontinuance of fluoxetine therapy in about 3% of patients receiving the drug. Although the incidence of vomiting appears to be similar in patients receiving fluoxetine or tricyclic antidepressants (e.g., imipramine), the incidence of nausea appears to be higher with fluoxetine. While the mechanism(s) of fluoxetine-induced GI effects has not been fully elucidated, serotonin has been shown to have complex effects on the GI tract (e.g., stimulation of small intestine motility, inhibition of gastric and large intestine motility).

Diarrhea occurs in about 12%, anorexia in about 9%, and dyspepsia in about 6% of patients receiving the drug; limited evidence suggests that the incidence of anorexia may be dose-related. Other adverse GI effects associated with fluoxetine therapy include abdominal pain and change in taste perception, which occur in approximately 3 and 2% of patients, respectively; taste loss has been reported rarely. Vomiting, melena, and flatulence reportedly occur in about 2% and gastroenteritis in about 1% of patients receiving the drug.

Increased appetite has been reported in more than 1% of patients receiving fluoxetine, but has not been definitely attributed to the drug. Other adverse GI effects, including aphthous stomatitis, dysphagia, eructation, esophagitis, gastritis, gingivitis, glossitis, melena, stomatitis, and thirst, have been reported in less than 1% of fluoxetine-treated patients; however, a causal relationship to the drug has not been established. Bloody diarrhea, GI hemorrhage, colitis, duodenal or gastric ulcer, enteritis, pancreatitis, fecal incontinence, hematemesis, hyperchlorhydria, increased salivation, mouth ulceration, salivary gland enlargement, tongue discoloration, and tongue edema have occurred rarely, but have not been definitely attributed to fluoxetine.

Epidemiologic case-control and cohort design studies have suggested that selective serotonin-reuptake inhibitors may increase the risk of upper GI bleeding. Although the precise mechanism for this increased risk remains to be clearly established, serotonin release by platelets is known to play an important role in hemostasis, and selective serotonin-reuptake inhibitors decrease serotonin uptake from the blood by platelets thereby decreasing the amount of serotonin in platelets. In addition, concurrent use of aspirin or other nonsteroidal anti-inflammatory agents was found to substantially increase the risk of GI bleeding in patients receiving selective serotonin-reuptake inhibitors in 2 of these studies. Although these studies focused on upper GI bleeding, there is some evidence suggesting that bleeding at other sites may be similarly potentiated. Further clinical studies are needed to determine the clinical importance of these findings. (See Cautions: Hematologic Effects and see also Drug Interactions: Drugs Affecting Hemostasis.)

■ **Dermatologic and Sensitivity Reactions** Rash (including maculopapular, purpuric, pustular, and vesiculobullous rash; erythema multiforme) and/or urticaria occurs in about 4% and pruritus occurs in about 2% of patients receiving fluoxetine. Adverse dermatologic effects, principally rash and pruritus, generally occur during the first few weeks of therapy and have required discontinuance of the drug in approximately 1% of patients.

Fluoxetine-induced rash and/or urticaria have been associated with systemic signs or symptoms such as fever, leukocytosis, arthralgia, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild elevation in serum aminotransferase (transaminase) concentrations in some patients. Serious systemic illnesses have developed rarely in patients with fluoxetine-induced dermatologic reactions to date. Although the diagnosis was equivocal in at least 2 of these patients, one patient was diagnosed as having a leukocytoclastic vasculitis and the other patient exhibited a severe desquamating syndrome that was variably diagnosed as either vasculitis or erythema multiforme. In addition, serum sickness reactions have developed in several other patients who experienced adverse dermatologic effects in association with fluoxetine therapy. Additional cases of systemic reactions possibly related to vasculitis have been reported in patients with rash. Although systemic reactions appear to occur rarely in patients receiving fluoxetine, such reactions may be serious and potentially may involve the lung, kidney, or liver; death reportedly has occurred in association with such reactions. Anaphylactoid reactions (including bronchospasm, angioedema, and/or urticaria) have been reported, and adverse pulmonary effects (including inflammatory processes of varying histopathology and/or fibrosis), which usually occurred with dyspnea as the only preceding symptom, have been reported rarely. It has not been established whether the systemic reactions and associated skin rash in fluoxetine-treated patients share a common underlying cause and represent a true syndrome induced by the drug or whether the temporal association between the rash and other systemic signs and symptoms occurred only by chance; in addition, a specific, underlying immunologic basis for these effects has not been identified. However, such systemic reactions are of potential concern since zimeldine (another selective serotonin-reuptake inhibitor that previously was commercially available outside the US) reportedly was associated with the development of Guillain-Barré syndrome following flu-like, hypersensitivity reactions to the drug; because of such reactions, zimeldine no longer is commercially available. Most patients with fluoxetine-induced rash and/or urticaria improve soon after discontinuance of therapy and/or administration of an antihistamine or corticosteroid, and most patients with such reactions to date have recovered completely without serious adverse sequelae. In addition, several patients who developed hypersensitivity reactions while receiving zimeldine subsequently received fluoxetine with no recurrence of a similar reaction. However, because of associated severe adverse systemic effects with fluoxetine and pharmacologically similar antidepressants (e.g., zimeldine), it is recommended that fluoxetine be discontinued if rash, urticaria, and/or other manifestations of hypersensitivity (e.g., fever, flu-like symptoms), for which alternative etiologies cannot be identified, occur during therapy with the drug.

Excessive sweating occurs in about 8% of patients receiving fluoxetine. Acne and allergic reactions have occurred in approximately 2 and 1% of patients, respectively. Adverse dermatologic and hypersensitivity reactions occurring in less than 1% of patients receiving fluoxetine include acne, cyst formation, dry skin, contact dermatitis, facial edema, alopecia, and herpes simplex; however, these effects have not been definitely attributed to the drug. Although a causal relationship has not been established, eczema, erythema nodosum, epidermal necrolysis, exfoliative dermatitis, Stevens-Johnson syndrome, seborrhea, psoriasis, fungal dermatitis, cellulitis, hirsutism, herpes zoster, skin discoloration, skin hypertrophy, subcutaneous nodules, and ecchymoses have been reported rarely.

■ **Metabolic Effects** Unlike tricyclic antidepressants, which commonly cause weight gain, weight gain occurs in less than 1% of patients receiving fluoxetine. Weight loss, however, frequently occurs during therapy with the drug. Normal-weight and overweight (i.e., body mass index exceeding 25 kg/m^2) depressed patients lost an average of 0.9–1.8 kg and 1.8 kg, respectively, following 6 weeks of therapy with the drug. In addition, weight loss exceeding 5% of body weight has been reported in approximately 13% of fluoxetine-treated patients. Weight loss associated with fluoxetine therapy appears to be reversible, with a gradual increase in body weight occurring following discontinuance of therapy with the drug. Such weight loss appears to result from decreased food consumption rather than adverse GI effects associated with the drug; there is some evidence that fluoxetine-induced weight loss may be dose-related. (See Pharmacology: Effects on Appetite and Body Weight.) In addition, weight loss appears to occur independent of the antidepressant effect of the drug. Although weight loss is commonly associated with fluoxetine therapy, less than 1% of patients discontinue the drug because of this effect. In some cases, however, substantial weight loss may be an undesirable effect of therapy with the drug, particularly in underweight depressed patients.

Fluoxetine potentially may alter blood glucose concentrations. Hypoglycemia has occurred in less than 1% of patients receiving fluoxetine and hypoglycemic reaction has occurred rarely. In addition, hyperglycemia has developed following discontinuance of the drug. Therefore, the possibility that insulin and/or oral sulfonylurea antidiabetic agent dosage adjustments may be necessary when fluoxetine therapy is initiated or discontinued in patients with diabetes mellitus should be considered.

Hypercholesterolemia, hyperlipidemia, and hypokalemia have been reported rarely in fluoxetine-treated patients; these adverse effects have not been definitely attributed to the drug.

■ **Ocular Effects** Visual disturbances, including blurred vision, occur in approximately 3% of patients receiving fluoxetine. Adverse ocular effects reported in less than 1% of fluoxetine-treated patients include amblyopia, conjunctivitis, eye pain, mydriasis, and photophobia. Blepharitis, cataract formation, corneal lesion, diplopia, ocular hemorrhage, glaucoma, iritis, ptosis, and strabismus have been reported rarely.

■ **Cardiovascular Effects** Current evidence suggests that fluoxetine is less cardiotoxic than most antidepressant agents (e.g., tricyclic antidepressants, monoamine oxidase inhibitors). Unlike tricyclic antidepressants, which may cause characteristic ECG changes such as prolongation of PR, QRS, and QT intervals and ST-segment and T-wave abnormalities, clinically important ECG changes (such as conduction abnormalities) have not been reported during controlled studies in fluoxetine-treated patients without preexisting cardiac disease. In addition, while tricyclic antidepressants commonly cause an increase in heart rate, heart rate reportedly is reduced by an average of approximately 3 beats/minute in patients receiving fluoxetine. (See Pharmacology: Cardiovascular Effects.)

Palpitations and hot flushes have been reported in approximately 1 and 2% of patients receiving fluoxetine, respectively. Chest pain occurs in about 1% of patients. Unlike tricyclic antidepressants, fluoxetine has been associated with hypotension (including orthostatic hypotension) relatively infrequently; in con-

trolled studies, orthostatic hypotension was reported in less than 1% of patients receiving the drug. Angina pectoris, cardiac arrhythmia, tachycardia, hemorrhage, hypertension, and syncope have occurred infrequently in fluoxetine-treated patients, although a causal relationship to the drug has not been established. First-degree AV block, bundle-branch block, bradycardia, ventricular arrhythmia, ventricular tachycardia (including torsades de pointes-type arrhythmias), myocardial infarction, thrombophlebitis, cerebral ischemia, vascular headache, and cerebrovascular accident have occurred rarely, but these adverse effects have not been definitely attributed to fluoxetine.

■ **Musculoskeletal Effects** Back, joint, muscle, and limb pain reportedly occur in approximately 1–2% of patients receiving fluoxetine. Arthritis, bursitis, tenosynovitis, muscle twitching, jaw pain, and neck pain or rigidity have occurred in less than 1% of fluoxetine-treated patients, but these adverse effects have not been directly attributed to the drug. Bone necrosis, osteoporosis, pathological fracture, chondrodystrophy, myositis, muscle hemorrhage, and rheumatoid arthritis have been reported rarely, although a causal relationship to fluoxetine has not been established.

■ **Hematologic Effects** Lymphadenopathy or anemia has been reported in 2% or less than 1% of patients receiving fluoxetine, respectively. Blood dyscrasia, leukopenia, thrombocythemia, pancytopenia, aplastic anemia, immune-related hemolytic anemia, lymphocytosis, increased sedimentation rate, increased bleeding time, petechiae, purpura, and iron deficiency anemia have occurred rarely, although a causal relationship to the drug has not been established. Thrombocytopenia also has been reported.

Abnormal bleeding has been reported in several patients receiving selective serotonin-reuptake inhibitors. Bleeding complications (e.g., ecchymosis, purpura, menorrhagia, rectal bleeding) have been reported infrequently in patients receiving selective serotonin-reuptake inhibitors. Although the precise mechanism for these reactions has not been established, it has been suggested that impaired platelet aggregation and prolonged bleeding time may be due at least in part to inhibition of serotonin reuptake into platelets and/or that increased capillary fragility and vascular tone may contribute to these cases. (See Cautions: GI Effects and see also Drug Interactions: Drugs Affecting Hemostasis.)

■ **Respiratory Effects** Upper respiratory infection has been reported in approximately 8% of fluoxetine-treated patients. Flu-like syndrome (see Cautions: Dermatologic and Sensitivity Reactions), pharyngitis, nasal congestion, sinusitis, sinus headache, cough, and dyspnea have occurred in approximately 1–3% of patients receiving the drug. Adverse respiratory effects reportedly occurring in at least 1% of patients but not directly attributable to fluoxetine therapy include bronchitis, rhinitis, and yawning, and those occurring in less than 1% of patients but not attributed to the drug include asthma, hyperventilation, pneumonia, and hiccups. Apnea, hypoxia, pulmonary edema, laryngeal edema, pulmonary fibrosis/alveolitis, eosinophilic pneumonia, pleural effusion, and hemoptysis have occurred rarely in patients receiving fluoxetine; however, these adverse effects have not been definitely attributed to the drug.

■ **Renal, Electrolyte, and Genitourinary Effects** ***Sexual Dysfunction*** Like other selective serotonin-reuptake inhibitors, adverse effects on sexual function have been reported in both men and women receiving fluoxetine. Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they also may occur as the result of pharmacologic therapy. It is difficult to determine the true incidence and severity of adverse effects on sexual function during fluoxetine therapy, in part because patients and clinicians may be reluctant to discuss these effects. Therefore, incidence data reported in product labeling and earlier studies are most likely underestimates of the true incidence of adverse sexual effects. Recent reports indicate that up to 50% of patients receiving selective serotonin-reuptake inhibitors describe some form of sexual dysfunction during treatment and the actual incidence may be even higher.

Ejaculatory disturbances (principally ejaculatory delay) are the most common adverse urogenital effects associated with fluoxetine in men, occurring in about 7% of men receiving the drug compared with less than 1% of those receiving placebo in controlled clinical studies for the treatment of obsessive-compulsive disorder or bulimia. In some cases, the adverse effect of ejaculatory delay has been used for therapeutic benefit in the treatment of premature ejaculation. (See Uses: Premature Ejaculation.) Other genital disorders reported in patients receiving the drug include impotence, penile (of the glans) anesthesia, and anorgasmy (in both males and females). Decreased or increased libido also reportedly occurs in up to 2% of patients. In addition, clitoral engorgement, sexual arousal, and orgasm reportedly occurred in at least one female patient receiving fluoxetine.

Management of sexual dysfunction caused by selective serotonin-reuptake inhibitor therapy includes waiting for tolerance to develop; using a lower dosage of the drug; using drug holidays; delaying administration of the drug until after coitus; or changing to another antidepressant. Although further study is needed, there is some evidence that adverse sexual effects of the selective serotonin-reuptake inhibitors may be reversed by concomitant use of certain drugs, including buspirone, 5-hydroxytryptamine-2 (5-HT_2) receptor antagonists (e.g., nefazodone), 5-HT_3 receptor inhibitors (e.g., granisetron), or α_2-adrenergic receptor antagonists (e.g., yohimbine), selective phosphodiesterase (PDE) inhibitors (e.g., sildenafil), or dopamine receptor agonists (e.g., amantadine, dextroamphetamine, pemoline [no longer commercially available in the US], methylphenidate). In most patients, sexual dysfunction is fully reversed 1–3 days after discontinuance of the antidepressant. Ejaculatory dysfunction associated with fluoxetine therapy also has responded to concomitant cyproheptadine therapy in a few patients.

Other Renal, Electrolyte, and Genitourinary Effects Treatment with SSRIs, including fluoxetine, and selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) may result in hyponatremia. In many cases, this hyponatremia appears to be due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and was reversible when fluoxetine was discontinued. Cases with serum sodium concentrations lower than 110 mEq/L have been reported. Geriatric individuals and patients receiving diuretics or who are otherwise volume depleted may be at greater risk of developing hyponatremia during therapy with SSRIs or SNRIs. Discontinuance of fluoxetine should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Because geriatric patients may be at increased risk for hyponatremia associated with these drugs, clinicians prescribing fluoxetine in such patients should be aware of the possibility that such reactions may occur. In addition, periodic monitoring of serum sodium concentrations (particularly during the first several months) in geriatric patients receiving SSRIs has been recommended by some clinicians.

Painful menstruation, sexual dysfunction, frequent micturition, and urinary tract infection have occurred in approximately 1–2% of patients receiving fluoxetine. Decreased or increased libido reportedly occur in 1–2% or less than 1% of patients, respectively. Abnormal ejaculation, impotence, penile (of the glans) anesthesia, amenorrhea, leukorrhea, menorrhagia, ovarian disorder, vaginitis, pelvic pain, menopause, urinary incontinence, urinary urgency, impaired urination, cystitis, and dysuria have been reported in less than 1% of fluoxetine-treated patients, although these adverse effects have not been definitely attributed to the drug. Dyspareunia, abortion, hypomenorrhea, metrorrhagia, uterine spasm, uterine hemorrhage, salpingitis, vaginal hemorrhage, and vaginal bleeding (which occurred following discontinuance of therapy) have occurred rarely, although a causal relationship to the drug has not been established. Albuminuria, hematuria, polyuria, pyuria, urinary tract disorder, pyelonephritis, urethritis, epididymitis, orchitis, urethral pain, and urolithiasis (including renal calculus formation) also have been reported rarely in patients receiving fluoxetine therapy, although such effects have not been directly attributed to the drug.

■ **Endocrine Effects** Hypothyroidism has been reported in less than 1% of patients receiving fluoxetine, and goiter and hyperthyroidism have occurred rarely; however, a causal relationship to the drug has not been established.

■ **Anticholinergic Effects** Although bothersome anticholinergic effects occur commonly in patients receiving tricyclic antidepressant agents, such effects occur less frequently with fluoxetine. Dry mouth, dizziness, and constipation have been reported in about 10, 6, and 5% of patients receiving the drug. Urinary retention has occurred in less that 1% of fluoxetine-treated patients; blurred vision also has been reported.

■ **Other Adverse Effects** Viral infection and influenza have been reported in approximately 3 and 1% of patients receiving fluoxetine, respectively. Fever or chills alone have occurred in more than 1% of patients receiving fluoxetine; however, fever with accompanying chills has been reported in less than 1% of patients. (See Cautions: Dermatologic and Sensitivity Reactions.) Hypothermia has occurred rarely; however, a causal relationship to the drug has not been definitely established.

Abnormal liver function test results, lymphadenopathy, and epistaxis have been reported in less than 1% of fluoxetine-treated patients, although such effects have not been definitely attributed to the drug. Adverse effects occurring rarely in patients receiving fluoxetine include hepatitis, hepatomegaly, liver tenderness, jaundice, cholecystitis, cholelithiasis, acute abdominal syndrome, moniliasis, serum sickness, and lupus erythematosus syndrome.

Ear pain and tinnitus have occurred in less than 1% of patients, and deafness has been reported rarely. Although not directly attributed to the drug, generalized and peripheral edema have been reported in less than 1% of fluoxetine-treated patients; dehydration and gout have occurred rarely.

Breast pain and fibrocystic breast disease have occurred in less than 1% of patients, and breast enlargement and female lactation have been reported rarely. Hyperprolactinemia also has occurred in patients receiving the drug. Although a causal relationship to fluoxetine has not been established for these effects, serotonin has been implicated as a possible physiologic factor in the release of prolactin. (See Pharmacology: Neuroendocrine Effects.)

■ **Precautions and Contraindications** Worsening of depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior may occur in both adult and pediatric (see Cautions: Pediatric Precautions) patients with major depressive disorder or other psychiatric disorders, whether or not they are taking antidepressants. This risk may persist until clinically important remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. However, there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term, placebo-controlled studies of antidepressants (i.e., selective serotonin-reuptake inhibitors [SSRIs] and other antidepressants) have shown an increased risk of suicidality in children, adolescents, and young adults (18–24 years of age) with major depressive disorder and other psychiatric disorders. An increased suicidality risk was not demonstrated with antidepressants compared with placebo in adults older than 24

years of age, and a reduced risk was observed in adults 65 years of age or older. It currently is unknown whether the suicidality risk extends to longer-term use (i.e., beyond several months); however, there is substantial evidence from placebo-controlled maintenance trials in adults with major depressive disorder that antidepressants can delay the recurrence of depression.

The US Food and Drug Administration (FDA) recommends that all patients being treated with antidepressants for any indication be appropriately monitored and closely observed for clinical worsening, suicidality, and unusual changes in behavior, particularly during initiation of therapy (i.e., the first few months) and during periods of dosage adjustments. Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, also should be advised to monitor patients on a daily basis for the emergence of agitation, irritability, or unusual changes in behavior, as well as the emergence of suicidality, and to report such symptoms immediately to a health care provider.

Although a causal relationship between the emergence of symptoms such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and/or mania and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consequently, consideration should be given to changing the therapeutic regimen or discontinuing therapy in patients whose depression is persistently worse or in patients experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, particularly if such manifestations are severe, abrupt in onset, or were not part of the patient's presenting symptoms. FDA also recommends that the drugs be prescribed in the smallest quantity consistent with good patient management, in order to reduce the risk of overdosage.

It is generally believed (though not established in controlled trials) that treating a major depressive episode with an antidepressant alone may increase the likelihood of precipitating a mixed or manic episode in patients at risk for bipolar disorder. Therefore, patients should be adequately screened for bipolar disorder prior to initiating treatment with an antidepressant; such screening should include a detailed psychiatric history (e.g., family history of suicide, bipolar disorder, and depression).

Potentially life-threatening serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions have been reported with SSRIs, including fluoxetine, and selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) alone, but particularly with concurrent administration of other serotonergic drugs (including serotonin [5-hydroxytryptamine; 5-HT] type 1 receptor agonists ["triptans"]), drugs that impair the metabolism of serotonin (e.g., monoamine oxidase [MAO] inhibitors), or antipsychotic agents or other dopamine antagonists. Symptoms of serotonin syndrome may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or GI symptoms (e.g., nausea, vomiting, diarrhea). In its most severe form, serotonin syndrome may resemble NMS, which is characterized by hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation in vital signs, and mental status changes. Patients receiving fluoxetine should be monitored for the development of serotonin syndrome or NMS-like signs and symptoms.

Fluoxetine is contraindicated in patients who currently are receiving or recently (i.e., within 2 weeks) have received therapy with MAO inhibitors used for treatment of depression. If concurrent therapy with fluoxetine and a 5-HT_1 receptor agonist (triptan) is clinically warranted, the patient should be observed carefully, particularly during initiation of therapy, when dosage is increased, or when another serotonergic agent is initiated. Concomitant use of fluoxetine and serotonin precursors (e.g., tryptophan) is not recommended. If signs and symptoms of serotonin syndrome or NMS develop during therapy, treatment with fluoxetine and any concurrently administered serotonergic or antidopaminergic agents, including antipsychotic agents, should be discontinued immediately and supportive and symptomatic treatment should be initiated. (See Drug Interactions: Serotonergic Drugs.)

Because clinical experience with fluoxetine in patients with concurrent systemic disease, including cardiovascular disease, hepatic impairment, and renal impairment, is limited, caution should be exercised when fluoxetine is administered to patients with any systemic disease or condition that may alter metabolism of the drug or adversely affect hemodynamic function. (See Dosage and Administration: Dosage.) Fluoxetine should be used with caution in patients with hepatic impairment, since prolonged elimination of the drug and its principal metabolite has been reported to occur in patients with liver cirrhosis. Because the safety of long-term fluoxetine therapy in patients with severe renal impairment has not been adequately evaluated to date, fluoxetine also should be used with caution in patients with severe renal impairment. (See Dosage and Administration: Dosage in Renal and Hepatic Impairment.) Although current evidence suggests that fluoxetine is less cardiotoxic than most older antidepressant agents (see Cautions: Cardiovascular Effects), the safety of fluoxetine in patients with a recent history of myocardial infarction or unstable cardiovascular disease has not been adequately evaluated to date.

Patients receiving fluoxetine should be advised to notify their clinician if they are taking or plan to take nonprescription (over-the-counter) or prescription medications or alcohol-containing beverages or products. (See Drug Interactions.)

Patients receiving fluoxetine should be cautioned about the concurrent use of nonsteroidal anti-inflammatory agents (including aspirin) or other drugs that affect coagulation since combined use of selective serotonin-reuptake inhibitors and these drugs has been associated with an increased risk of bleeding. (See Cautions: GI Effects and see also Drug Interactions: Drugs Affecting Hemostasis.)

Fluoxetine generally is less sedating than many other currently available antidepressants and does not appear to produce substantial impairment of cognitive or psychomotor function. However, patients should be cautioned that fluoxetine may impair their ability to perform activities requiring mental alertness or physical coordination (e.g., operating machinery, driving a motor vehicle) and to avoid such activities until they experience how the drug affects them.

Patients receiving fluoxetine should be advised to notify their clinician if they develop rash or hives during therapy with the drug. Pending further accumulation of data, monitoring for such effects is particularly important since these effects have been associated with the development of potentially serious systemic reactions in patients receiving fluoxetine or pharmacologically similar antidepressants (e.g., zimeldine). (See Cautions: Dermatologic and Sensitivity Reactions.)

Seizures have been reported in patients receiving therapeutic dosages and following acute overdosage of fluoxetine. Because of limited experience with fluoxetine in patients with a history of seizures, therapy with the drug should be initiated with caution in such patients.

Because fluoxetine may alter blood glucose concentrations in patients with diabetes mellitus (see Cautions: Metabolic Effects), the possibility that insulin and/or oral sulfonylurea antidiabetic agent dosage adjustments may be necessary when fluoxetine therapy is initiated or discontinued should be considered.

Because fluoxetine therapy has been commonly associated with anorexia and weight loss, the drug should be used with caution in patients who may be adversely affected by these effects (e.g., underweight patients).

Treatment with SSRIs, including fluoxetine, and selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) may result in hyponatremia. In many cases, this hyponatremia appears to be due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and was reversible when fluoxetine was discontinued. Cases with serum sodium concentrations lower than 110 mEq/L have been reported. Geriatric individuals and patients receiving diuretics or who are otherwise volume depleted may be at greater risk of developing hyponatremia during therapy with SSRIs or SNRIs. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls; more severe and/or acute cases have been associated with hallucinations, syncope, seizures, coma, respiratory arrest, and death. Discontinuance of fluoxetine should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. (See Cautions: Renal, Electrolyte, and Genitourinary Effects and see also Cautions: Geriatric Precautions.)

Fluoxetine therapy is contraindicated in patients currently receiving, or having recently received, thioridazine therapy. In addition, concurrent use of fluoxetine in patients receiving pimozide is contraindicated. (See Thioridazine and also see Pimozide under Drug Interactions: Antipsychotic Agents.)

Fluoxetine is contraindicated in patients with known hypersensitivity to the drug.

■ **Pediatric Precautions** Safety and efficacy of fluoxetine in pediatric patients have not been established in children younger than 8 years of age for the management of major depressive disorder (see Pediatric Considerations under Uses: Major Depressive Disorder) or in children younger than 7 years of age for the management of obsessive-compulsive disorder.

FDA warns that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder and other psychiatric disorders. The risk of suicidality for these drugs was identified in a pooled analysis of data from a total of 24 short-term (4–16 weeks), placebo-controlled studies of 9 antidepressants (i.e., fluoxetine, bupropion, citalopram, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, venlafaxine) in over 4400 children and adolescents with major depressive disorder, obsessive-compulsive disorder (OCD), or other psychiatric disorders. The analysis revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in pediatric patients receiving antidepressants than in those receiving placebo. However, a more recent meta-analysis of 27 placebo-controlled trials of 9 antidepressants (SSRIs and others) in patients younger than 19 years of age with major depressive disorder, OCD, or non-OCD anxiety disorders suggests that the benefits of antidepressant therapy in treating these conditions may outweigh the risks of suicidal behavior or suicidal ideation. No suicides occurred in these pediatric trials.

The risk of suicidality in FDA's pooled analysis differed across the different psychiatric indications, with the highest incidence observed in the major depressive disorder studies. In addition, although there was considerable variation in risk among the antidepressants, a tendency toward an increase in suicidality risk in younger patients was found for almost all drugs studied. It is currently unknown whether the suicidality risk in pediatric patients extends to longer-term use (i.e., beyond several months).

As a result of this analysis and public discussion of the issue, FDA has directed manufacturers of all antidepressants to add a boxed warning to the labeling of their products to alert clinicians of this suicidality risk in children and adolescents and to recommend appropriate monitoring and close observation of patients receiving these agents. (See Cautions: Precautions and Contraindications.) The drugs that are the focus of the revised labeling are all drugs

included in the general class of antidepressants, including those that have not been studied in controlled clinical trials in pediatric patients, since the available data are not adequate to exclude any single antidepressant from an increased risk. In addition to the boxed warning and other information in professional labeling on antidepressants, FDA currently recommends that a patient medication guide explaining the risks associated with the drugs be provided to the patient each time the drugs are dispensed. Caregivers of pediatric patients whose depression is persistently worse or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality during antidepressant therapy should consult their clinician regarding the best course of action (e.g., whether the therapeutic regimen should be changed or the drug discontinued). *Patients should not discontinue use of selective serotonin-reuptake inhibitors without first consulting their clinician; it is very important that the drugs not be abruptly discontinued, as withdrawal effects may occur.* (See Dosage and Administration: Dosage.)

Anyone considering the use of fluoxetine in a child or adolescent for any clinical use must balance the potential risks of therapy with the clinical need.

Important toxicity, including myotoxicity, long-term neurobehavioral and reproductive toxicity, and impaired bone development, has been observed following exposure of juvenile animals to fluoxetine; some of these effects occurred at clinically relevant exposures to the drug. In a study in which fluoxetine (3, 10, or 30 mg/kg) was orally administered to young rats from weaning (postnatal day 21) through adulthood (day 90), male and female sexual development was delayed at all dosages, and growth (body weight gain, femur length) was decreased during the dosing period in animals receiving the highest dosage. At the end of the treatment period, serum levels of creatine kinase (a marker of muscle damage) were increased in animals receiving the intermediate and highest dosage, and abnormal muscle and reproductive organ histopathology (skeletal muscle degeneration and necrosis, testicular degeneration and necrosis, epididymal vacuolation and hypospermia) was observed at the highest dosage. When animals were evaluated after a recovery period (up to 11 weeks after drug cessation), neurobehavioral abnormalities (decreased reactivity at all dosages and learning deficit at the highest dosage) and reproductive functional impairment (decreased mating at all dosages and impaired fertility at the highest dosage) were noted; testicular and epididymal microscopic lesions and decreased sperm concentrations were observed in the high-dosage group indicating that the reproductive organ effects seen at the end of treatment were irreversible. Reversibility of fluoxetine-induced muscle damage was not assessed in this study. Adverse effects similar to those observed in rats treated with fluoxetine during the juvenile period have not been reported after administration of fluoxetine to adult animals. Plasma exposures (AUC) to fluoxetine in juvenile rats receiving the low, intermediate, and high dosages in this study were approximately 0.1–0.2, 1–2, and 5–10 times, respectively, the average exposure in pediatric patients receiving the maximum recommended dosage of 20 mg daily. Exposures to norfluoxetine, the principal active metabolite of fluoxetine, in rats were approximately 0.3–0.8, 1–8, and 3–20 times the pediatric exposure at the maximum recommended dosage, respectively.

A specific effect of fluoxetine on bone development has been reported in mice treated with fluoxetine during the juvenile period. In mice treated with fluoxetine (5 or 20 mg/kg given intraperitoneally) for 4 weeks beginning at 4 weeks of age, bone formation was reduced resulting in decreased bone mineral content and density. These dosages did not affect overall growth (e.g., body weight gain or femoral length). The dosages given to juvenile mice in this study were approximately 0.5 and 2 times the maximum recommended dose for pediatric patients on a mg/m^2 basis.

In a study conducted in mice, fluoxetine administration (10 mg/kg intraperitoneally) during early postnatal development (postnatal days 4 to 21) produced abnormal emotional behaviors (decreased exploratory behavior in elevated plus-maze, increased shock avoidance latency) in adulthood (12 weeks of age). The dosage used in this study was approximately equal to the pediatric maximum recommended dosage on a mg/m^2 basis. Because of the early dosing period in this study, the clinical importance of these findings for the labeled pediatric use in humans is unknown.

As with other SSRIs, decreased weight gain has been observed in association with the use of fluoxetine in children and adolescents. In one clinical trial in pediatric patients 8–17 years of age, height gain averaged about 1.1 cm less and weight gain averaged about 1 kg less after 19 weeks of fluoxetine therapy relative to placebo-treated patients. In addition, fluoxetine therapy was associated with a decrease in plasma alkaline phosphatase concentrations. Because the safety of fluoxetine in pediatric patients has not been systematically assessed for chronic therapy longer than several months in duration and studies that directly evaluate the long-term effects of fluoxetine on the growth, development, and maturation of children and adolescents are lacking, height and weight should be monitored periodically in pediatric patients receiving fluoxetine. The clinical importance of these findings on long-term growth currently is not known, but the manufacturer will conduct a phase IV study to evaluate any potential impact of fluoxetine therapy on long-term pediatric growth. For further information on adverse effects associated with the use of fluoxetine in pediatric patients, see the opening discussion in Cautions.

■ **Geriatric Precautions** The efficacy of fluoxetine has been established in clinical studies in geriatric patients. Although no overall differences in efficacy or safety were observed between geriatric and younger patients, the possibility that some older patients particularly those with systemic disease or those who are receiving other drugs concomitantly (see Pharmacokinetics: Elimination and also see Uses: Major Depressive Disorder) may exhibit increased sensitivity to the drug cannot be ruled out.

In pooled data analyses, a *reduced* risk of suicidality was observed in adults 65 years of age or older with antidepressant therapy compared with placebo. (See Cautions: Precautions and Contraindications.)

Limited evidence suggests that geriatric patients may be more likely than younger patients to develop fluoxetine-induced hyponatremia and transient syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Therefore, clinicians prescribing fluoxetine in geriatric patients should be aware of the possibility that such reactions may occur. In addition, periodic monitoring (especially during the first several months) of serum sodium concentrations in geriatric patients receiving the drug has been recommended by some clinicians.

As with other psychotropic drugs, geriatric patients receiving antidepressants appear to have an increased risk of hip fracture. Despite the fewer cardiovascular and anticholinergic effects associated with SSRIs, these drugs did not show any advantage over tricyclic antidepressants with regard to hip fracture in a case-control study. In addition, there was little difference in the rates of falls between nursing home residents receiving SSRIs and those receiving tricyclic antidepressants in a retrospective study. Therefore, all geriatric individuals receiving either type of antidepressant should be considered at increased risk of falls, and appropriate measures should be taken.

■ **Mutagenicity and Carcinogenicity** Fluoxetine and norfluoxetine did not exhibit mutagenic activity in vitro in mammalian cell (e.g., mouse lymphoma, rat hepatocyte DNA repair) or microbial (the *Salmonella* microbial mutagen [Ames]) test systems, or with the in vivo sister chromatid-exchange assay in Chinese hamster bone marrow cells. No evidence of carcinogenesis was seen in rats or mice receiving oral fluoxetine dosages of about 7.5 or 9 times the maximum recommended human dosage of the drug, respectively, for 24 months.

■ **Pregnancy, Fertility, and Lactation** ***Pregnancy*** Some neonates exposed to fluoxetine and other selective serotonin-reuptake inhibitors (SSRIs) or selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) late in the third trimester of pregnancy have developed complications that have sometimes been severe and required prolonged hospitalization, respiratory support, enteral nutrition, and other forms of supportive care in special care nurseries. Such complications can arise immediately upon delivery and usually last several days or up to 2–4 weeks. Clinical findings reported to date in the neonates have included respiratory distress, cyanosis, apnea, seizures, temperature instability or fever, feeding difficulty, dehydration, excessive weight loss, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, reduced or lack of reaction to pain stimuli, and constant crying. These clinical features appear to be consistent with either a direct toxic effect of the SSRI or SNRI or, possibly, a drug withdrawal syndrome. It should be noted that, in some cases, the clinical picture was consistent with serotonin syndrome (see Drug Interactions: Serotonergic Drugs). When treating a pregnant woman with fluoxetine during the third trimester of pregnancy, the clinician should carefully consider the potential risks and benefits of such therapy. Consideration may be given to cautiously tapering fluoxetine therapy in the third trimester prior to delivery if the drug is administered during pregnancy. (See Dosage and Administration: Treatment of Pregnant Women during the Third Trimester.)

FDA states that decisions about management of depression in pregnant women are challenging and that the patient and her clinician must carefully consider and discuss the potential benefits and risks of SSRI therapy during pregnancy for the individual woman. Two recent studies provide important information on risks associated with discontinuing or continuing antidepressant therapy during pregnancy.

The first study, which was prospective, naturalistic, and longitudinal in design, evaluated the potential risk of relapsed depression in pregnant women with a history of major depressive disorder who discontinued or attempted to discontinue antidepressant (SSRIs, tricyclic antidepressants, or others) therapy during pregnancy compared with that in women who continued antidepressant therapy throughout their pregnancy; all women were euthymic while receiving antidepressant therapy at the beginning of pregnancy. In this study, women who discontinued antidepressant therapy were found to be 5 times more likely to have a relapse of depression during their pregnancy than were women who continued to receive their antidepressant while pregnant, suggesting that pregnancy does not protect against a relapse of depression.

The second study suggests that infants exposed to SSRIs in late pregnancy may have an increased risk of persistent pulmonary hypertension of the newborn (PPHN), which is associated with substantial neonatal morbidity and mortality. PPHN occurs at a rate of 1–2 neonates per 1000 live births in the general population in the US. In this retrospective case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately sixfold higher for infants exposed to SSRIs after the twentieth week of gestation compared with infants who had not been exposed to SSRIs during this period. The study was too small to compare the risk of PPHN associated with individual SSRIs, and the findings have not been confirmed. Although the risk of PPHN identified in this study still is low (6–12 cases per 1000) and further study is needed, the findings add to concerns from previous reports that infants exposed to SSRIs late in pregnancy may experience adverse serotonergic effects.

Fluoxetine and its principal metabolite norfluoxetine have been shown to cross the placenta in animals. There are no adequate and controlled studies to

date using fluoxetine in pregnant women, and the drug should be used during pregnancy only when clearly needed. Women should be advised to notify their clinician if they are or plan to become pregnant. FDA states that women who are pregnant or thinking about becoming pregnant should not discontinue any antidepressant, including fluoxetine, without first consulting their clinician. The decision whether or not to continue antidepressant therapy should be made only after careful consideration of the potential benefits and risks of antidepressant therapy for each individual pregnant patient. If a decision is made to discontinue treatment with fluoxetine or other SSRIs before or during pregnancy, discontinuance of therapy should be done in consultation with the clinician in accordance with the prescribing information for the antidepressant, and the patient should be closely monitored for possible relapse of depression. In addition, the prolonged elimination of the drug and its active metabolite from the body after discontinuance of therapy should be considered when a woman of childbearing potential receiving fluoxetine plans to become pregnant.

Most epidemiologic studies of pregnancy outcome following first trimester exposure to SSRIs, including fluoxetine, conducted to date have not revealed evidence of an increased risk of major congenital malformations. In a prospective, controlled, multicenter study, maternal use of several SSRIs (sertraline, fluvoxamine, paroxetine) in a limited number of pregnant women did not appear to increase the risk of congenital malformation, miscarriage, stillbirth, or premature delivery when used during pregnancy at recommended dosages. Birth weight and gestational age in neonates exposed to the drugs were similar to those in the control group. In another small study based on medical records review, the incidence of congenital anomalies reported in infants born to women who were treated with fluoxetine and other SSRIs during pregnancy was comparable to that observed in the general population. However, the results of epidemiologic studies indicate that exposure to paroxetine during the first trimester of pregnancy may increase the risk for congenital malformations, particularly cardiovascular malformations. (See Pregnancy, under Cautions: Pregnancy, Fertility, and Lactation, in Paroxetine 28:16.04.20.) Additional epidemiologic studies are needed to more thoroughly evaluate the relative safety of fluoxetine and other SSRIs during pregnancy, including their potential teratogenic risks and possible effects on neurobehavioral development.

The effect of fluoxetine on labor and delivery is not known.

Fertility Reproduction studies in rats using fluoxetine dosages 5–9 times the maximum recommended human daily dosage have not revealed evidence of impaired fertility. However, a slight decrease in neonatal survival that probably was related to reduced maternal food consumption and suppressed weight gain was reported in the offspring. Like some other SSRIs, pretreatment with fluoxetine inhibits methoxydimethyltryptamine-induced ejaculation in rats; this effect is blocked by metergoline, a serotonin antagonist. Alterations in sexual function also have been reported in patients receiving the drug. (See Sexual Dysfunction under Cautions: Renal, Electrolyte, and Genitourinary Effects and see also Cautions: Pediatric Precautions.)

Lactation Fluoxetine and its metabolites distribute into human milk. Limited data indicate that fluoxetine and norfluoxetine concentrations are 20–30% of concurrent maternal plasma drug concentrations. Crying, sleep disturbance, vomiting, and watery stools developed in an infant who nursed from a woman receiving fluoxetine; plasma fluoxetine and norfluoxetine concentrations in the infant on the second day of feeding were 340 and 208 ng/mL, respectively. Therefore, fluoxetine should not be used in nursing women, and women should be advised to notify their physician if they plan to breast-feed. In addition, the slow elimination of fluoxetine and norfluoxetine from the body after discontinuance of the drug should be considered.

Drug Interactions

As with other drugs, the possibility that fluoxetine may interact with any concomitantly administered drug by a variety of mechanisms, including pharmacodynamic and pharmacokinetic interactions, should be considered. The potential for interactions exists not only with concomitantly administered drugs but also with drugs administered for several weeks after discontinuance of fluoxetine therapy due to the prolonged elimination of fluoxetine and its principal metabolite, norfluoxetine. (See Pharmacokinetics: Elimination.)

■ **Serotonergic Drugs** Use of selective serotonin-reuptake inhibitors (SSRIs) such as fluoxetine concurrently or in close succession with other drugs that affect serotonergic neurotransmission may result in serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions. Symptoms of serotonin syndrome may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or GI symptoms (e.g., nausea, vomiting, diarrhea). Although the syndrome appears to be relatively uncommon and usually mild in severity, serious and potentially life-threatening complications, including seizures, disseminated intravascular coagulation, respiratory failure, and severe hyperthermia, as well as death occasionally have been reported. In its most severe form, serotonin syndrome may resemble NMS, which is characterized by hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation in vital signs, and mental status changes. The precise mechanism of these reactions is not fully understood; however, they appear to result from excessive serotonergic activity in the CNS, probably mediated by activation of serotonin 5-HT_{1A} receptors. The possible involvement of dopamine and 5-HT_2 receptors also has been suggested, although their roles remain unclear.

Serotonin syndrome most commonly occurs when 2 or more drugs that affect serotonergic neurotransmission are administered either concurrently or in close succession. Serotonergic agents include those that increase serotonin synthesis (e.g., the serotonin precursor tryptophan), stimulate synaptic serotonin release (e.g., some amphetamines, dexfenfluramine [no longer commercially available in the US], fenfluramine [no longer commercially available in the US]), inhibit the reuptake of serotonin after release (e.g., SSRIs, selective serotonin- and norepinephrine-reuptake inhibitors [SNRIs], tricyclic antidepressants, trazodone, dextromethorphan, meperidine, tramadol), decrease the metabolism of serotonin (e.g., monoamine oxidase [MAO] inhibitors), have direct serotonin postsynaptic receptor activity (e.g., buspirone), or nonspecifically induce increases in serotonergic neuronal activity (e.g., lithium salts). Selective agonists of serotonin (5-hydroxytryptamine; 5-HT) type 1 receptors ("triptans") and dihydroergotamine, agents with serotonergic activity used in the management of migraine headache, and St. John's wort (*Hypericum perforatum*) also have been implicated in serotonin syndrome.

The combination of SSRIs and MAO inhibitors may result in serotonin syndrome or NMS-like reactions. Such reactions have also been reported when SSRIs have been used concurrently with tryptophan, lithium, dextromethorphan, sumatriptan, dihydroergotamine, or antipsychotics or other dopamine antagonists. In rare cases, the serotonin syndrome reportedly has occurred in patients receiving the recommended dosage of a single serotonergic agent (e.g., clomipramine) or during accidental overdosage (e.g., sertraline intoxication in a child). Some other drugs that have been implicated in precipitating symptoms suggestive of serotonin syndrome or NMS-like reactions include buspirone, bromocriptine, dextropropoxyphene, linezolid, methylenedioxymethamphetamine (MDMA; "ecstasy"), selegiline (a selective MAO-B inhibitor), and sibutramine (an SNRI used for the management of obesity). Other drugs that have been associated with the syndrome but for which less convincing data are available include carbamazepine, fentanyl, and pentazocine.

Clinicians should be aware of the potential for serious, possibly fatal reactions associated with serotonin syndrome or NMS-like reactions in patients receiving 2 or more drugs that affect serotonergic neurotransmission, even if no such interactions with the specific drugs have been reported to date in the medical literature. Pending further accumulation of data, serotonergic drugs should be used cautiously in combination and such combinations avoided whenever clinically possible. Serotonin syndrome may be more likely to occur when initiating therapy with a serotonergic agent, increasing the dosage, or following the addition of another serotonergic drug. Some clinicians state that patients who have experienced serotonin syndrome may be at higher risk for recurrence of the syndrome upon reinitiation of serotonergic drugs. Pending further experience in such cases, some clinicians recommend that therapy with serotonergic agents be limited following recovery. In cases in which the potential benefit of the drug is thought to outweigh the risk of serotonin syndrome, lower potency agents and reduced dosages should be used, combination serotonergic therapy should be avoided, and patients should be monitored carefully for manifestations of serotonin syndrome. If signs and symptoms of serotonin syndrome or NMS develop during therapy, treatment with fluoxetine and any concurrently administered serotonergic or antidopaminergic agents, including antipsychotic agents, should be discontinued immediately and supportive and symptomatic treatment should be initiated.

Serotonin Syndrome **Manifestations.** Serotonin syndrome is characterized by mental status and behavioral changes, altered muscle tone or neuromuscular activity, autonomic instability with rapid fluctuations of vital signs, hyperthermia, and diarrhea. Some clinicians have stated that the diagnosis of serotonin syndrome can be made based on the presence of at least 3 of the following manifestations: mental status changes (e.g., confusion, hypomania), agitation, myoclonus, hyperreflexia, fever, shivering, tremor, diaphoresis, ataxia, and diarrhea in the setting of a recent addition or an increase in dosage of a serotonergic agent; the absence of other obvious causes of mental status changes and fever (e.g., infection, metabolic disorders, substance abuse or withdrawal); and no recent initiation or increase in dosage of an antipsychotic agent prior to the onset of the signs and symptoms (in order to rule out NMS). In some cases, features of the serotonin syndrome have resembled those associated with NMS, which may occur in patients receiving phenothiazines or other antipsychotic agents. (See Extrapyramidal Reactions in Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.)

Other signs and symptoms associated with serotonin syndrome have included restlessness, irritability, insomnia, aggressive behavior, headache, drowsiness, dizziness, disorientation, loss of coordination, anxiety, euphoria, hallucinations, dilated pupils, nystagmus, paresthesias, rigidity, clonus, seizures, and coma. Nausea, vomiting, abdominal cramping, flushing, hypertension, hypotension, tachycardia, tachypnea, and hyperventilation also have occurred.

The onset of the serotonin syndrome can range from minutes after initiating therapy with a second serotonergic agent to several weeks after receiving a stable dosage. Preliminary evidence to date suggests that neither the occurrence nor the severity of serotonin syndrome is related to the dose or duration of serotonergic drug therapy.

The incidence of serotonin syndrome is unknown, but it is likely that the syndrome is underreported because it is not recognized or appears in various degrees of severity (mild, moderate, or severe). In addition, serotonin syndrome may be confused with or resemble NMS in some cases.

Treatment. Mild cases of serotonin syndrome generally respond within 12–24 hours to the immediate discontinuance of serotonergic agents and general supportive therapy. Symptoms rarely last more than 72–96 hours in the

absence of complications. Supportive therapy in such cases may include hospitalization, adequate hydration, control of myoclonus and hyperreflexia with benzodiazepines such as clonazepam (and possibly propranolol), and control of fever with acetaminophen and external cooling, if necessary. Other possible causes of altered mental status and fever also should be considered and treated accordingly.

Patients with severe hyperthermia (i.e., a temperature of more than 40.5°C) are considered to have more severe cases of serotonin syndrome which are associated with more serious complications and mortality. Muscular rigidity often accompanies hyperthermia and may respond to benzodiazepine therapy. Such patients should be managed with aggressive cooling measures, including external cooling, the institution of muscular paralysis (to decrease body temperature, help prevent rhabdomyolysis and disseminated intravascular coagulation from muscular rigidity refractory to benzodiazepines, and facilitate intubation), and maintenance of a patent airway with endotracheal intubation. Seizures may be treated with benzodiazepines and, if necessary, other anticonvulsants (e.g., barbiturates). Patients who develop hypertension, cardiac arrhythmias, and other serious complications such as disseminated intravascular coagulation or rhabdomyolysis associated with serotonin syndrome should receive appropriate therapy for these conditions.

Although there is no specific therapy for serotonin syndrome, nonspecific serotonin (5-HT_1 and 5-HT_2) receptor antagonists such as cyproheptadine and methysergide and drugs with 5-HT_{1A} receptor affinity such as propranolol have been used with some success in a limited number of patients whose symptoms persisted or were unusually severe. Dantrolene, bromocriptine, and chlorpromazine (for sedation, to help reduce fever, and because of its 5-HT-receptor blocking activity) also have been used in a limited number of patients with serotonin syndrome but with inconsistent results; the possibility that chlorpromazine may lower the seizure threshold in this setting should be considered.

Monoamine Oxidase Inhibitors Potentially serious, sometimes fatal serotonin syndrome or NMS-like reactions have been reported in patients receiving serotonin-reuptake inhibitors in combination with an MAO inhibitor. Such reactions also have been reported in patients who recently have discontinued a selective serotonin-reuptake inhibitor and have been started on an MAO inhibitor.

Probably because of its extensive clinical use and the prolonged elimination half-life of both fluoxetine and norfluoxetine, fluoxetine has been the selective serotonin-reuptake inhibitor most commonly implicated in serotonin syndrome. In at least 2 cases, serotonin syndrome developed when MAO inhibitor therapy was initiated after the discontinuance of fluoxetine therapy. Shivering, diplopia, nausea, confusion, and anxiety reportedly occurred in one patient 6 days after discontinuance of fluoxetine therapy and 4 days after initiation of tranylcypromine therapy; signs and symptoms resolved without apparent sequelae within 24 hours following discontinuance of the MAO inhibitor in this patient. In another case, the initiation of tranylcypromine therapy more than 5 weeks after discontinuance of fluoxetine reportedly resulted in serotonin syndrome.

Concurrent administration of fluoxetine and MAO inhibitors is contraindicated. Because both fluoxetine and its principal metabolite have relatively long half-lives, at least 5 weeks should elapse between discontinuance of fluoxetine therapy and initiation of MAO inhibitor therapy, since administration of an MAO inhibitor prior to elapse of this time may increase the risk of serious adverse effects. Based on clinical experience with concurrent administration of tricyclic antidepressants and MAO inhibitors, at least 2 weeks should elapse following discontinuance of an MAO inhibitor prior to initiation of fluoxetine therapy.

Linezolid. Linezolid, an anti-infective agent that is a nonselective and reversible MAO inhibitor, has been associated with drug interactions resulting in serotonin syndrome, including some associated with SSRIs, and potentially may also cause NMS-like reactions. Therefore, at least one manufacturer of fluoxetine states that linezolid should be used with caution in patients receiving fluoxetine. The manufacturer of linezolid states that, unless patients are carefully observed for signs and/or symptoms of serotonin syndrome, the drug should not be used in patients receiving SSRIs. Some clinicians suggest that linezolid only be used with caution and close monitoring in patients concurrently receiving SSRIs, and some suggest that SSRI therapy should be discontinued before linezolid is initiated and not reinitiated until 2 weeks after linezolid therapy is completed.

Moclobemide. Moclobemide, a selective and reversible MAO-A inhibitor (not commercially available in the US), also has been associated with serotonin syndrome and such reactions have been fatal in several cases in which the drug was given in combination with the selective serotonin-reuptake inhibitor citalopram or with clomipramine. Pending further experience with such combinations, some clinicians recommend that concurrent therapy with moclobemide and selective serotonin-reuptake inhibitors be used only with extreme caution and serotonin-reuptake inhibitors should have been discontinued for some time (depending on the elimination half-lives of the drug and its active metabolites) before initiating moclobemide therapy.

Selegiline. Selegiline, a selective MAO-B inhibitor used in the management of parkinsonian syndrome, also has been reported to cause serotonin syndrome when given concurrently with selective serotonin-reuptake inhibitors (fluoxetine, paroxetine, sertraline). Although selegiline is a selective MAO-B inhibitor at therapeutic dosages, the drug appears to lose its selectivity for the MAO-B enzyme at higher dosages (e.g., those exceeding 10 mg/kg), thereby increasing the risk of serotonin syndrome in patients receiving higher dosages of the drug either alone or in combination with other serotonergic agents. The manufacturer of selegiline recommends avoiding concurrent selegiline and selective serotonin-reuptake inhibitor therapy. In addition, the manufacturer of selegiline recommends that a drug-free interval of at least 2 weeks elapse between discontinuance of selegiline and initiation of selective serotonin-reuptake inhibitor therapy. Because of the long half-lives of fluoxetine and its principal metabolite, at least 5 weeks should elapse or even longer (particularly if fluoxetine has been prescribed chronically and/or at higher dosages) between discontinuance of fluoxetine and initiation of selegiline therapy.

Isoniazid. Isoniazid, an antituberculosis agent, appears to have some MAO-inhibiting activity. In addition, iproniazid (not commercially available in the US), another antituberculosis agent structurally related to isoniazid that also possesses MAO-inhibiting activity, reportedly has resulted in serotonin syndrome in at least 2 patients when given in combination with meperidine. Pending further experience, clinicians should be aware of the potential for serotonin syndrome when isoniazid is given in combination with selective serotonin-reuptake inhibitor therapy or other serotonergic agents.

Tryptophan and Other Serotonin Precursors Adverse nervous system effects (e.g., agitation, restlessness, aggressive behavior, insomnia, poor concentration, headache, paresthesia, incoordination, worsening of symptoms of obsessive-compulsive disorder), adverse GI effects (e.g., nausea, abdominal cramps, diarrhea), palpitation, and/or chills reportedly have occurred in a limited number of patients receiving fluoxetine concurrently with tryptophan, a serotonin precursor. Such symptoms generally resolved within several weeks following discontinuance of tryptophan despite continued fluoxetine therapy. Although the mechanism for this interaction has not been fully elucidated, it has been suggested that these adverse effects resemble the serotonin syndrome observed in animals and therefore may result from a marked increase in serotonin availability when tryptophan and potent serotonin-reuptake inhibitors such as fluoxetine are administered concurrently. Because of the potential risk of serotonin syndrome or NMS-like reactions, concurrent use of tryptophan or other serotonin precursors should be avoided in patients receiving fluoxetine.

Sibutramine Because of the possibility of developing potentially serious, sometimes fatal serotonin syndrome or NMS-like reactions, sibutramine should be used with caution in patients receiving fluoxetine.

5-HT_1 Receptor Agonists ("Triptans") Weakness, hyperreflexia, and incoordination have been reported rarely during postmarketing surveillance in patients receiving sumatriptan concomitantly with an SSRI (e.g., fluoxetine, citalopram, escitalopram, fluvoxamine, paroxetine, sertraline). Oral or subcutaneous sumatriptan and SSRIs were used concomitantly in some clinical studies without unusual adverse effects. However, an increase in the frequency of migraine attacks and a decrease in the effectiveness of sumatriptan in relieving migraine headache have been reported in a patient receiving subcutaneous injections of sumatriptan intermittently while undergoing fluoxetine therapy.

Clinicians prescribing 5-HT_1 receptor agonists, SSRIs, and SNRIs should consider that triptans often are used intermittently and that either the 5-HT_1 receptor agonist, SSRI, or SNRI may be prescribed by a different clinician. Clinicians also should weigh the potential risk of serotonin syndrome or NMS-like reactions with the expected benefit of using a triptan concurrently with SSRI or SNRI therapy. If concomitant treatment with fluoxetine and a triptan is clinically warranted, the patient should be observed carefully, particularly during treatment initiation, dosage increases, and following the addition of other serotonergic agents. Patients receiving concomitant triptan and fluoxetine therapy should be informed of the possibility of serotonin syndrome or NMS-like reactions and advised to immediately seek medical attention if they experience symptoms of these syndromes.

Other Selective Serotonin-reuptake Inhibitors and Selective Serotonin- and Norepinephrine-reuptake Inhibitors Concomitant administration of fluoxetine with other SSRIs or SNRIs potentially may result in serotonin syndrome or NMS-like reactions and is therefore not recommended.

Antipsychotic Agents and Other Dopamine Antagonists Concomitant use of antipsychotic agents and other dopamine antagonists with fluoxetine potentially may result in serotonin syndrome or NMS-like reactions. If signs and symptoms of serotonin syndrome or NMS occur, treatment with fluoxetine and any concurrently administered antidopaminergic or serotonergic agents should be immediately discontinued and supportive and symptomatic treatment initiated. (See Drug Interactions: Antipsychotic Agents.)

Tramadol and Other Serotonergic Drugs Because of the potential risk of serotonin syndrome or NMS-like reactions, caution is advised whenever SSRIs, including fluoxetine, and SNRIs are concurrently administered with other drugs that may affect serotonergic neurotransmitter systems, including tramadol and St. John's wort (*Hypericum perforatum*).

Pentazocine, an opiate partial agonist analgesic, has been reported to cause transient symptoms of diaphoresis, ataxia, flushing, and tremor suggestive of the serotonin syndrome when used concurrently with fluoxetine.

Serotonin syndrome rarely may occur following concomitant use of fluoxetine and stimulants because stimulants can release serotonin, and amphetamine is metabolized by the cytochrome P-450 (CYP) 2D6 isoenzyme, which is inhibited by some SSRIs (e.g., fluoxetine, paroxetine).

■ **Drugs Undergoing Metabolism by Hepatic Microsomal Enzymes** ***Drugs Metabolized by Cytochrome P-450 (CYP) 2D6*** Fluoxetine, like many other antidepressants (e.g., other selective serotonin-

reuptake inhibitors, many tricyclic antidepressants), is metabolized by the drug-metabolizing cytochrome P-450 (CYP) 2D6 isoenzyme (debrisoquine hydroxylase). In addition, like many other drugs metabolized by CYP2D6, fluoxetine inhibits the activity of CYP2D6 and potentially may increase plasma concentrations of concomitantly administered drugs that also are metabolized by this enzyme. Fluoxetine may make normal CYP2D6 metabolizers resemble "poor metabolizers". Although similar interactions are possible with other selective serotonin-reuptake inhibitors, there is considerable variability among the drugs in the extent to which they inhibit CYP2D6; fluoxetine and paroxetine appear to be more potent in this regard than sertraline.

Concomitant use of fluoxetine with other drugs metabolized by CYP2D6 has not been systematically studied. The extent to which this potential interaction may become clinically important depends on the extent of inhibition of CYP2D6 by the antidepressant and the therapeutic index of the concomitantly administered drug. The drugs for which this potential interaction is of greatest concern are those that are metabolized principally by CYP2D6 and have a narrow therapeutic index, such as tricyclic antidepressants, class IC antiarrhythmics (e.g., propafenone, flecainide, encainide), vinblastine, and some phenothiazines (e.g., thioridazine).

Caution should be exercised whenever concurrent therapy with fluoxetine and other drugs metabolized by CYP2D6 is considered. If fluoxetine therapy is initiated in a patient already receiving a drug metabolized by CYP2D6, the need for decreased dosage of that drug should be considered. In addition, a low initial dosage should be used whenever a drug that is predominantly metabolized by CYP2D6 and has a relatively narrow therapeutic margin (e.g., tricyclic antidepressants, class IC antiarrhythmics) is initiated in a patients who is receiving or has received fluoxetine during the previous 5 weeks. Because of the risk of serious ventricular arrhythmias and sudden death potentially associated with increased plasma concentrations of thioridazine, thioridazine is contraindicated in any patient who is receiving or has received fluoxetine during the previous 5 weeks. (See Thioridazine under Drug Interactions: Antipsychotic Agents.)

Drugs Metabolized by Cytochrome P-450 (CYP) 3A4 Although fluoxetine can inhibit the cytochrome P-450 (CYP) 3A4 isoenzyme, results of in vitro and in vivo studies indicate that the drug is a much less potent inhibitor of this enzyme than many other drugs. In one in vivo drug interaction study, concomitant administration of single doses of the CYP3A4 substrate terfenadine (no longer commercially available in the US) and fluoxetine did not increase plasma concentrations of terfenadine. In addition, in vitro studies have shown that ketoconazole, a potent inhibitor of CYP3A4 activity, is at least 100 times more potent than fluoxetine or norfluoxetine as an inhibitor of several substrates of this enzyme (e.g., astemizole [no longer commercially available in the US], cisapride, midazolam). Some clinicians state that concomitant use of fluoxetine with astemizole or terfenadine is not recommended since substantially increased plasma concentrations of unchanged astemizole or terfenidine could occur, resulting in an increased risk of serious adverse cardiac effects. However, the manufacturer of fluoxetine states that the extent of fluoxetine's inhibition of CYP3A4 activity is unlikely to be of clinical importance.

■ **Tricyclic and Other Antidepressants** Concurrent administration of fluoxetine and a tricyclic antidepressant (e.g., nortriptyline, desipramine, imipramine) reportedly has resulted in adverse effects associated with tricyclic toxicity (including sedation, decreased energy, lightheadedness, psychomotor retardation, dry mouth, constipation, memory impairment). In patients receiving imipramine or desipramine, initiation of fluoxetine therapy reportedly resulted in plasma concentrations of these tricyclic antidepressants that were at least 2–10 times higher; this effect persisted for 3 weeks or longer after fluoxetine was discontinued. Elevated plasma trazodone concentrations and adverse effects possibly associated with trazodone toxicity (e.g., sedation, unstable gait) also have been reported during concomitant fluoxetine and trazodone therapy. Although the mechanism for this possible interaction has not been established, it has been suggested that fluoxetine may inhibit the hepatic metabolism of tricyclic antidepressants. (See Drugs Metabolized by Cytochrome P-450 (CYP) 2D6 under Drug Interactions: Drugs Undergoing Metabolism by Hepatic Microsomal Enzymes.) Further study of this potential interaction is needed, but current evidence suggests that patients receiving fluoxetine and a tricyclic antidepressant or trazodone concomitantly should be closely observed for adverse effects; monitoring of plasma tricyclic or trazodone concentrations also should be considered and their dosage reduced as necessary. Because fluoxetine may increase plasma concentrations and prolong the elimination half-life of tricyclic antidepressants, the need for more prolonged monitoring following combined tricyclic and fluoxetine overdose should be considered. In addition, because of the prolonged elimination of fluoxetine and norfluxetine, the possibility that the drug may interact with tricyclic antidepressants after recent discontinuance of fluoxetine also should be considered.

■ **Antipsychotic Agents** Concomitant use of antipsychotic agents with fluoxetine potentially may result in serotonin syndrome or NMS-like reactions. If signs and symptoms of serotonin syndrome or NMS occur, treatment with fluoxetine and any concurrently administered antipsychotic agent should be immediately discontinued and supportive and symptomatic treatment initiated. (See Drug Interactions: Serotonergic Drugs.)

Some clinical data suggest a possible pharmacodynamic and/or pharmacokinetic interaction between SSRIs, including fluoxetine, and some antipsychotic agents.

Clozapine Concomitant use of fluoxetine and clozapine can increase plasma concentrations of clozapine and enhance clozapine's pharmacologic effects secondary to suspected inhibition of clozapine metabolism by fluoxetine. Increased plasma clozapine concentrations also have been reported in patients receiving other SSRIs (e.g., fluvoxamine, paroxetine). There has been at least one fatality related to clozapine toxicity following ingestion of clozapine, fluoxetine, and alcohol. The manufacturer of clozapine states that caution should be used and patients closely monitored if clozapine is used in patients receiving SSRIs, and a reduction in clozapine dosage should be considered.

Haloperidol Elevated plasma concentrations of haloperidol have been observed in patients receiving concomitant fluoxetine therapy. Severe extrapyramidal symptoms (e.g., tongue stiffness, parkinsonian symptoms, akathisia), which required hospitalization and were refractory to conventional therapy (including anticholinergic antiparkinsonian agents, diphenhydramine, and diazepam), reportedly occurred in a patient receiving fluoxetine and haloperidol concurrently; this patient previously had experienced only mild adverse extrapyramidal effects with haloperidol therapy alone. The extrapyramidal symptoms gradually abated following discontinuance of both drugs, and the patient subsequently tolerated haloperidol therapy with evidence of only a slight parkinsonian gait. The clinical importance of this possible interaction has not been established, and additional study is required to determine the safety of combined fluoxetine and antipsychotic therapy.

Olanzapine Concomitant administration of fluoxetine (60 mg as a single dose or 60 mg daily for 8 days) with a single 5-mg dose of oral olanzapine caused a small increase in peak plasma olanzapine concentrations (averaging 16%) and a small decrease (averaging 16%) in olanzapine clearance; the elimination half-life was not substantially affected. Fluoxetine is an inhibitor of CYP2D6, and thereby may affect a minor metabolic pathway for olanzapine. Although the changes in pharmacokinetics are statistically significant when olanzapine and fluoxetine are given concurrently, the changes are unlikely to be clinically important in comparison to the overall variability observed between individuals; therefore, routine dosage adjustment is not recommended.

When fluoxetine is used in fixed combination with olanzapine (Symbyax®), the drug interactions associated with olanzapine should also be considered. (See Drug Interactions in Olanzapine 28:16.08.04.)

Pimozide Clinical studies evaluating pimozide in combination with other antidepressants have demonstrated an increase in adverse drug interactions or QT_c prolongation during combined therapy. In addition, rare case reports have suggested possible additive cardiovascular effects of fluoxetine and pimozide, resulting in bradycardia. Marked changes in mental status (e.g., stupor, inability to think clearly) and hypersalivation also were reported in one woman who received both drugs concurrently. Although a specific study evaluating concurrent fluoxetine and pimozide therapy has not been performed to date, concurrent use of these drugs is contraindicated because of the potential for adverse drug interactions or QT_c prolongation.

Risperidone Extrapyramidal symptoms followed by persistent tardive dyskinesia (dyskinetic tongue movements) have occurred in one 18-year-old who received risperidone concomitantly with fluoxetine; however, a causal relationship has not been established. The AUC of risperidone increased during concomitant fluoxetine therapy in one study in psychotic patients, and the AUC of active drug (risperidone plus 9-hydroxyrisperidone) increased in poor and extensive metabolizers (determined by CYP2D6 genotyping); there was no evidence of increased severity or incidence of extrapyramidal symptoms in this 30-day study.

Thioridazine Although specific drug interaction studies evaluating concomitant use of fluoxetine and thioridazine are not available, concomitant use of other SSRIs (e.g., fluvoxamine) has resulted in increased plasma concentrations of the antipsychotic agent. Because of the risk of serious ventricular arrhythmia and sudden death associated with elevated plasma concentrations of thioridazine, thioridazine is contraindicated in any patient who is receiving or has received fluoxetine during the previous 5 weeks. (See Drugs Metabolized by Cytochrome P-450 (CYP) 2D6 under Drug Interactions: Drugs Undergoing Metabolism by Hepatic Microsomal Enzymes.)

■ **Benzodiazepines** Fluoxetine appears to inhibit the metabolism of diazepam, as evidenced by increases in the elimination half-life and plasma concentration of diazepam and decreases in diazepam clearance and the rate of formation of desmethyldiazepam (an active metabolite of diazepam) during concomitant use of the drugs. Although clinically important increase in psychomotor impairment has not been noted when fluoxetine and diazepam were administered concomitantly as compared with administration of diazepam alone, concomitant administration of alprazolam and fluoxetine has resulted in increased plasma concentrations of alprazolam and further psychomotor performance impairments. Pending further accumulation of data, the possibility that a clinically important interaction could occur in geriatric or other susceptible patients should be considered.

■ **Buspirone** Buspirone has serotonergic activity and may have been partially responsible for a case of serotonin syndrome that resulted in the death of a patient receiving fluoxetine, buspirone, and an MAO inhibitor (tranylcypromine) concomitantly. (See Drug Interactions: Serotonergic Drugs.)

In a patient with depression, generalized anxiety disorder, and panic attacks who was receiving concomitant buspirone and trazodone therapy, an increase in anxiety symptoms to a level comparable to that observed prior to buspirone

therapy occurred when fluoxetine was added to the regimen. Although the mechanism of this possible interaction has not been established, it was suggested that fluoxetine may have either directly antagonized the therapeutic activity of buspirone or may have precipitated the anxiety symptoms through a separate mechanism. However, combined use of the drugs also has been reported to potentiate therapeutic efficacy in patients with obsessive-compulsive disorder.

■ **Lithium** Fluoxetine and lithium have been used concurrently in a limited number of patients without apparent adverse effects. However, both increased and decreased serum lithium concentrations and adverse neuromuscular effects possibly associated with lithium toxicity and/or serotonin syndrome (e.g., ataxia, dizziness, dysarthria, stiffness of the extremities) have been reported during combined therapy with the drugs. Lithium appears to have some serotonergic activity, and serotonin syndrome has been reported following the initiation of lithium therapy in at least one patient receiving fluoxetine. (See Drug Interactions: Serotonergic Drugs.) The clinical importance of this potential interaction remains to be determined and further substantiation is required; however, caution should be exercised when fluoxetine and lithium are administered concurrently. It is recommended that serum lithium concentrations be monitored closely during concomitant fluoxetine therapy.

■ **Anticonvulsants** ***Carbamazepine*** Fluoxetine can increase plasma carbamazepine and carbamazepine 10,11-epoxide (CBZ-E, an active metabolite) concentrations, and carbamazepine toxicity (e.g., ocular changes, vertigo, tremor) has been reported in some patients maintained on carbamazepine following initiation of fluoxetine. It has been suggested that fluoxetine-induced inhibition of hepatic metabolism (e.g., inhibition of epoxide hydrolase) of carbamazepine and/or CBZ-E may be principally responsible for such increases; alteration in protein binding does not appear to be principally responsible for this interaction. The patient and plasma concentrations of carbamazepine and its metabolite should be monitored closely whenever fluoxetine therapy is initiated or discontinued; carbamazepine dosage should be adjusted accordingly.

Phenytoin Initiation of fluoxetine in patients stabilized on phenytoin has resulted in increased plasma phenytoin concentrations and clinical manifestations of phenytoin toxicity.

■ **β-Adrenergic Blocking Agents** Concomitant use of fluoxetine and a β-adrenergic blocking agent has resulted in increased plasma concentrations that have enhanced the β-adrenergic blocking effects of the drug, possibly resulting in cardiac toxicity. Metoprolol is metabolized by the CYP2D6 isoenzyme and fluoxetine is known to potently inhibit this enzyme. Although specific data are lacking, β-adrenergic blocking agents that are renally eliminated (e.g., atenolol) may be a safer choice. Patients who were previously stabilized on propranolol or metoprolol should be monitored for toxicity (e.g., bradycardia, conduction defects, hypotension, heart failure, central nervous system disturbances) following initiation of fluoxetine therapy.

■ **Protein-bound Drugs** Because fluoxetine is highly protein bound, the drug theoretically could be displaced from binding sites by, or it could displace from binding sites, other protein-bound drugs such as oral anticoagulants and digitoxin (no longer commercially available in the US). Pending further accumulation of data, patients receiving fluoxetine with any highly protein-bound drug should be observed for potential adverse effects associated with such therapy. (See Drug Interactions: Drugs Affecting Hemostasis.)

■ **Drugs Affecting Hemostasis** ***Warfarin*** Concomitant use of fluoxetine and warfarin has resulted in altered anticoagulant effects, including increased bleeding. Therefore, patients receiving warfarin should be carefully monitored whenever fluoxetine is initiated or discontinued.

Other Drugs that Interfere with Hemostasis Epidemiologic case-control and cohort design studies that have demonstrated an association between selective serotonin-reuptake inhibitor therapy and an increased risk of upper GI bleeding also have shown that concurrent use of aspirin or other nonsteroidal anti-inflammatory agents substantially increases the risk of GI bleeding. Although these studies focused on upper GI bleeding, there is some evidence suggesting that bleeding at other sites may be similarly potentiated. The precise mechanism for this increased risk remains to be clearly established; however, serotonin release by platelets is known to play an important role in homostasis, and selective serotonin-reuptake inhibitors decrease serotonin uptake from the blood by platelets, thereby decreasing the amount of serotonin in platelets. Patients receiving fluoxetine should be cautioned about the concomitant use of drugs that interfere with hemostasis, including aspirin and other nonsteroidal anti-inflammatory agents.

■ **Alcohol** Concurrent administration of single or multiple doses of fluoxetine and alcohol does not appear to alter blood or Breathalyzer® alcohol, plasma fluoxetine, or plasma norfluoxetine concentrations in healthy individuals, suggesting that there is no pharmacokinetic interaction between fluoxetine and alcohol. In addition, fluoxetine does not appear to potentiate the psychomotor and cognitive impairment or cardiovascular effects induced by alcohol. However, the drug's ability to reduce alcohol consumption in animals and humans suggests that there may be a serotonergically mediated, pharmacodynamic interaction between fluoxetine and alcohol within the CNS. (See Pharmacology: Effects on Alcohol Intake, and also see Uses: Alcohol Dependence.)

■ **Electroconvulsive Therapy** The effects of fluoxetine in conjunction with electroconvulsive therapy (ECT) for the management of depression have not been evaluated to date in clinical studies. Prolonged seizures reportedly have occurred rarely during concurrent use of fluoxetine and ECT.

■ **Antidiabetic Agents** Fluoxetine potentially may alter blood glucose concentrations in patients with diabetes mellitus. (See Cautions: Metabolic Effects.) Therefore, dosage adjustments of insulin and/or sulfonylurea antidiabetic agents may be necessary when fluoxetine therapy is initiated or discontinued in such patients.

Acute Toxicity

Limited information is available on the acute toxicity of fluoxetine.

■ **Pathogenesis** The acute lethal dose of fluoxetine in humans is not known. The median oral LD_{50} of fluoxetine has been reported to be approximately 452 and 248 mg/kg in rats and mice, respectively. In animals, oral administration of single large doses of the drug has resulted in hyperirritability and seizures. Tonic-clonic seizures occurred in 5 of 6 dogs given a toxic dose of fluoxetine orally; the seizures ceased immediately after IV administration of diazepam. In these dogs, the lowest plasma fluoxetine concentration at which seizures occurred reportedly was only twice the maximum plasma concentration reported in humans receiving 80 mg of the antidepressant daily during long-term therapy. Single large oral doses of fluoxetine reportedly do not cause QT- or PR-interval prolongation or widening of the QRS complex in dogs, although tachycardia and an increase in blood pressure have occurred.

The risk of fluoxetine overdosage may be increased in patients with a genetic deficiency in the cytochrome P-450 (CYP) isoenzyme 2D6.

■ **Manifestations** In general, overdosage of fluoxetine may be expected to produce effects that are extensions of the drug's pharmacologic and adverse effects. Animal studies and case reports in humans indicate that possible effects of overdosage include agitation, restlessness, hypomania, vertigo, insomnia, tremor, and other signs of CNS excitation; nausea and vomiting; and tachycardia and/or increased blood pressure. Seizures have been reported in at least one patient after overdosage of fluoxetine. Acute overdosage of fluoxetine alone reportedly has resulted in nystagmus, drowsiness, coma, urticaria, spontaneous emesis, and ST-segment depression. Nausea and vomiting appear to occur commonly following acute ingestion of relatively large single doses of the drug.

Several fatalities following fluoxetine overdosage have been reported to date. One of the deaths occurred in a patient who reportedly ingested 1.8 g of fluoxetine and an unknown quantity of maprotiline; plasma fluoxetine and maprotiline concentrations in this patient were approximately 4570 and 4180 ng/mL, respectively. Another patient died after concomitantly ingesting fluoxetine, codeine, and temazepam; plasma fluoxetine, norfluoxetine, codeine, and temazepam concentrations in this patient reportedly were 1930, 1110, 1800, and 3800 ng/mL, respectively. A fatal overdose also has been reported in a patient ingesting fluoxetine and alcohol concomitantly. There also are a few reported cases of overdose in which fatality was attributed to fluoxetine alone. In one such case, death was associated with extracted blood fluoxetine and norfluoxetine concentrations of 6000 and 5000 ng/mL, respectively, and biliary concentrations of 13,000 ng/mL each for the drug and metabolite. A patient enrolled in a clinical study of fluoxetine reportedly died following intentional ingestion of an unknown quantity of amitriptyline, clobazam, and pentazocine; however, it is not known whether this patient also ingested fluoxetine with the other drugs.

A patient with a history of seizures who reportedly ingested 3 g of fluoxetine and an unknown quantity of aspirin experienced 2 tonic-clonic seizures, tachycardia, dizziness, blurred vision, unsustained clonus, and ECG changes. The seizures occurred about 9 hours post-ingestion, lasted approximately 2–3 minutes, and remitted spontaneously without anticonvulsant therapy. Although the actual amount of fluoxetine absorbed by this patient may have been less than expected because of vomiting and gastric lavage, the plasma fluoxetine concentration reportedly was 2461 ng/mL when seizures occurred; the patient recovered with no apparent sequelae. Another patient reported that he experienced sleepiness and nausea that lasted for several days following the intentional ingestion of 840 mg of fluoxetine with alcohol; this patient did not seek medical treatment. Drowsiness, lethargy, and nausea occurred in a patient who reportedly ingested 1.4 g of fluoxetine and 15 mg of clonazepam. No ECG abnormalities were reported in 2 patients who intentionally ingested 200 mg and 1 g of fluoxetine.

A child with a genetic deficiency in the CYP2D6 isoenzyme died following prolonged therapy with fluoxetine, methylphenidate, and clonidine. Autopsy findings revealed blood, brain, and other tissue concentrations of fluoxetine and norfluoxetine that were several-fold higher than expected. Poor metabolism of fluoxetine via CYP2D6 was the likely cause of fluoxetine intoxication in this child.

■ **Treatment** Because fatalities and severe toxicity have been reported following overdosage of selective serotonin-reuptake inhibitors, particularly in large overdosage and when taken with other drugs or alcohol, some clinicians recommend that any overdosage involving these drugs be managed aggressively. Because suicidal ingestion often involves more than one drug, clinicians treating fluoxetine overdosage should be alert to possible toxic manifestations caused by drugs other than fluoxetine.

Clinicians also should consider the possibility of serotonin syndrome or NMS-like reactions in patients presenting with similar clinical features and a recent history of fluoxetine ingestion and/or ingestion of other serotonergic and/

or antipsychotic agents or other dopamine antagonists. (See Cautions: Precautions and Contraindications and see also Drug Interactions: Serotonergic Drugs.)

Management of fluoxetine overdosage generally involves symptomatic and supportive care. A patent airway should be established and maintained, and adequate oxygenation and ventilation should be assured. ECG and vital sign monitoring is recommended following acute overdosage with the drug, although the value of ECG monitoring in predicting the severity of fluoxetine-induced cardiotoxicity is not known. (See Acute Toxicity: Manifestations, in the Tricyclic Antidepressants General Statement.) There is no specific antidote for fluoxetine intoxication.

Following recent (i.e., within 4 hours) ingestion of a potentially toxic amount of fluoxetine and in the absence of signs and symptoms of cardiac toxicity, the stomach should be emptied immediately by inducing emesis or by gastric lavage. If the patient is comatose, having seizures, or lacks the gag reflex, gastric lavage may be performed if an endotracheal tube with cuff inflated is in place to prevent aspiration of gastric contents. Since administration of activated charcoal (which may be used in conjunction with sorbitol or a saline cathartic) may be as effective or more effective than induction of emesis or gastric lavage, its use has been recommended either in the initial management of fluoxetine overdosage or following induction of emesis or gastric lavage in patients who have ingested a potentially toxic quantity of the drug.

Based on data from animal studies, IV diazepam should be considered for the management of fluoxetine-induced seizures that do not remit spontaneously. If seizures are not controlled or recur following administration of diazepam, administration of phenytoin or phenobarbital has been recommended by some clinicians.

Fluoxetine and norfluoxetine are not substantially removed by hemodialysis. Because of the large volume of distribution and extensive protein binding of the drug and its principal metabolite, peritoneal dialysis, forced diuresis, hemoperfusion, and/or exchange transfusion probably are also ineffective in removing substantial amounts of fluoxetine and norfluoxetine from the body. Clinicians should consider consulting a poison control center for additional information on the management of fluoxetine overdosage.

Chronic Toxicity

Fluoxetine has not been studied systematically in animals or humans to determine whether therapy with the drug is associated with tolerance or psychologic and/or physical dependence. One patient receiving the drug for the management of obesity reportedly experienced nervousness 2 days following discontinuance of fluoxetine therapy. However, it is unclear whether this adverse effect represented a withdrawal reaction since both the parent drug and its principal metabolite have relatively long half-lives, and withdrawal reactions following discontinuance of fluoxetine therapy may therefore be more delayed. Although clinical experience to date has not revealed substantial evidence of drug-seeking behavior or a withdrawal syndrome associated with discontinuance of fluoxetine therapy, it is difficult to predict from the limited data currently available the extent to which a CNS-active drug like fluoxetine may be misused, diverted, and/or abused.

Despite the lack of substantial evidence for abuse potential or dependence liability, clinicians should carefully evaluate patients for a history of substance abuse prior to initiating fluoxetine therapy. If fluoxetine therapy is initiated in patients with a history of substance abuse, such patients should be monitored closely for signs of misuse or abuse of the drug (e.g., development of tolerance, use of increasing doses, drug-seeking behavior).

The potential for misuse of fluoxetine by depressed patients with concurrent eating disorders and/or those who may seek the drug for its appetite-suppressant effects also should be considered. One patient with an undisclosed history of anorexia nervosa and laxative abuse who was given fluoxetine for depression ingested larger-than-prescribed doses (e.g., 90–120 mg/day) and lost 9.1 kg within 2 months; this patient falsely claimed mood improvement in order to continue receiving the drug for its anorectic and weight-reducing effects.

Fluoxetine has produced phospholipidosis following long-term administration in animals; however, no evidence of phospholipidosis has been reported in humans receiving the drug to date. Additional study is needed to determine the clinical importance of these findings in patients receiving long-term fluoxetine therapy. (See Pharmacology: Effects on Phospholipids.)

Pharmacology

The pharmacology of fluoxetine is complex and in many ways resembles that of other antidepressant agents, particularly those agents (e.g., citalopram, clomipramine, escitalopram, fluvoxamine, paroxetine, sertraline, trazodone) that predominantly potentiate the pharmacologic effects of serotonin (5-HT). Like other selective serotonin-reuptake inhibitors (SSRIs), fluoxetine is a potent and highly selective reuptake inhibitor of serotonin and has little or no effect on other neurotransmitters.

■ **Nervous System Effects** The precise mechanism of antidepressant action of fluoxetine is unclear, but the drug has been shown to selectively inhibit the reuptake of serotonin at the presynaptic neuronal membrane. Fluoxetine-induced inhibition of serotonin reuptake causes increased synaptic concentrations of serotonin in the CNS, resulting in numerous functional changes associated with enhanced serotonergic neurotransmission. Like other selective serotonin-reuptake inhibitors (fluvoxamine, paroxetine, sertraline), fluoxetine appears to have minimal or no effect on the reuptake of norepinephrine or dopamine and does not exhibit clinically important anticholinergic, antihistaminic, or α_1-adrenergic blocking activity at usual therapeutic dosages.

Although the mechanism of antidepressant action of antidepressant agents may involve inhibition of the reuptake of various neurotransmitters (i.e., norepinephrine, serotonin) at the presynaptic neuronal membrane, it has been suggested that postsynaptic receptor modification is mainly responsible for the antidepressant action observed during long-term administration of antidepressant agents. During long-term therapy with most antidepressants (e.g., tricyclic antidepressants, monoamine oxidase [MAO] inhibitors), these adaptive changes generally consist of subsensitivity of the noradrenergic adenylate cyclase system in association with a decrease in the number of β-adrenergic receptors; such effects on noradrenergic receptor function commonly are referred to as "down-regulation." In addition, some antidepressants reportedly decrease the number of 5-HT binding sites following chronic administration. Fluoxetine may exert its antidepressant activity by somewhat different mechanisms than those usually associated with tricyclic and some other antidepressants. Although some evidence indicates that long-term administration of fluoxetine does not substantially decrease the number of β-adrenergic binding sites or reduce the sensitivity of β-adrenergic receptors, a decrease in the number of β-adrenergic binding sites in the brain has been reported in at least one study in animals. Data regarding the effects of fluoxetine on the number of serotonin (5-HT_1 and/or 5-HT_2) binding sites have been conflicting, with either no change or a reduction in the number of binding sites being reported during chronic administration of the drug. Increased postsynaptic receptor binding of GABA B also has been reported following prolonged administration of many antidepressants, including fluoxetine. The clinical importance of these findings for fluoxetine has not been fully elucidated to date, and further study is needed to determine the role, if any, of binding site alteration in the antidepressant action of fluoxetine and other antidepressants.

The precise mechanism of action responsible for the efficacy of fluoxetine in the treatment of obsessive-compulsive disorder is unclear. However, based on the efficacy of other selective serotonin-reuptake inhibitors (e.g., fluvoxamine, paroxetine, sertraline) and clomipramine in the treatment of obsessive-compulsive disorder and the potency of these drugs in inhibiting serotonin reuptake, a serotonergic hypothesis has been developed to explain the pathogenesis of the condition. The hypothesis postulates that a dysregulation of serotonin is responsible for obsessive-compulsive disorder and that fluoxetine and these other agents are effective because they correct this imbalance. Although the available evidence supports the serotonergic hypothesis of obsessive-compulsive disorder, additional studies are necessary to confirm this hypothesis.

Serotonergic Effects Fluoxetine is a highly selective inhibitor of serotonin reuptake at the presynaptic neuronal membrane. In addition, the potency and selectivity of serotonin-reuptake inhibition exhibited by fluoxetine's principal metabolite, norfluoxetine, appear to be similar to those of the parent drug. Fluoxetine- and norfluoxetine-induced inhibition of serotonin reuptake causes increased synaptic concentrations of serotonin, resulting in numerous functional changes associated with enhanced serotonergic neurotransmission.

Data from in vitro studies suggest that fluoxetine is approximately equivalent to or less potent than clomipramine as a serotonin-reuptake inhibitor; however, in vivo studies indicate that the serotonin-reuptake inhibiting effect of fluoxetine may be more potent than that of clomipramine on a weight as well as an equimolar basis. This apparent discrepancy may be explained at least in part by the relatively long elimination half-lives of fluoxetine and norfluoxetine. In addition, metabolism via *N*-demethylation decreases the potency and specificity of serotonin-reuptake inhibition of clomipramine but not fluoxetine. Data from both in vivo and in vitro studies indicate that fluoxetine also is a more potent serotonin-reuptake inhibitor than other currently available antidepressant agents, including imipramine and trazodone. Fluoxetine appears to have practically no affinity for serotonin (e.g., 5-HT_1 and 5-HT_2) receptors in vitro, although limited in vivo data suggest that the drug may bind to low-affinity sites on 5-HT receptors.

Fluoxetine appears to decrease the turnover of serotonin in the CNS, probably as a result of a decrease in the rate of serotonin synthesis. The drug reportedly decreases brain concentrations of 5-hydroxyindoleacetic acid (5-HIAA), the principal metabolite of serotonin; reduces the uptake of radiolabeled tryptophan by synaptosomes; and reduces the rate of conversion of tryptophan to serotonin. Fluoxetine also inhibits spontaneous firing of serotonergic neurons in the dorsal raphe nucleus.

Like other serotonin-reuptake inhibitors, administration of fluoxetine alone does not produce the serotonin behavioral syndrome (a characteristic behavioral pattern caused by central stimulation of serotonin activity) in animals. However, the drug potentiates the serotonin behavioral syndrome induced by oxitriptan (l-5-hydroxytryptophan, l-5HTP), MAO inhibitors, and MAO inhibitors combined with tryptophan.

Effects on Other Neurotransmitters Like other selective serotonin-reuptake inhibitors, fluoxetine appears to have little or no effect on the reuptake of other neurotransmitters such as norepinephrine or dopamine. In addition, the drug appears to have a substantially higher selectivity ratio of serotonin-to-norepinephrine reuptake inhibiting activity than tricyclic antidepressant agents, including clomipramine.

Unlike tricyclic and some other antidepressants, fluoxetine does not exhibit clinically important anticholinergic, α_1-adrenergic blocking, or antihistaminic activity at usual therapeutic dosages. As a result, the incidence of adverse effects commonly associated with blockade of muscarinic cholinergic receptors

(e.g., dry mouth, blurred vision, urinary retention, constipation, confusion), α_1-adrenergic receptors (e.g., orthostatic hypotension), and histamine H_1- and H_2-receptors (e.g., sedation) is lower in fluoxetine-treated patients. In vitro studies have demonstrated that the drug possesses only weak affinity for α_1- and α_2-adrenergic, β-adrenergic, H_1 and H_2, muscarinic, opiate, GABA-benzodiazepine, and dopamine receptors.

Effects on Sleep Like tricyclic and most other antidepressants, fluoxetine suppresses rapid eye movement (REM) sleep. Although not clearly established, there is some evidence that the REM-suppressing effects of antidepressant agents may contribute to the antidepressant activity of these drugs. In animal studies, fluoxetine produces a dose-related suppression of REM sleep; the drug generally appears to reduce the amount of REM sleep by increasing REM latency (the time to onset of REM sleep) and by decreasing the number rather than the duration of REM episodes. Limited data in animals suggest that REM rebound does not occur following discontinuance of fluoxetine. The precise mechanism has not been fully elucidated, but results of animal studies indicate that fluoxetine's effects on REM sleep are serotonergically mediated. Like other specific serotonin-reuptake inhibitors (e.g., zimeldine [previously zimelidine]), the effects of fluoxetine on non-REM sleep reported to date have been variable and do not appear to be as clearly defined as those of tricyclic antidepressants, which usually increase slow-wave sleep.

Effects on EEG Limited data currently are available regarding the effects of fluoxetine on the EEG. Substantial EEG changes did not occur following oral administration of single 30-mg doses of the drug in healthy individuals. An increase in alpha activity and a decrease in fast beta activity and slow activity were noted following single oral 60-mg doses in this study; such changes are characteristic of desipramine-type antidepressants and appear to indicate increased vigilance. Single 75-mg doses of fluoxetine produced an increase in slow and fast activity and a decrease in alpha activity; such EEG changes are similar to those observed with amitriptyline and imipramine and suggest possible sedative activity.

Effects on Psychomotor Function Fluoxetine does not appear to cause clinically important sedation and does not interfere with psychomotor performance. Controlled studies in healthy young adults 21–45 of years and in adults with major depression did not demonstrate any adverse effects on psychomotor performance in those receiving the drug. No adverse effects on psychomotor performance or cognitive function were observed in men with depression older than 60 years of age who received 20-mg doses of fluoxetine in a controlled study. Results of this study showed that overall cognition, as assessed by the critical flicker fusion thresholds test, generally was better in patients receiving fluoxetine than in those receiving amitriptyline (a tricyclic antidepressant); however, less sedating tricyclic antidepressants (e.g., desipramine) were not included in the study and it is possible that fluoxetine may not have such an advantage over these other agents. In a controlled study evaluating the effects of fluoxetine (20 mg daily for 22 days) on psychomotor performance and car driving in healthy adults, the drug did not affect the highway driving or the car following tests but slightly impaired performance in correctly detecting changes in visual signals was evident in the sustained attention test.

Analgesic Effects Like other serotonin-reuptake inhibitors (e.g., zimeldine), fluoxetine exhibits analgesic activity in some analgesic test systems when administered alone in animals, but the lack of such effects observed in other test systems suggests that demonstration of analgesic activity may be test-dependent. Fluoxetine has potentiated opiate agonist-induced analgesia in most but not all studies, possibly as a result of the drug's ability to enhance serotonergic neurotransmission. The clinical importance of these effects in the management of acute and chronic pain remains to be determined.

Effects on Respiration Usual therapeutic dosages of fluoxetine do not appear to affect respiration substantially in humans; however, the effect of higher dosages of the drug on respiratory function remains to be established. In animals, administration of single 20-mg/kg doses of fluoxetine reportedly increased blood Po_2 concentrations but did not alter blood P_{co_2} concentrations. The drug also has been shown to attenuate morphine-induced respiratory depression, although the precise mechanism for this effect has not been established.

Effects on Thermoregulation Data are conflicting regarding the effect of fluoxetine on thermoregulation. In animals, fluoxetine has produced dose-dependent hypothermia in some studies, suggesting that serotonin may play a role in thermoregulation, but the drug has produced only slight or minimal hypothermia in other studies.

The drug has been used safely in at least one patient with established susceptibility to malignant hyperthermia; however, additional experience with the drug is needed to confirm the safety of fluoxetine in patients known to be susceptible to this condition.

■ **Cardiovascular Effects** The cardiovascular effects of fluoxetine have been studied in animals and to a limited extent in humans. Unlike some other antidepressant agents (e.g., tricyclic antidepressants, MAO inhibitors), fluoxetine has been associated with only minimal cardiovascular effects. The absence of substantial anticholinergic activity, α_1-adrenergic blocking activity, catecholamine-potentiating effects, and quinidine-like cardiotoxic effects appears to be the principal reason for the general lack of cardiovascular effects associated with fluoxetine.

Fluoxetine does not exhibit clinically important α_1-adrenergic blocking activity and does not inhibit catecholamine reuptake. Unlike tricyclic antidepressants, fluoxetine does not block the neuronal reuptake of norepinephrine and therefore does not potentiate the pressor response associated with administration of norepinephrine. In addition, the drug does not inhibit the reuptake of and has no effect on the pressor response to tyramine.

Fluoxetine does not appear to have substantial arrhythmogenic activity; however, safety of the drug in patients with a recent history of myocardial infarction or unstable cardiovascular disease has not been adequately evaluated to date. Fluoxetine generally does not appear to affect cardiac conduction, and clinically important ECG changes have not been reported in patients without preexisting heart disease receiving therapeutic dosages of the drug. Unlike tricyclic antidepressants, which commonly cause an increase in heart rate, fluoxetine reportedly reduces heart rate by an average of about 3 beats/minute in patients receiving usual therapeutic dosages of the antidepressant. (See Cautions: Cardiovascular Effects.) Unlike tricyclics, the drug does not appear to exhibit direct quinidine-like cardiotoxic activity, although the cardiovascular effects associated with fluoxetine overdosage have not been fully established to date. (See Acute Toxicity.)

■ **Effects on Appetite and Body Weight** Like some other serotonergic agents (e.g., fenfluramine [no longer commercially available in the US], zimeldine), fluoxetine possesses anorectic activity. Although the precise mechanism has not been clearly established, results of animal studies indicate that the drug's appetite-inhibiting action may result from serotonin-reuptake blockade and the resultant increase in serotonin availability at the neuronal synapse. Following administration of single and multiple doses of fluoxetine in both meal-fed and free-feeding animals, a reduction in food intake usually occurs, particularly at relatively high doses of the drug (i.e., 10 mg/kg). The anorectic effect of fluoxetine appears to be potentiated by oxitriptan. Tolerance to the anorectic effect of fluoxetine has not developed following short-term administration in humans and animals; however, long-term studies in humans are necessary to fully determine whether tolerance develops during chronic therapy with the drug.

In animal studies, fluoxetine has been shown to suppress palatability-induced food consumption (as determined by the volume of sweetened versus plain water ingested). Like fenfluramine, fluoxetine also appears to selectively suppress carbohydrate and overall food intake while maintaining protein intake. Such carbohydrate intake-suppressing and protein-sparing effects may be of potential clinical importance in the management of obesity; however, additional study is necessary. (See Uses: Obesity.) Fluoxetine therapy also has resulted in decreases in body weight in normal-weight and obese animals as well as in depressed, nondepressed, and obese individuals receiving the drug. (See Uses: Obesity and also see Cautions: Metabolic Effects.)

■ **Effects on Alcohol Intake** Like some other serotonergic agents, fluoxetine produces a dose-dependent decrease in voluntary alcohol intake in normal and alcohol-preferring animals. Like some other serotonin-reuptake inhibitors (e.g., citalopram, zimeldine), fluoxetine has been shown to reduce alcohol consumption in a limited number of heavy drinkers receiving 60 mg of the drug daily. Because serotonin appears to be involved in the regulation of alcohol intake, it has been suggested that fluoxetine may attenuate alcohol consumption via enhanced serotonergic neurotransmission. In addition, there is some evidence that such effects may be at least partially mediated by the renin-angiotensin-aldosterone system. (See Uses: Alcohol Dependence and see Drug Interactions: Alcohol.)

■ **Neuroendocrine Effects** Fluoxetine affects the endocrine system. Like other selective inhibitors of serotonin reuptake, the drug has produced a dose-related increase in serum corticosterone concentrations in animals. Fluoxetine also reportedly potentiates oxitriptan-induced elevation in serum corticosterone concentrations. Such effects appear to be serotonergically mediated. Following parenteral administration of fluoxetine in animals, the elevation in serum corticosterone concentration generally lasts only a few hours, although fluoxetine-induced inhibition of serotonin reuptake is known to persist for longer than 24 hours. Therefore, it has been suggested that other compensatory mechanisms, possibly including decreased firing of serotonergic neurons, may contribute to the restoration of normal hypothalamic-pituitary-adrenal (HPA) axis function despite prolonged blockade of serotonin reuptake by the drug. Fluoxetine also has increased corticotropin (ACTH) and vasopressin (antidiuretic hormone, ADH) concentrations in peripheral plasma and has increased corticotropin and corticotropin-releasing factor (CRF, corticoliberin) concentrations in hypophysial portal blood. These effects may represent the initial step in fluoxetine-induced elevation of plasma corticosterone concentrations.

The effects of fluoxetine on serum prolactin concentrations have not been clearly established. In some animal studies, fluoxetine potentiated tryptophan-induced increases in serum prolactin concentrations, although administration of the drug alone in animals and humans usually does not substantially alter prolactin concentrations. However, administration of fluoxetine alone reportedly increased serum prolactin concentrations in young but not old male rats in one study. Fluoxetine-induced effects on prolactin secretion appear to be serotonergically mediated.

■ **Effects on Phospholipids** Like many other cationic, amphiphilic drugs (e.g., amiodarone, fenfluramine, imipramine, ranitidine), fluoxetine reportedly increases tissue phospholipid concentrations following chronic ad-

ministration in animal studies; however, such effects have not been demonstrated in humans receiving fluoxetine to date. Histologic examination following long-term (i.e., 1–12 months) fluoxetine administration in animals has revealed the presence of characteristic concentric, lamellar inclusion bodies associated with phospholipidosis in alveolar macrophages of the lung, Kupffer cells of the liver, and adrenal cortical cells; an increase in phospholipid content of the lung also has been reported. Fluoxetine-induced phospholipid accumulation in these animals was reversible within 1–2 months following discontinuance of the drug.

Studies in humans receiving fluoxetine have not revealed biochemical or clinical evidence of drug-induced phospholipidosis to date. There was no evidence of increased phospholipid content or changes in lamellar inclusion bodies in peripheral blood lymphocytes of either healthy individuals receiving 1 month of fluoxetine therapy or depressed patients receiving long-term (0.9–2.6 years) therapy with the drug. In addition, ophthalmologic examination and chest radiographs in patients receiving fluoxetine during clinical studies have not revealed evidence of phospholipidosis induced by the drug. Although data from clinical studies suggest that fluoxetine-induced phospholipidosis is unlikely to occur in humans receiving long-term therapy with the drug, further study is needed to fully determine whether the phospholipidosis observed in animal studies is clinically important in humans receiving therapeutic dosages of the drug.

■ **Other Effects** Fluoxetine has demonstrated some antimyoclonic activity in animals and humans when used in combination with oxitriptan. Although the mechanism of fluoxetine's antimyoclonic activity has not been fully elucidated, some forms of myoclonus appear to be related to impaired serotonergic neurotransmission. Therefore, it has been suggested that fluoxetine-induced enhancement of serotonergic neurotransmission via serotonin-reuptake blockade potentially may contribute to oxitriptan-induced increases in CNS serotonin concentrations in the management of this condition. (See Uses: Myoclonus.)

Fluoxetine also has reduced cataplexy in both humans and animals. (See Uses: Cataplexy.)

Fluoxetine reportedly has produced a dose-related elevation in plasma β-endorphin and β-lipotropin concentrations in healthy individuals receiving single oral doses of the drug.

Pharmacokinetics

In all human studies described in the Pharmacokinetics section, fluoxetine was administered as the hydrochloride salt.

■ **Absorption** Fluoxetine hydrochloride appears to be well absorbed from the GI tract following oral administration. The oral bioavailability of fluoxetine in humans has not been fully elucidated to date, but at least 60–80% of an oral dose appears to be absorbed. However, the relative proportion of an oral dose reaching systemic circulation unchanged currently is not known. The oral conventional capsules and tablets, delayed-release capsules, and solution of fluoxetine hydrochloride reportedly are bioequivalent. However, onset of absorption of fluoxetine hydrochloride delayed-release capsules (Prozac® Weekly®) is delayed 1–2 hours relative to the onset of absorption when the drug is administered as a conventional preparation. Limited data from animals suggest that the drug may undergo first-pass metabolism and extraction in the liver and/or lung following oral administration. In these animals (beagles), approximately 72% of an oral dose reached systemic circulation unchanged. Food appears to cause a slight decrease in the rate, but not the extent, of absorption of fluoxetine in humans.

Peak plasma fluoxetine concentrations usually occur within 4–8 hours (range: 1.5–12 hours) after oral administration of conventional preparations. Following oral administration of a single 40-mg dose of the drug in healthy fasting adults, peak plasma concentrations of approximately 15–55 ng/mL are attained. Peak plasma fluoxetine concentrations following administration of single oral doses of 20–80 mg are approximately proportional and are linearly related to dose, although there appears to be considerable interindividual variation in plasma concentrations attained with a given dose. The manufacturer states that the peak plasma concentrations achieved following weekly administration of fluoxetine 90-mg delayed-release capsules are in the range of the average concentrations achieved following daily administration of 20-mg conventional preparations; however, average trough concentrations are reported to be lower following weekly administration of the delayed-release preparation. Peak-to-trough fluctuations in plasma concentrations of fluoxetine and norfluoxetine (the principal metabolite) reportedly are greater following weekly administration of the delayed-release capsules (164 and 43%, respectively) compared with daily administration of conventional preparations (24 and 17%, respectively).

Preliminary data suggest that fluoxetine may exhibit nonlinear accumulation following multiple dosing. (See Pharmacokinetics: Elimination.) The relatively slow elimination of fluoxetine and its active metabolite, norfluoxetine, leads to clinically important accumulation of these active species in chronic use and delayed attainment of steady state, even when a fixed dose is used. In healthy adults receiving 40 mg of fluoxetine daily for 30 days, plasma concentrations of 91–302 and 72–258 ng/mL of fluoxetine and norfluoxetine, respectively, were attained. These plasma concentrations of fluoxetine were higher than those predicted by single-dose studies because fluoxetine's metabolism is not proportional to dose. In addition, prolonged administration of the drug and/or patient's disease states did not appear to affect steady-state concentrations. In one study, steady-state plasma fluoxetine and norfluoxetine concentrations did not differ substantially among healthy individuals receiving 4 weeks of fluoxetine therapy, depressed patients receiving 5 weeks of fluoxetine therapy, or depressed patients receiving more than a year of fluoxetine therapy.

Average steady-state fluoxetine and norfluoxetine concentrations, however, were affected by patient age. In pediatric patients with major depressive disorder or obsessive-compulsive disorder (OCD) who received fluoxetine 20 mg daily for up to 62 days, average steady-state concentrations of fluoxetine and norfluoxetine in children 6–12 years of age were 2- and 1.5-fold higher, respectively, than in adolescents 13–17 years of age who received the same fluoxetine regimen. These results are consistent with those observed in another study in 94 pediatric patients 8–17 years of age diagnosed with major depressive disorder, and can be almost entirely explained by differences in children's weight. Higher average steady-state fluoxetine and norfluoxetine concentrations also were observed in children relative to adults; however, these concentrations were within the range of concentrations observed in the adult population. As in adults, fluoxetine and norfluoxetine accumulated extensively following multiple oral dosing. Following daily oral administration of the drug, steady-state plasma fluoxetine and norfluoxetine concentrations generally are achieved within about 2–4 weeks.

The manufacturer states that average steady-state plasma fluoxetine concentrations are approximately 50% lower with weekly administration of the 90-mg delayed-release capsules compared with daily administration of a 20-mg conventional preparation. In patients being switched from daily therapy with fluoxetine 20-mg conventional preparations to weekly therapy with fluoxetine 90-mg delayed-release capsules, peak plasma fluoxetine concentrations reportedly were 1.7 times higher with the weekly regimen than with the established daily regimen when there was no transition period (i.e., therapy with delayed-release fluoxetine was initiated the day after the last daily dose of fluoxetine 20 mg). When weekly therapy was initiated one week after the last daily dose of fluoxetine 20 mg, peak plasma fluoxetine concentrations for the 2 regimens were similar. (See Dosage and Administration: Dosage.)

The onset of antidepressant activity following oral administration of fluoxetine hydrochloride usually occurs within the first 1–3 weeks of therapy, but optimum therapeutic effect usually requires 4 weeks or more of therapy with the drug. Maximal EEG changes and behavioral changes on psychometric tests reportedly occur about 8–10 hours after single oral doses of the drug; the delay in maximal CNS effects compared with achievement of peak plasma fluoxetine concentrations may relate to formation of an active metabolite or to delayed distribution of the parent drug and its principal metabolite into the CNS.

The relationship between plasma fluoxetine and norfluoxetine concentrations and the therapeutic and/or toxic effects of the drug has not been clearly established. In a group of patients receiving fluoxetine for the management of major depressive disorder, there was no correlation between plasma fluoxetine, norfluoxetine, or total fluoxetine plus norfluoxetine concentrations and either the antidepressant response or the weight-reducing effect of the drug.

■ **Distribution** Distribution of fluoxetine and its metabolites into human body tissues and fluids has not been fully characterized. Limited pharmacokinetic data obtained during long-term administration of fluoxetine to animals suggest that the drug and some of its metabolites, including norfluoxetine, are widely distributed in body tissues, with highest concentrations occurring in the lungs and liver. The drug crosses the blood-brain barrier in humans and animals. In animals, fluoxetine:norfluoxetine ratios reportedly were similar in the cerebral cortex, corpus striatum, hippocampus, hypothalamus, brain stem, and cerebellum 1 hour after administration of a single dose of the drug.

The apparent volumes of distribution of fluoxetine and norfluoxetine in healthy adults each reportedly average 20–45 L/kg. Limited data suggest that the volume of distribution of fluoxetine is not altered substantially following multiple dosing. The apparent volume of distribution of norfluoxetine reportedly is higher in patients with cirrhosis than in healthy individuals, although this difference may reflect decreases in the rates of formation and elimination of the metabolite rather than changes in volume of distribution. The volumes of distribution of fluoxetine and norfluoxetine do not appear to be altered substantially in patients with renal impairment.

At in vitro plasma concentrations of 200–1000 ng/mL, fluoxetine is approximately 94.5% bound to plasma proteins, including albumin and α_1-acid glycoprotein (α_1-AGP); the extent of protein binding appears to be independent of plasma concentration. The extent of fluoxetine protein binding does not appear to be altered substantially in patients with hepatic cirrhosis or renal impairment, including those undergoing hemodialysis.

It is not known whether fluoxetine or its metabolites cross the placenta in humans, but fluoxetine and norfluoxetine reportedly cross the placenta in rats following oral administration. Fluoxetine and norfluoxetine are distributed into milk. Limited data indicate that concentrations of the drug and this metabolite in milk are about 20–30% of concurrent plasma concentrations.

■ **Elimination** Fluoxetine and norfluoxetine, the principal metabolite, are eliminated slowly. Following a single oral dose of fluoxetine in healthy adults, the elimination half-life of fluoxetine reportedly averages approximately 2–3 days (range: 1–9 days) and that of norfluoxetine averages about 7–9 days (range: 3–15 days). The plasma half-life of fluoxetine exhibits considerable interindividual variation, which may be related to genetic differences in the

rate of *N*-demethylation of the drug in the liver. The absence of either a bimodal or trimodal distribution of clearance values suggests that the rate of such metabolism may be under polygenic control. The half-life of fluoxetine reportedly is prolonged (to approximately 4–5 days) after administration of multiple versus single doses, suggesting a nonlinear pattern of drug accumulation during long-term administration. Norfluoxetine appears to exhibit dose-proportional pharmacokinetics following multiple dosing, although limited data indicate that the rate of formation of the metabolite is decreased slightly once steady-state plasma concentrations have been achieved.

Following oral administration of single doses of fluoxetine in healthy individuals, total apparent plasma clearances of fluoxetine and norfluoxetine average approximately 346 mL/minute (range: 94–703 mL/minute) and 145 mL/minute (range: 61–284 mL/minute), respectively. Limited data suggest that plasma clearance of fluoxetine decreases by approximately 75% following multiple oral doses of the drug once steady-state plasma fluoxetine concentrations have been achieved. Plasma clearances of fluoxetine and norfluoxetine also reportedly are decreased in patients with chronic liver disease (e.g., cirrhosis). Evidence from single-dose studies indicates that clearances of the drug and its principal metabolite are not altered substantially in patients with renal impairment.

The exact metabolic fate of fluoxetine has not been fully elucidated. The drug appears to be metabolized extensively, probably in the liver, to norfluoxetine and several other metabolites. Norfluoxetine (desmethylfluoxetine), the principal metabolite, is formed by *N*-demethylation of fluoxetine, which may be under polygenic control. The potency and selectivity of norfluoxetine's serotonin-reuptake inhibiting activity appear to be similar to those of the parent drug. Both fluoxetine and norfluoxetine undergo conjugation with glucuronic acid in the liver, and limited evidence from animals suggests that both the parent drug and its principal metabolite also undergo *O*-dealkylation to form *p*-trifluoromethylphenol, which subsequently appears to be metabolized to hippuric acid.

Following oral administration, fluoxetine and its metabolites are excreted principally in urine. In healthy individuals, approximately 60% of an orally administered, radiolabeled dose of fluoxetine is excreted in urine within 35 days, with approximately 72.8% of excreted drug as unidentified metabolites, 10% as norfluoxetine, 9.5% as norfluoxetine glucuronide, 5.2% as fluoxetine glucuronide, and 2.5% as unchanged drug. Approximately 12% of the dose was eliminated in feces within 28 days following oral administration, but the relative proportion of unabsorbed versus absorbed drug that is excreted in feces (e.g., via biliary elimination) is not known.

The effect of age on the elimination of fluoxetine has not been fully elucidated. Single-dose studies suggest that the pharmacokinetics of fluoxetine in healthy geriatric individuals do not differ substantially from those in younger adults. However, because the drug has a relatively long half-life and nonlinear disposition following multiple-dose administration, single-dose studies are not sufficient to exclude the possibility of altered pharmacokinetics in geriatric individuals, particularly those with systemic disease and/or in those receiving multiple medications concomitantly. The elimination half-lives of fluoxetine and norfluoxetine may be prolonged in patients with hepatic impairment. Following a single oral dose of the drug in patients with hepatic cirrhosis, the elimination half-lives of fluoxetine and norfluoxetine reportedly average approximately 7 and 12 days, respectively.

The elimination half-lives of fluoxetine and norfluoxetine do not appear to be altered substantially in patients with renal impairment following oral administration of single doses of the drug, although multiple-dose studies are needed to determine whether accumulation of the parent drug and/or its metabolites occurs during long-term therapy in such patients.

Fluoxetine and norfluoxetine are not removed substantially by hemodialysis. Because of the large volume of distribution and extensive protein binding of the drug and its principal metabolite, peritoneal dialysis, forced diuresis, hemoperfusion, and/or exchange transfusion also are likely to be ineffective in removing substantial amounts of fluoxetine and norfluoxetine from the body.

Chemistry and Stability

■ **Chemistry** Fluoxetine, a selective serotonin-reuptake inhibitor (SSRI) antidepressant, is a phenylpropylamine-derivative. The drug differs structurally from other selective serotonin-reuptake inhibitor antidepressants (e.g., citalopram, paroxetine, sertraline) and also differs structurally and pharmacologically from other currently available antidepressant agents (e.g., tricyclic antidepressants, monoamine oxidase inhibitors).

Fluoxetine contains a *p*-trifluoromethyl substituent that appears to contribute to the drug's high selectivity and potency for inhibiting serotonin reuptake, possibly as a result of its electron-withdrawing effect and lipophilicity. The commercially available drug is a racemic mixture of 2 optical isomers. Limited in vivo and in vitro data suggest that the pharmacologic activities of the optical isomers do not differ substantially, although the dextrorotatory isomer appears to have slightly greater serotonin-reuptake inhibiting activity and a longer duration of action than the levorotatory isomer.

Fluoxetine is commercially available as the hydrochloride salt, which occurs as a white to off-white crystalline solid and has a solubility of 14 mg/mL in water.

■ **Stability** Fluoxetine hydrochloride capsules and the oral solution should be stored in tight, light-resistant containers, both at 15–30°C. Fluoxetine tablets and delayed-release capsules should be stored at 15–30°C.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Fluoxetine Hydrochloride

Oral		
Capsules	10 mg (of fluoxetine)*	**Fluoxetine Hydrochloride Capsules**
		Prozac®, Pulvules®, Dista
		Sarafem®, Pulvules®, Lilly
	20 mg (of fluoxetine)*	**Fluoxetine Hydrochloride Capsules**
		Prozac®, Pulvules®, Dista
		Sarafem®, Pulvules®, Lilly
	40 mg (of fluoxetine)*	**Fluoxetine Hydrochloride Capsules**
		Prozac®, Pulvules®, Dista
Capsules, delayed-release (containing enteric-coated pellets)	90 mg (of fluoxetine)	**Prozac®, Weekly, Dista**
Solution	20 mg (of fluoxetine) per 5 mL*	**Fluoxetine Hydrochloride Oral Solution**
		Prozac®, Dista
Tablets	10 mg (of fluoxetine)*	**Fluoxetine Hydrochloride Tablets** (scored)
		Sarafem®, Warner Chilcott
	15 mg (of fluoxetine)*	**Sarafem®, Warner Chilcott**
	20 mg (of fluoxetine)*	**Fluoxetine Hydrochloride Tablets**
		Sarafem®, Warner Chilcott

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Fluoxetine Hydrochloride Combinations

Oral		
Capsules	25 mg (of fluoxetine) with Olanzapine 6 mg	**Symbyax® (combination), Lilly**
	25 mg (of fluoxetine) with Olanzapine 12 mg	**Symbyax® (combination), Lilly**
	50 mg (of fluoxetine) with Olanzapine 6 mg	**Symbyax® (combination), Lilly**
	50 mg (of fluoxetine) with Olanzapine 12 mg	**Symbyax® (combination), Lilly**

†Use is not currently included in the labeling approved by the US Food and Drug Administration

Paroxetine

■ Paroxetine hydrochloride and paroxetine mesylate, selective serotonin-reuptake inhibitors (SSRIs), are antidepressant agents.

Uses

Paroxetine is commercially available in the US as paroxetine hydrochloride (e.g., Paxil®, Paxil CR®) and as paroxetine mesylate (i.e., Pexeva®). The US Food and Drug Administration (FDA) considers paroxetine mesylate (Pexeva®) conventional tablets to be a pharmaceutical *alternative* (as described in section 505[b][2] of the Federal Food, Drug, and Cosmetic Act) and not a pharmaceutical (generic) equivalent to paroxetine hydrochloride conventional tablets (e.g., Paxil®), since both contain the same active moiety (paroxetine) but have different salts. The clinical studies that established efficacy of paroxetine in various conditions have been conducted with paroxetine hydrochloride. Because paroxetine hydrochloride and paroxetine mesylate contain the same active moiety (paroxetine), clinical efficacy is expected to be similar between the 2 different salts.

Paroxetine hydrochloride conventional tablets and oral suspension are used in the treatment of major depressive disorder, obsessive-compulsive disorder, panic disorder with or without agoraphobia, social phobia (social anxiety disorder), generalized anxiety disorder, and posttraumatic stress disorder. Paroxetine hydrochloride extended-release tablets are used in the treatment of major depressive disorder, panic disorder with or without agoraphobia, social phobia, and premenstrual dysphoric disorder (PMDD). Paroxetine mesylate conventional tablets are used in the treatment of major depressive disorder, obsessive-compulsive disorder, and panic disorder with or without agoraphobia. In addition, paroxetine has been used in the treatment of premature ejaculation†,