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)*	**Serafem®**, 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†,

diabetic neuropathy†, chronic headache†, and depression associated with bipolar disorder†.

■ **Major Depressive Disorder** Paroxetine is used in the treatment of major depressive disorder. 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.)

The efficacy of paroxetine for the management of major depression has been established by placebo-controlled studies of 6 weeks' duration in adult outpatients from 18–73 years of age who met DSM-III criteria for major depressive disorder. In these studies, paroxetine hydrochloride was found to be more effective than placebo in improving scores by at least 2 on the Hamilton Depression Rating Scale (HDRS) and the Clinical Global Impression and Severity of Illness Scale. Paroxetine hydrochloride also was more effective than placebo in improving HDRS subfactor scores, including the depressed mood item, sleep disturbance factor, and the anxiety factor.

The efficacy of paroxetine hydrochloride extended-release tablets for the management of depression has been established in 2 flexible-dosage, controlled studies of 12-weeks' duration in adults 18–88 years of age who met DSM-IV criteria for major depressive disorder. In these studies, paroxetine was more effective than placebo in improving scores on the HDRS, the Hamilton depressed mood item, and the Clinical Global Impression-Severity of Illness Scale.

In a study of depressed outpatients who had responded by the end of an initial 8-week open treatment phase to paroxetine (mean dosage: approximately 30 mg daily; HDRS total score of less than 8) and were randomized to continue paroxetine or receive placebo for 1 year, the relapse rate in the paroxetine-treated patients (15%) was substantially lower than that in those who received placebo (39%). An analysis of these data for possible gender-related effects on treatment outcome did not suggest any difference in efficacy based on the gender of the patient. In controlled studies of depressed patients who had responded to a 6-week course of paroxetine or imipramine and were randomized to receive either the same antidepressant or placebo for up to 1 year, both paroxetine and imipramine were more effective than placebo in maintaining euthymia; however, paroxetine was better tolerated than imipramine during long-term therapy. While the optimum duration of paroxetine therapy has not been established, many experts state that acute depressive episodes require several months or longer of sustained antidepressant therapy. In addition, some clinicians recommend that long-term antidepressant therapy be considered in certain patients at risk for recurrence of depressive episodes (such as those with highly recurrent unipolar depression). In placebo-controlled studies, paroxetine has been shown to be effective for the long-term (e.g., up to 1 year) management of depression. In addition, the drug has been used in some patients for longer periods (e.g., up to 4 years) without apparent loss of clinical effect or increased toxicity. However, when paroxetine is used for extended periods, the need for continued therapy should be reassessed periodically. (See Dosage and Administration: Dosage.)

The efficacy of paroxetine as an antidepressant in hospital settings has not been studied adequately to date; however, the drug has been shown to be effective in hospitalized patients with severe depression in at least one controlled study.

As with other antidepressants, the possibility that paroxetine may precipitate hypomanic or manic attacks in patients with bipolar or other major affective disorder should be considered. Paroxetine is *not* approved for use in treating bipolar depression.

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 paroxetine in patients with depression is greater than that of placebo and comparable to that of usual dosages of tricyclic antidepressants (e.g., amitriptyline, imipramine, doxepin), other SSRIs (e.g., fluoxetine, fluvoxamine, sertraline), and other antidepressants (e.g., nefazodone). The onset of antidepressant action of paroxetine appears to be comparable to that of tricyclic antidepressants and other SSRIs, although there is some evidence that the onset of action may occur slightly earlier with paroxetine than with imipramine and fluoxetine.

In general, response rates in patients with major depression are similar for currently available antidepressants, and 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 that 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 SSRIs and tricyclic antidepressants, particularly less frequent anticholinergic effects, cardiovascular effects, and/or weight gain with SSRIs, 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 paroxetine and other SSRIs 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 SSRIs share the same overall tolerability profile, certain patients may tolerate one drug in this class better than another. Antidepressants other than SSRIs may be preferred in patients in whom certain adverse GI effects (e.g., nausea, anorexia), nervous system effects (e.g., anxiety, nervousness, insomnia), and/or weight loss are not tolerated or are of concern, since such effects appear to occur more frequently with paroxetine 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 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., paroxetine, citalopram, desvenlafaxine, duloxetine, escitalopram, fluvoxamine, mirtazapine, nefazodone, sertraline, venlafaxine) was not conclusively established in clinical trials in pediatric patients with major depressive disorder. In addition, 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. (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 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 paroxetine 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, and hyponatremia). Some clinicians state that SSRIs including paroxetine 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 suicidal ideation) 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 citalopram, escitalopram, fluoxetine, paroxetine, or sertraline are generally considered as first-line agents in the treatment of depressed patients with dementia since they usually are 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 controlled study comparing paroxetine and imipramine in patients with coexisting depression and dementia, both drugs were found to be effective; however, paroxetine was better tolerated (fewer anticholinergic and serious adverse effects).

Cardiovascular Considerations. The relatively low incidence of adverse cardiovascular effects, including orthostatic hypotension and conduction disturbances, associated with paroxetine and other SSRIs may be advantageous in patients in whom the cardiovascular effects associated with tricyclic antidepressants may be hazardous. In a controlled trial comparing paroxetine and nortriptyline in patients with stable ischemic disease, both antidepressants were found to be effective in treating depression and neither drug substantially affected blood pressure or conduction intervals; however, paroxetine did not produce sustained effects on heart rate or rhythm or heart rate variability whereas nortriptyline increased heart rate and reduced heart rate variability. Most clinical studies of paroxetine for the management of depression did not include individuals with cardiovascular disease (e.g., those with a recent history of myocardial infarction or unstable cardiovascular disease), and further experience in such patients is necessary to confirm the relative lack of cardiotoxicity reported with the drug to date. (See Cautions: Cardiovascular Effects and see Cautions: Precautions and Contraindications.)

Sedative Considerations. Because paroxetine 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 or in patients who are prone to accidents; however, an antidepressant with more prominent sedative effects (e.g., trazodone) may be preferable in certain 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.) 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 is currently 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 Suicidality under Cautions: Nervous System Effects, and see Cautions: Precautions and Contraindications.)

Other Considerations. Paroxetine has been effective in patients with moderate to severe depression, endogenous depression, reactive depression (including traumatic grief), depression associated with human immunodeficiency virus (HIV) infection, and depression associated with anxiety and/or agitation.

■ **Obsessive-Compulsive Disorder** Paroxetine is used in the treatment of obsessive-compulsive disorder when obsessions or compulsions cause marked distress, are time-consuming (take longer than 1 hour daily), or interfere substantially with the patient's normal routine, occupational or academic functioning, or usual social activities or relationships. Obsessions are recurrent and persistent 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 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 recognition.

The efficacy of paroxetine hydrochloride for the management of obsessive-compulsive disorder in adults has been established by 2 multicenter, placebo-controlled studies of 12 weeks' duration. In these clinical studies, paroxetine was more effective than placebo in reducing the severity of obsessive-compulsive manifestations in adult outpatients with moderate to severe obsessive-compulsive disorder (Yale-Brown Obsessive-Compulsive Scale [YBOCS] baseline values of 23–26). In a fixed-dose study of 12 weeks' duration involving paroxetine dosages of 20, 40, or 60 mg daily, patients receiving 40 or 60 mg of the drug daily experienced substantially greater reductions in the YBOCS total score (approximately 6 and 7 points, respectively) than those receiving paroxetine 20 mg daily (approximately 4 points) or placebo (approximately 3 points). The effective dosage of paroxetine was 40 or 60 mg daily. In a 12-week study with flexible dosing of paroxetine (20–60 mg daily) or clomipramine (25–250 mg daily) compared with placebo, paroxetine-treated patients exhibited a mean reduction of approximately 7 points on the YBOCS total score, which was substantially greater than the mean reduction of approximately 4 points in patients receiving placebo. No age- or gender-related differences in outcome were noted in either of these studies.

The efficacy of paroxetine for long-term use (i.e., longer than 12 weeks) has been demonstrated in a 6-month relapse prevention trial, which was an extension of the fixed-dose study of 12 weeks' duration in patients who had responded to paroxetine. Patients who received paroxetine relapsed substantially less frequently than those receiving placebo in a double-blind placebo-controlled study. The manufacturers 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 paroxetine is used for extended periods, dosage should be adjusted so that patients are maintained on the lowest effective dosage, and the need for continued therapy with the drug should be reassessed periodically.

Results from comparative studies to date suggest that paroxetine and other SSRIs (e.g., fluoxetine, fluvoxamine, sertraline) are as effective as 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. Like clomipramine, SSRIs reduce but do not completely eliminate obsessions and compulsions.

Many clinicians consider an SSRI (e.g., paroxetine, fluoxetine, fluvoxamine, 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 (anticholinergic effects, cardiovascular effects, sedation) associated with clomipramine therapy. Consideration of individual patient characteristics (age, concurrent medical conditions), pharmacokinetics of the drug, potential drug interactions, and cost of therapy may also influence clinicians when selecting between SSRIs and clomipramine as first-line therapy in patients with obsessive-compulsive disorder.

Pediatric Considerations In children† with obsessive-compulsive disorder, cognitive behavioral therapy and/or serotonin-reuptake inhibitors (such as clomipramine and SSRIs) may be beneficial. Controlled studies evaluating paroxetine in this setting currently are lacking and it remains to be established whether one serotonin-reuptake inhibitor is more effective than another. Pending further data, some experts state that the choice of an agent may depend on their adverse effect profile, potential for adverse drug interactions, and the presence of comorbid conditions. Although clomipramine has been more extensively studied to date than SSRI, it has the most prominent anticholinergic effects, requires electrocardiographic (ECG) monitoring, and is the most toxic following acute overdosage. SSRIs do not require ECG monitoring; however, they are associated with headache, nausea, insomnia, and agitation. If a decision is made to initiate SSRI therapy in a child with obsessive-compulsive disorder, some experts recommend starting with a low initial dosage and then gradually increasing the dosage as tolerated. If there is no clinical response after 10–12 weeks, consideration should be given to switching to another SSRI or clomipramine. (See Cautions: Pediatric Precautions.)

Although combined clomipramine and SSRI therapy has been effective in a limited number of children and adolescents with obsessive-compulsive disorder, very close monitoring of the ECG, blood clomipramine concentrations, and vital signs is necessary because of the risks of potentially dangerous drug interactions (including serotonin syndrome) and adverse effects with such combinations. (See Drug Interactions: Serotonergic Drugs.) As in adults, the optimal duration of pharmacologic therapy in children with obsessive-compulsive disorder remains unclear. Although periodic trials of gradual withdrawal from drug therapy are advisable, some children appear to require long-term maintenance therapy to prevent relapse.

■ **Panic Disorder** Paroxetine 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 paroxetine hydrochloride for the management of panic disorder with or without agoraphobia has been established by multicenter, double-blind, placebo-controlled studies in adult outpatients who met DSM-IIIR criteria for panic disorder with or without agoraphobia. In a fixed-dose study of 10 weeks' duration in which paroxetine was given in dosages of 10, 20, and 40 mg daily, a substantially greater reduction in panic attack frequency from placebo was noted only in the patients receiving paroxetine 40 mg daily; at the end of the study, 76% of patients receiving paroxetine 40 mg daily were free of panic attacks compared with 44% of those receiving placebo. In 2 studies of 12 weeks' duration employing a flexible dosing schedule, greater improvement was reported in patients receiving paroxetine 10–60 mg daily than in those receiving placebo. In one study, 51% of the paroxetine recipients compared with 32% of the placebo recipients were free of panic attacks at the end of the study, and in the other study which was conducted in patients receiving standardized cognitive behavioral therapy, 33% of patients receiving paroxetine 10–60 mg daily had a reduction in panic attack frequency to 0 or 1 panic attacks during the study period compared with 14% of those receiving placebo. The mean paroxetine dosage for those completing these 2 flexible-dose studies was approximately 40 mg daily.

In these studies, paroxetine was found to be substantially more effective than placebo in the treatment of panic disorder in at least 2 out of 3 measures of panic attack frequency and on the Clinical Global Impression Severity of Illness Scale. The results of the studies conducted to date demonstrate that paroxetine reduces global anxiety, depressive symptoms, phobic avoidance, and improves overall impairment associated with panic disorder.

The efficacy of paroxetine hydrochloride extended-release tablets for the management of panic disorder with or without agoraphobia has been established in multicenter, placebo-controlled, flexible-dosage studies in patients with panic disorder with or without agoraphobia. In 2 studies, paroxetine extended-release tablets were more effective than placebo, but a third study failed to show any benefit compared with placebo.

The efficacy of paroxetine for long-term use (i.e., longer than 12 weeks) has been demonstrated in controlled studies. In a 3-month relapse prevention trial which was an extension of the 10-week, fixed-dose study, patients who were responders to paroxetine were randomized to receive either paroxetine (10, 20, or 40 mg daily) or placebo. The patients receiving long-term therapy with paroxetine relapsed substantially less frequently than those receiving placebo. In another controlled study, patients receiving paroxetine therapy for 1 year demonstrated not only long-term efficacy but also continued improvement. The manufacturers and some clinicians state that panic disorder is a chronic condition; therefore, it is reasonable to continue therapy in responding patients. Dosage adjustment may be necessary to maintain the patient on the lowest effective dosage, and patients should be reassessed periodically to determine the need for continued therapy.

Subgroup analysis in controlled studies for possible age- or gender-related effects on treatment outcome did not suggest any difference in efficacy based on either the age or sex of the patient.

The results of controlled studies suggest that paroxetine is as effective as and better tolerated than clomipramine in the treatment of panic disorder. In addition, paroxetine was found to have a more rapid onset of action than clomipramine in reducing the number of panic attacks in one study.

Unlike imipramine which reduces heart rate variability in patients with panic disorder (a condition associated with decreased heart rate variability and consequently an increased risk of serious cardiovascular problems including sudden cardiac death), paroxetine has been shown to normalize heart rate variability in a limited number of patients with panic disorder. The clinical importance of these findings with regard to potentially decreasing cardiovascular mortality in patients with panic disorder remains to be determined.

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), monoamine oxidase (MAO) inhibitors (e.g., phenelzine), selective serotonin-reuptake inhibitors (SSRIs; e.g., citalopram, fluoxetine, sertraline, paroxetine), 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 com-

pared 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.

■ **Social Phobia** Paroxetine hydrochloride is used in the treatment of social phobia (social anxiety disorder). According to DSM-IV, social phobia is characterized by a marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. Exposure to the feared situation almost invariably provokes anxiety, which may approach the intensity of a panic attack. The feared situations are avoided or endured with intense anxiety or distress. The avoidance, fear, or anxious anticipation of encountering the social or performance situation interferes significantly with the person's daily routine, occupational or academic functioning, or social activities or relationships, or there is marked distress about having the phobias. Lesser degrees of performance anxiety or shyness generally do not require psychotherapy or pharmacologic treatment.

The efficacy of paroxetine hydrochloride in the treatment of social phobia has been established in 3 multicenter, placebo-controlled studies in adult outpatients who met DSM-IV criteria for social phobia. In 2 studies of 12 weeks' duration in which paroxetine was given in dosages ranging from 20–50 mg daily, significant improvement in the Clinical Global Impressions (CGI) Improvement score and Liebowitz Social Anxiety Scale (LSAS) were noted. In these studies, 69 or 77% of paroxetine-treated patients were CGI Improvement responders compared with 29 or 42% of placebo-treated patients. In the third study, paroxetine was given in fixed dosages of 20, 40, or 60 mg daily for 12 weeks. There was significant improvement in the CGI Improvement responder criterion and LSAS Total Score in patients receiving 20 mg daily compared with placebo. Although there were trends in superiority noted in those receiving 40 or 60 mg daily compared with placebo, the results did not reach statistical significance and there was no indication that dosages exceeding 20 mg daily provide any additional benefit.

Subgroup analysis of these controlled studies in adult outpatients with social anxiety disorder did not reveal any evidence of age- or gender-related differences in treatment outcome. Safety and efficacy of paroxetine for the treatment of social phobia in children or adolescents have not been established to date.

■ **Anxiety Disorders** Paroxetine hydrochloride is used in the management of generalized anxiety disorder. According to DSM-IV-TR, generalized anxiety disorder is characterized by excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (e.g., work or school performance). Patients with generalized anxiety disorder find it difficult to control the worry. The anxiety and worry are accompanied by at least 3 of the following somatic symptoms in adults and at least 1 of these symptoms in children: restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, and sleep disturbance (e.g., difficulty falling or staying asleep, restless unsatisfying sleep). These symptoms cause clinically important distress or impairment in social, occupational, or other important areas of functioning and are not caused by direct physiologic effects of substances (e.g., medications, drugs of abuse, toxin exposure) or by a general medical condition (e.g., hyperthyroidism). Although patients with generalized anxiety disorder may have another underlying mental disorder (axis I disorder), the focus of the anxiety and worry is unrelated to the latter disorder and does not occur only during the course of a mood, psychotic, or pervasive developmental disorder.

Selective serotonin-reuptake inhibitors (SSRIs) are among several classes of antidepressants recommended by some clinicians as first-line treatment for generalized anxiety disorder because of their safety, tolerability (e.g., lack of physical dependence problems commonly associated with benzodiazepines), and proven efficacy in the treatment of depression and other anxiety disorders (e.g., obsessive-compulsive disorder, panic disorder) that frequently present as comorbid conditions in patients with generalized anxiety disorder. Because an estimated 80% of patients with generalized anxiety disorder will have a comorbid mood disorder (e.g., depression) during their lifetime, an SSRI or a drug that predominantly inhibits serotonin and norepinephrine reuptake (e.g., venlafaxine) is preferred by some clinicians for treatment of patients with long-standing generalized anxiety disorder and in those with several comorbid mood or anxiety disorders. However, the efficacy of antidepressants, including paroxetine, in the management of generalized anxiety disorder in patients with comorbid conditions such as depression has yet to be established, since such patients have been excluded from study entry, and therefore further research is needed.

Efficacy of paroxetine hydrochloride for the management of generalized anxiety disorder has been established in 2 randomized, multicenter, placebo-controlled studies of 8 weeks' duration in adult outpatients who met DSM-IV criteria for generalized anxiety disorder. One study employed fixed paroxetine dosages, and the other employed a flexible dosing schedule. In the flexible-dose study, approximately 62% of patients receiving paroxetine (20–50 mg daily; mean dosage of 26.8 mg daily) had a score of 1 ("very much improved") or 2 ("much improved") on the Clinical Global Impressions (CGI) Global Improvement scale, and approximately 36% of these patients had complete or nearly complete resolution of anxiety (defined as a Hamilton Rating Scale for Anxiety [HAM-A] total score of 7 or less), compared with approximately 47 and 23%, respectively, of patients receiving placebo. These results were similar to those seen in the fixed-dose study, in which a score of 1 or 2 on the CGI Global Improvement scale was attained by 62, 68, or 46%, respectively, and a HAM-A total score of 10 or less was attained by 49, 52, or 33%, respectively, of patients receiving paroxetine 20 or 40 mg daily or placebo. However, in a third study, reductions in HAM-A total score attained by patients receiving flexible dosages of paroxetine (20–50 mg daily; mean dosage of 23.8 mg daily) were not substantially different than those attained by patients receiving placebo. Subgroup analysis of these controlled studies in adult outpatients with generalized anxiety disorder did not reveal any evidence of gender- or race-related differences in treatment outcome.

Systematic evaluation of continuing paroxetine for periods of up to 6 months in patients with generalized anxiety disorder who had responded while taking paroxetine during an 8-week acute treatment phase has demonstrated a benefit of such maintenance therapy. In a double-blind, 24-week relapse prevention trial that was an extension of a single-blind, 8-week acute treatment study, patients who had responded to paroxetine 20–50 mg daily were randomized to receive either paroxetine at the same dosage or placebo. Relapse during the double-blind phase was defined as an increase of 2 or more points on the CGI-Severity of Illness scale to a score of 4 or higher or drug discontinuance due to lack of efficacy. The paroxetine-treated patients experienced a significantly lower relapse rate over the 24-week period compared with those receiving placebo. In addition, 73% of patients receiving a total of 32 weeks of paroxetine therapy achieved remission (defined as a HAM-A total score of 7 or less) compared with about 34% of those who received 8 weeks of therapy and then received 24 weeks of placebo. Because generalized anxiety disorder is a chronic condition, it is reasonable to continue therapy in responding patients. Dosage adjustment may be necessary to maintain patients receiving long-term paroxetine therapy on the lowest effective dosage, and patients should be reassessed periodically to determine the need for continued therapy.

Results of a comparative study indicate that the anxiolytic effects of paroxetine are comparable to those of imipramine, a tricyclic antidepressant, and slightly superior to those of 2′-chlordesmethyldiazepam, a benzodiazepine (not commercially available in the US). In this study, during the first 2 weeks of therapy, 2′-chlordesmethyldiazepam displayed greater anxiolytic efficacy, as measured by HAM-A score, than paroxetine or imipramine; however, following 8 weeks of therapy, a 50% or greater decrease in HAM-A score was attained by 68, 72, or 55% of patients receiving paroxetine, imipramine, or 2′-chlordesmethyldiazepam, respectively. Antidepressants such as paroxetine appear to affect predominantly psychic symptoms, whereas benzodiazepines such as 2′-chlordesmethyldiazepam appear to affect predominately somatic symptoms associated with generalized anxiety disorder.

■ **Posttraumatic Stress Disorder** Paroxetine hydrochloride is used in the treatment of posttraumatic stress disorder (PTSD). PTSD is an anxiety disorder that involves the development of certain characteristic symptoms following personal exposure to an extreme traumatic stressor. According to DSM-IV, PTSD requires exposure to a traumatic event(s) that involved actual or threatened death or serious injury, or threat to the physical integrity of self or others, and the response to the event must involve intense fear, helplessness, or horror (in children the response may be expressed by disorganized or agitated behavior). PTSD is characterized by persistent symptoms of *reexperiencing* the trauma (e.g., intrusive, distressing recollections of the event; recurrent distressing dreams of the event; acting or feeling as if the event were recurring including illusions, hallucinations, or flashbacks; intense distress at exposure to internal or external cues that symbolize or resemble an aspect of the event; physiologic reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the event), persistent *avoidance* of stimuli associated with the trauma and numbing of general responsiveness (e.g., efforts to avoid thoughts, feelings, or conversations related to the event; efforts to avoid activities, places, or people that arouse recollections of the event; inability to recall an important aspect of the event; markedly diminished interest or participation in significant activities; feeling of detachment or estrangement from others; restricted emotions and/or range of affect not present before the event; sense of a foreshortened future); and persistent symptoms of *increased arousal* (e.g., difficulty sleeping; irritability/outbursts of anger; difficulty concentrating; hypervigilance; exaggerated startle response). According to DSM-IV, a PTSD diagnosis requires the presence of 1 or more symptoms of *reexperiencing*, 3 or more symptoms of *avoidance*, and 2 or more symptoms of *increased arousal*, all of which must be present for at least 1 month and cause clinically important distress or impairment in social, occupational, or other important areas of functioning. PTSD, like other anxiety disorders, rarely occurs alone, and patients with PTSD often present with comorbid disorders (e.g., major depressive disorder, substance abuse disorders, panic disorder, generalized anxiety disorders, obsessive-compulsive disorder, social phobia); it is unknown whether these comorbid disorders precede or follow the onset of PTSD.

Psychotherapy alone or in combination with pharmacotherapy generally is considered the treatment of choice for PTSD. Pharmacologic therapy may be indicated in addition to psychotherapy for initial treatment of PTSD in patients who have comorbid disorders (e.g., major depressive disorder, bipolar disorder, other anxiety disorders) and also may be indicated in those who do not respond to initial treatment with psychotherapy alone. If pharmacotherapy is indicated in patients with PTSD, selective serotonin-reuptake inhibitors (SSRIs; e.g.,

fluoxetine, paroxetine, sertraline) usually are considered the drugs of choice (except in patients with bipolar disorder who require treatment with mood-stubilizing agents).

Efficacy of paroxetine hydrochloride in the treatment of PTSD has been established in 2 multicenter, placebo-controlled studies of 12 weeks' duration in adult outpatients (66–68% women) with a primary diagnosis (DSM-IV) of PTSD following physical or sexual assault (48–54%), witnessing injury or death (17–19%), serious accident or injury (6–13%), or exposure to combat (5–8%). The mean duration of PTSD for these patients was approximately 13 years and 41 or 40% of patients had secondary depressive disorders or non-PTSD anxiety disorders, respectively. In these studies, patients receiving fixed (20 or 40 mg daily) or flexible (20–50 mg daily; mean: 27.6 mg daily) dosages of paroxetine had substantially greater changes from baseline on the Clinician-Administered PTSD Scale Part 2 (CAPS-2) score, a multi-item instrument that measures 3 aspects of PTSD with the following symptom clusters: reexperiencing/intrusion, avoidance/numbing, and hyperarousal, and were more likely to have a score of 1 (very much improved) or 2 (much improved) on the Clinical Global Impression-Global Improvement Scale (CGI-I) compared with those receiving placebo. Treatment response in the fixed-dose study appeared to be unaffected by patient's gender, type of trauma, duration of PTSD, or severity of baseline PTSD or comorbid conditions. A third study, also a flexible-dose study comparing paroxetine (20–50 mg daily) with placebo, demonstrated paroxetine to be substantially superior to placebo as assessed by improvement from baseline for CAPS-2 total score, but not by proportion of responders on the CGI-I.

Use of paroxetine in the treatment of chronic PTSD did not appear to produce a complete remission in a substantial proportion of patients receiving the drug in clinical studies. Therefore, some clinicians suggest combined use of psychotherapy with pharmacotherapy in order to optimize treatment outcome; however, further studies are needed.

■ **Premenstrual Dysphoric Disorder** Like some other selective serotonin-reuptake inhibitors (SSRIs; e.g., fluoxetine, sertraline), paroxetine is used in the treatment of premenstrual dysphoric disorder (previously late luteal phase dysphoric disorder). In women suffering from severe premenstrual dysphoric disorder treated daily for 3 menstrual cycles with paroxetine, maprotiline, or placebo, paroxetine was found to be superior to maprotiline or placebo in improving symptoms associated with this disorder. In women with severe premenstrual dysphoric disorder receiving paroxetine 5–30 mg daily for 10 consecutive menstrual cycles, paroxetine also markedly reduced symptoms (premenstrual irritability, depressed mood, increase in appetite, anxiety/tension). The improvement in symptoms continued throughout the entire treatment period; sedation, dry mouth, and nausea occurred commonly but declined during therapy whereas adverse sexual effects (reduced libido, anorgasmia) persisted. Additional controlled studies are needed to determine whether the efficacy of the drug is sustained during longer-term, maintenance therapy in women with this condition. For further information on use of SSRIs in the treatment of premenstrual dysphoric disorder, see Uses: Premenstrual Dysphoric Disorder, in Fluoxetine Hydrochloride 28:16.04.20.

■ **Premature Ejaculation** Like some other SSRIs, paroxetine has been used with some success in the treatment of premature ejaculation†. In a placebo-controlled study in men with premature ejaculation, paroxetine (20 mg daily for the first week followed by 40 mg daily for 5 additional weeks) produced substantially greater clinical improvement (increased intravaginal ejaculation latency time, increased number of thrusts before ejaculation) than placebo. Nearly all the patients in this study reported some improvement in ejaculatory latency during the first week of paroxetine therapy. In an open study, paroxetine 20 mg daily improved premature ejaculation within about 14 days with all patients studied reporting a longer interval before ejaculation. When dosages of 20 or 40 mg daily were compared in patients with primary premature ejaculation, 20 mg daily was found to be sufficient; further study is needed to determine whether higher dosages may further increase ejaculation latency. In a study comparing paroxetine 20 mg daily for 6 months with paroxetine 20 mg daily for 14 days followed by 10 mg daily for a total of 6 months, both regimens were found to be similarly effective in improving premature ejaculation and were well tolerated. There is some evidence that paroxetine may be more effective than other SSRIs in terms of increasing intravaginal ejaculation latency time.

Additional studies have investigated the use of paroxetine on an "as needed" basis for the treatment of premature ejaculation. In one study, men with premature ejaculation (mean age: 39.5 years; mean pretreatment ejaculatory latency time: 0.3 minutes) were randomized to receive 20 mg of paroxetine or placebo 3–4 hours before planned intercourse; at 4 weeks, the mean ejaculatory latency time was 3.2–3.5 minutes in those receiving the drug compared with 0.45–0.6 minutes in those receiving placebo. However, mean ejaculatory latency time was even longer in another group of men (mean age: 40.5 years; mean pretreatment ejaculatory latency time: 0.5 minutes) who received an initial regimen of paroxetine 10 mg daily for 3 weeks and then received paroxetine 20 mg on an as needed basis for 4 weeks.

Further controlled studies are necessary to confirm these findings, to determine the optimal dosage regimen, and to evaluate the long-term efficacy of paroxetine in patients with this condition. Some clinicians advise that a trial with drug therapy may be particularly useful in patients with premature ejaculation who fail or refuse behavioral or psychotherapeutic treatment or when partners are unwilling to cooperate with such therapy.

■ **Diabetic Neuropathy** Tricyclic antidepressants generally have been considered a mainstay of therapy for the treatment of diabetic neuropathy. However, because of potentially improved patient tolerability, therapy with selective serotonin-reuptake inhibitors (SSRIs) or selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs; e.g., duloxetine, venlafaxine) has been attempted as an alternative. In a controlled study, paroxetine (40 mg daily) was effective in a limited number of patients in substantially reducing the symptoms associated with diabetic neuropathy† and was somewhat less effective but better tolerated than imipramine. Because patients who did not respond as well to paroxetine as to imipramine had lower plasma paroxetine concentrations, it was suggested that dosage adjustment based on plasma concentration monitoring potentially may be useful in the management of this condition. When compared with earlier results obtained with imipramine in the management of diabetic neuropathy, SSRIs such as citalopram, fluoxetine, paroxetine, and sertraline generally appear to be less effective but better tolerated overall. Additional study and experience are needed to elucidate the relative roles of SSRIs versus tricyclic antidepressants, SNRIs, anticonvulsants (e.g., pregabalin, gabapentin), and other forms of treatment in the management of this condition.

■ **Chronic Headache** Paroxetine has been used in a limited number of patients with chronic headache† with some success. In an open study, patients with chronic daily headache unresponsive to previous therapy were treated with paroxetine 10–50 mg daily for 3–9 months; most of the patients showed reductions in the number of headache days per month. Fatigue, insomnia, and urogenital disturbances were the most common adverse effects reported in this study. In a double-blind, crossover study in nondepressed patients with chronic tension-type headache comparing paroxetine (20–30 mg daily) and sulpiride (a dopamine antagonist; not commercially available in the US), both drugs improved headache although sulpiride appeared to provide greater relief. Additional controlled studies are needed to confirm these preliminary findings.

■ **Bipolar Disorder** Paroxetine has been used for the short-term management of acute depressive episodes in patients with bipolar disorder†. While antidepressants such as selective serotonin-reuptake inhibitors (SSRIs) have shown good efficacy in the treatment of unipolar depression, the drugs generally have been studied as adjuncts to mood stabilizing agents such as lithium or valproate in the management of bipolar disorder; antidepressant monotherapy is *not* recommended, given the risk of precipitating a switch into mania. The American Psychiatric Association (APA) currently recommends that paroxetine be reserved for patients who had an inadequate therapeutic response to optimal therapy with first-line agents (i.e., lithium, lamotrigine) or who do not tolerate these drugs. If paroxetine was effective for the management of an acute depressive episode, including during the continuation phase, then maintenance therapy with the drug should be considered to prevent recurrence of major depressive episodes. For further information on the management of bipolar disorder, see Uses: Bipolar Disorder, in Lithium Salts 28:28.

Dosage and Administration

■ **Administration** Paroxetine hydrochloride and paroxetine mesylate are administered orally.

Paroxetine hydrochloride conventional tablets, extended-release tablets, and suspension usually are administered once daily in the morning. Since food does not appear to substantially affect GI absorption of paroxetine hydrochloride, the drug generally can be administered without regard to meals; however, administration with food may minimize adverse GI effects. The manufacturer of paroxetine hydrochloride makes no specific recommendations about administration of paroxetine with regard to food.

Paroxetine mesylate conventional tablets are administered once daily, usually in the morning, without regard to meals.

Paroxetine hydrochloride oral suspension should be shaken well just prior to administration of each dose.

Extended-release tablets of paroxetine hydrochloride should be swallowed whole and should *not* be chewed or crushed.

■ **Dosage** Paroxetine is commercially available in the US as paroxetine hydrochloride (e.g., Paxil®, Paxil CR®) and as paroxetine mesylate (i.e., Pexeva®). Conventional tablets of Paxil® and Pexeva® are *not* bioequivalent. 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.

Dosages of paroxetine hydrochloride and paroxetine mesylate are expressed in terms of paroxetine.

Patients receiving paroxetine 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.)

The manufacturers recommend that an interval of at least 2 weeks elapse when switching a patient from a monoamine oxidase (MAO) inhibitor to paroxetine or when switching from paroxetine to an MAO inhibitor. For additional information on potentially serious drug interactions that may occur between paroxetine and MAO inhibitors or other serotonergic agents, see Cautions: Precautions and Contraindications and see also Drug Interactions: Serotonergic Drugs.

Clinical experience regarding the optimal timing of switching from other antidepressants to paroxetine therapy is limited. Therefore, care and prudent medical judgment should be exercised when switching from other antidepressants, particularly from long-acting agents (e.g., fluoxetine), to paroxetine. Because some adverse reactions resembling serotonin syndrome have developed when fluoxetine therapy has been abruptly discontinued and therapy with another serotonin-reuptake inhibitor (sertraline) initiated immediately afterward, a washout period may be advisable when transferring a patient from fluoxetine to another SSRI. However, the appropriate duration of the washout period when switching from other serotonin-reuptake inhibitors to paroxetine has not been clearly established. Pending further experience in patients being transferred from therapy with another antidepressant to paroxetine and as the clinical situation permits, it generally is recommended that the previous antidepressant be discontinued according to the recommended guidelines for the specific antidepressant prior to initiation of paroxetine therapy.

Because withdrawal effects may occur (see Cautions: Nervous System Effects and see Chronic Toxicity), abrupt discontinuance of paroxetine should be avoided. The manufacturers and some clinicians recommend that paroxetine therapy be discontinued gradually (e.g., over a period of several weeks) and the patient monitored carefully when paroxetine therapy is discontinued to prevent the possible development of withdrawal reactions. If intolerable symptoms occur following dosage reduction or upon discontinuance of treatment, paroxetine therapy may be reinstituted at the previously prescribed dosage until such symptoms abate. Clinicians may resume dosage reductions at that time but at a more gradual rate.

Major Depressive Disorder For the management of major depressive disorder in adults, the recommended initial dosage of paroxetine is 20 mg daily as conventional tablets or suspension or 25 mg daily as extended-release tablets. If no clinical improvement is apparent, dosage may be increased in increments of 10 mg daily for conventional tablets or suspension or 12.5 mg daily for extended-release tablets at intervals of not less than 1 week up to a maximum of 50 mg daily for conventional tablets or suspension or 62.5 mg daily for extended-release tablets. While a relationship between dosage and antidepressant effect has not been established, efficacy of the drug was demonstrated in clinical trials employing 20–50 mg daily dosages as conventional tablets or suspension and 25–62.5 daily dosages as extended-release tablets. Like with other antidepressants, the full antidepressant effects may be delayed.

While the optimum duration of paroxetine therapy has not been established, many experts state that acute depressive episodes require several months or longer of sustained antidepressant therapy. In addition, some clinicians recommend that long-term antidepressant therapy be considered in certain patients at risk for recurrence of depressive episodes (such as those with highly recurrent unipolar depression). Whether the dosage of paroxetine required to induce remission is identical to the dosage needed to maintain and/or sustain euthymia is unknown. In a controlled study, a paroxetine dosage of 40 mg daily was more effective in preventing recurrences of depression than 20 mg daily in patients with recurrent, unipolar depression. Systematic evaluation of paroxetine hydrochloride has shown that its antidepressant efficacy is maintained for periods of up to 1 year in patients receiving a mean dosage of 30 mg daily as conventional tablets or suspension, which corresponds to a 37.5 mg dosage of paroxetine extended-release tablets. In addition, the drug has been used in some patients for longer periods (e.g., up to 4 years) without apparent loss of clinical effect or increased toxicity. If paroxetine 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 should be reassessed periodically.

Obsessive-Compulsive Disorder For the management of obsessive-compulsive disorder in adults, the recommended initial dosage of paroxetine is 20 mg daily as conventional tablets or suspension. If no clinical improvement is apparent, dosage may be increased in 10-mg increments at intervals of not less than 1 week. The manufacturers recommend a paroxetine dosage of 40 mg daily in the treatment of obsessive-compulsive disorder. Efficacy of the drug was demonstrated in clinical trials employing paroxetine dosages of 20–60 mg daily. The manufacturers state that paroxetine dosage should not exceed 60 mg daily.

Although the optimum duration of paroxetine therapy required to prevent recurrence of obsessive-compulsive symptoms has not been established to date, the efficacy of paroxetine for long-term use (i.e., longer than 12 weeks) has been demonstrated in a 6-month relapse prevention trial. Patients who received paroxetine relapsed substantially less frequently than those receiving placebo. The manufacturers and many clinicians 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 paroxetine 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.

Panic Disorder For the management of panic disorder in adults, the recommended initial dosage of paroxetine is 10 mg daily as conventional tablets or suspension or 12.5 mg daily as extended-release tablets. Dosage should be increased in 10-mg increments for those receiving conventional tablets or suspension or in 12.5-mg increments for those receiving extended-release tablets at intervals of not less than 1 week. The manufacturers recommend dosages of 40 mg daily for paroxetine conventional tablets or suspension in the treatment of panic disorder. Efficacy of the drug was demonstrated in clinical trials employing 10–60 mg daily as conventional tablets or suspension or 12.5–75 mg daily as extended-release tablets. The manufacturers state that paroxetine dosages should not exceed 60 mg daily for conventional tablets or suspension and 75 mg daily for extended-release tablets.

Although the optimum duration of paroxetine therapy required to prevent recurrence of panic disorder has not been established to date, the efficacy of paroxetine for long-term use (i.e., longer than 12 weeks) has been demonstrated in a 3-month relapse prevention trial. Patients who were treated with paroxetine hydrochloride conventional tablets or suspension (10–40 mg daily) relapsed substantially less frequently than those receiving placebo. The manufacturers and some clinicians state that panic disorder is a chronic condition; therefore, it is reasonable to continue therapy in responding patients. Dosage adjustment may be necessary to maintain the patient on the lowest effective dosage, and patients receiving the drug for extended periods should be reassessed periodically to determine the need for continued therapy.

Social Phobia For the management of generalized social phobia (social anxiety disorder) in adults, the recommended dosage of paroxetine (administered as paroxetine hydrochloride) is 20 mg daily as conventional tablets or suspension or 12.5 mg daily as extended-release tablets. Dosage of the extended-release tablets may be increased in increments of 12.5 mg daily at intervals of not less than 1 week. Efficacy of the drug was demonstrated in clinical trials employing dosages of 20–60 mg daily as conventional tablets or suspension or 12.5–37.5 mg daily as extended-release tablets. The manufacturer of paroxetine hydrochloride states that no additional clinical benefit was observed at dosages exceeding 20 mg daily for conventional tablets or suspension and that the maximum dosage for extended-release tablets should not exceed 37.5 mg daily.

Although the efficacy of paroxetine for long-term therapy (i.e., longer than 12 weeks) has not been demonstrated in controlled studies to date, the manufacturer of paroxetine hydrochloride states that it is reasonable to consider continuation of therapy for a patient who responds to the drug. If paroxetine 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 should be reassessed periodically.

Anxiety Disorder For the management of generalized anxiety disorder in adults, the recommended initial dosage of paroxetine (administered as paroxetine hydrochloride) is 20 mg daily as conventional tablets or suspension. Although dosages of 20–50 mg daily were effective in clinical studies, there is insufficient evidence to indicate that dosages exceeding 20 mg daily provide additional clinical benefit. Dosage of paroxetine should be increased in 10-mg increments at intervals of not less than 1 week.

The optimum duration of paroxetine therapy for the management of generalized anxiety disorder has not been established to date. Because this disorder is chronic, it is reasonable to continue therapy in responding patients. In general, patients with generalized anxiety disorder usually require at least 8 weeks of treatment to achieve a Hamilton Rating Scale for Anxiety (HAM-A) score of 10 or less, which has been shown to be the score at which specific treatment effects can begin to be distinguished from nonspecific placebo effects. However, available data suggest that some patients may require an extended duration of treatment in order to achieve a HAM-A score of 7–10 or less. In a 32-week, multicenter, relapse-prevention study in outpatients with generalized anxiety disorder and a mean baseline HAM-A score of 26.5, about 34% of patients achieved remission (defined as a HAM-A total score of 7 or less) following 8 weeks of paroxetine therapy compared with 73% of patients following 32 weeks of paroxetine therapy. In addition, patients receiving long-term therapy with the drug relapsed substantially less frequently than those receiving placebo.

Because of the prolonged nature of depressive episodes in patients with generalized anxiety disorder and comorbid depression, some clinicians currently recommend that such patients be treated for at least 12 months to ensure remission of both anxiety and depression. If paroxetine is used for extended periods, dosage should be adjusted so that patients are maintained on the lowest effective dosage, and the need for continued therapy with the drug should be reassessed periodically.

Posttraumatic Stress Disorder For the management of posttraumatic stress disorder (PTSD) in adults, the recommended dosage of paroxetine (administered as paroxetine hydrochloride) is 20 mg daily as conventional tablets or suspension. Although efficacy has been established for dosages ranging from 20–50 mg daily, there is insufficient evidence to suggest a greater benefit with 40 mg daily compared with 20 mg daily. If a dosage increase above 20 mg daily is considered necessary, it should be in increments of 10 mg daily at intervals of at least 1 week.

Some clinicians suggest that an adequate trial period for determining the effectiveness of paroxetine in patients with PTSD is 8 weeks; patients who have not achieved at least a 25% reduction in PTSD symptoms at week 8 generally are unlikely to respond to continued paroxetine therapy and use of alternative agents is recommended in such patients. In addition, although the optimum duration of paroxetine therapy required to prevent recurrence of PTSD has not been established to date, some clinicians recommend up to 24 months of drug therapy in patients who achieve good response (i.e., greater than 75% reduction in PTSD symptoms and response maintained for at least 3 months). Although the efficacy of paroxetine for long-term therapy (i.e., longer than 12 weeks) has not been demonstrated in controlled studies to date, PTSD is a chronic condition for which it is reasonable to continue paroxetine therapy as long as a response is maintained. If paroxetine is used for extended periods,

dosage should be adjusted so that the patient is maintained on the lowest possible effective dosage, and the need for continued therapy with the drug should be reassessed periodically.

Premenstrual Dysphoric Disorder For the treatment of premenstrual dysphoric disorder (previously late luteal phase dysphoric disorder), the recommended initial dosage of paroxetine (administered as paroxetine hydrochloride) is 12.5 mg daily as extended-release tablets. Dosage should be increased at intervals of not less than 1 week. In clinical trials, both the 12.5-mg and 25-mg daily dosages were shown to be effective.

Efficacy of paroxetine for long-term therapy (i.e., longer than 3 menstrual cycles) has not been demonstrated in controlled studies to date. However, women commonly report that symptoms worsen with age until relieved by the onset of menopause. Therefore, the manufacturer of paroxetine hydrochloride states that it is reasonable to consider continuation of therapy for a patient who responds to the drug. Patients should be periodically reassessed to determine the need for continued treatment.

Premature Ejaculation For the treatment of premature ejaculation†, paroxetine has been given in a dosage of 10–40 mg daily to increase ejaculatory latency time. Alternatively, patients have taken paroxetine on an "as needed" basis for the treatment of premature ejaculation using 20-mg doses of the drug 3–4 hours before planned intercourse. However, one study noted more prolonged ejaculatory latency time if patients received paroxetine in a dosage of 10 mg daily for 3 weeks prior to using 20-mg doses of the drug on an as needed basis.

Diabetic Neuropathy In patients with diabetic neuropathy†, paroxetine has been given in a dosage of 40 mg daily to reduce the symptoms associated with the disease.

Chronic Headache In the management of chronic headache†, paroxetine has been given in a dosage of 10–50 mg daily for 3–9 months to reduce the number of headaches per month.

■ **Dosage in Geriatric and Debilitated Patients** In geriatric or debilitated patients, an initial paroxetine dosage of 10 mg daily as conventional tablets or suspension or 12.5 mg daily as extended-release tablets is recommended; if no clinical improvement is apparent, dosage may be titrated up to a maximum of 40 mg daily (for conventional tablets or suspension) or 50 mg (for extended-release tablets).

■ **Dosage in Renal and Hepatic Impairment** In patients with severe renal or hepatic impairment, an initial paroxetine dosage of 10 mg daily as conventional tablets or suspension or 12.5 mg daily as extended-release tablets is recommended. If no clinical improvement is apparent, dosage may be titrated with caution up to a maximum of 40 mg daily (for conventional tablets or suspension) or 50 mg (for extended-release tablets). (See Pharmacokinetics: Elimination and see Cautions: Precautions and Contraindications.)

■ **Treatment of Pregnant Women during the Third Trimester** Because some neonates exposed to paroxetine 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 paroxetine therapy in the third trimester prior to delivery if the drug is administered during pregnancy. (See Cautions: Pregnancy, Fertility, and Lactation.)

Cautions

The adverse effect profile of paroxetine is similar to that of other selective serotonin-reuptake inhibitors (SSRIs; e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline). Paroxetine is commercially available in the US as paroxetine hydrochloride (e.g., Paxil®, Paxil CR®) and as paroxetine mesylate (i.e., Pexeva®). The main clinical studies with paroxetine have been conducted with paroxetine hydrochloride, and the incidences of adverse effects reported in this section are from clinical trials using the hydrochloride salt. Because paroxetine hydrochloride and paroxetine mesylate contain the same active moiety (paroxetine), tolerability is expected to be similar between the 2 different salts. However, direct comparison studies have not been conducted to date, and the possibility that differences in tolerability between paroxetine hydrochloride and paroxetine mesylate may exist should be taken into consideration.

Because paroxetine 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, constipation), cardiovascular effects, drowsiness, and weight gain, is lower in patients receiving paroxetine. However, certain adverse GI (e.g., nausea, anorexia) and nervous system (e.g., somnolence, anxiety, nervousness, insomnia) effects appear to occur more frequently with paroxetine and other SSRIs than with tricyclic antidepressants.

Overall, the adverse effect profile of paroxetine in patients with depression, obsessive-compulsive disorder, panic disorder, social phobia, generalized anxiety disorder, or posttraumatic stress disorder (PTSD) appears to be similar. In controlled studies, the most common adverse effects occurring more frequently in patients receiving paroxetine than in those receiving placebo included nervous system effects such as asthenia, somnolence, dizziness, insomnia, tremor, and nervousness; GI effects such as nausea, decreased appetite, constipation, diarrhea, and dry mouth; impotence, ejaculatory dysfunction (principally ejaculatory delay), and other male genital disorders; female genital disorders (principally anorgasmia or difficulty reaching climax/orgasm); and sweating. The incidence of many of these adverse effects appears to be dose related in patients with depression; however, there was no clear evidence of dose-related adverse events in patients with obsessive-compulsive disorder or social phobia. In addition, there was no clear relationship between the incidence of adverse events and dose except for asthenia, dry mouth, anxiety, decreased libido, tremor, and abnormal ejaculation in the treatment of panic disorder and asthenia, constipation, and abnormal ejaculation in the treatment of generalized anxiety disorder.

Patients receiving paroxetine may develop tolerance to some adverse effects (e.g., nausea, dizziness) with continued therapy (e.g., after 4–6 weeks); however, tolerance is less likely to develop to other adverse effects such as dry mouth, somnolence, and asthenia. During short-term (6 weeks or less) studies, nausea was the most common adverse effect, whereas during long-term studies, headache, sweating, weight gain, and constipation were among the most common. Discontinuance of paroxetine therapy was required in 20% of patients with depression, about 16% of patients with social phobia, about 12% of patients with obsessive-compulsive disorder or PTSD, about 11% of patients with generalized anxiety disorder, and about 9% of patients with panic disorder in clinical trials, principally because of adverse psychiatric (e.g., somnolence, insomnia, agitation, tremor), other nervous system (e.g., dizziness, asthenia), GI (e.g., nausea, vomiting, diarrhea, constipation, dry mouth), or male urogenital (e.g., abnormal ejaculation, impotence) effects or because of sweating.

■ **Nervous System Effects** Somnolence, which appears to be dose related, is among the most common adverse effects of paroxetine, occurring in approximately 23% of depressed patients receiving the drug in short-term controlled clinical trials. Somnolence required discontinuance of therapy in about 2% of patients. Headache occurred in about 18 or 15% of patients receiving paroxetine in short- or long-term controlled clinical trials, respectively. In addition, migraine or vascular headache has been reported in up to 1% or less than 0.1% of paroxetine-treated patients, respectively. Asthenia, which also appears to be dose related, occurred in 15% of depressed patients receiving the drug in short-term controlled clinical trials and required discontinuance of therapy in about 2% of patients.

Dizziness, which appears to be dose related, occurred in about 13% of patients receiving paroxetine in short-term controlled clinical trials. Insomnia occurred in about 13 or 8% of patients receiving the drug in short- or long-term controlled clinical trials, respectively. 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. In clinical trials, less than 2% of patients discontinued paroxetine because of insomnia.

Tremor occurred in about 8%, nervousness or anxiety each in about 5%, paresthesia in about 4%, and agitation in about 2% of patients receiving paroxetine in short-term controlled clinical trials. The incidence of tremor and paresthesia may be dose related. Agitation and tremor each resulted in discontinuance of the drug in about 1% of patients receiving the drug in clinical trials. Drugged feeling or confusion occurred in about 2 or 1% of patients, respectively.

The incidence of seizures during paroxetine therapy appears to be similar to that observed during therapy with most other currently available antidepressants. Seizures, including tonic-clonic (grand mal) seizures, occurred in less than 0.1% of patients receiving paroxetine in clinical trials. (See Cautions: Precautions and Contraindications.) In addition, myoclonus has been reported in about 1% of patients receiving the drug.

Hypomania, mania, manic reaction, and manic-depressive reaction have been reported in approximately 1% of patients receiving paroxetine in short- or long-term controlled clinical trials, which is similar to the incidence reported in patients receiving active control agents (i.e., other antidepressants). The incidence of these adverse effects was 0.3% in unipolar patients receiving placebo. In a subset of patients classified as having bipolar disorder, the incidence of manic episodes was 2.2% in patients receiving paroxetine and 11.6% in patients receiving other antidepressants. (See Cautions: Precautions and Contraindications.) 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 initial findings.

Amnesia, CNS stimulation, impaired concentration; precipitation or worsening of depression, emotional lability, and vertigo each have been reported in at least 1% of patients receiving paroxetine; however, a causal relationship to the drug has not been established. Abnormal thinking, lack of emotion, neurosis, paralysis, paranoid reaction, alcohol abuse, depersonalization, delirium, euphoria, hallucinations, hostility, ataxia, dyskinesia, hyperkinesia, hypesthesia, hypokinesia, and incoordination have been reported in up to 1% of patients receiving the drug, although these adverse effects have not been definitely attributed to paroxetine.

Extrapyramidal reactions associated with paroxetine, which are uncommon, appear to be a class effect of SSRIs and dose related. Reactions occurring *early* during therapy with the drug may be secondary to preexisting parkinsonian

syndrome and/or concomitant therapy. Paroxetine and other SSRIs have been associated with the development of akathisia, which is characterized by an inner sense of restlessness and psychomotor agitation such as an inability to sit or stand still usually associated with subjective distress. Akathisia is most likely to occur within the first few weeks of therapy with these drugs. Other extrapyramidal symptoms reported in patients receiving paroxetine include dystonia, bradykinesia, cogwheel rigidity, hypertonia, oculogyric crisis (associated with concomitant use of pimozide), tremor, and trismus; however, a causal relationship to the drug has not been established.

Adverse nervous system effects reported in less than 0.1% of patients receiving paroxetine include akinesia, antisocial reaction, aphasia, choreoathetosis, circumoral paresthesias, delusions, drug dependence, dysarthria, fasciculations, gait abnormalities, hyperalgesia, hyperreflexia, decreased reflexes, hysteria, meningitis, myelitis, neurulgia, neuropathy, nystagmus, psychotic depression, stupor, and torticollis; these effects have not been definitely attributed to the drug. Fatigue also has been reported. 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 paroxetine, other SSRIs, and selective serotonin- und norepinephrine-reuptake inhibitors. (See Cautions: Precautions and Contraindications, Drug Interactions: Serotonergic Drugs, and Acute Toxicity.)

Status epilepticus has been reported during postmarketing surveillance in patients receiving paroxetine, although a causal relationship to the drug has not been established. Guillain-Barré syndrome has been reported rarely in association with paroxetine; however, a causal relationship to the drug has not been clearly established.

Withdrawal Effects Withdrawal syndrome, manifested as dizziness, blurred vision, sweating, nausea, insomnia, tremor, confusion, lethargy, insomnia, sensory disturbances, anxiety or nervousness, headache, paresthesias, hypomanic-like symptoms (including hyperactivity, decreased need for sleep, irritability, agitation, aggressiveness, volatility, explosive vocal und temper outbursts), and ego-dystonic impulsive behavior (including shoplifting, homicidal impulses, suicidal impulses and gestures) following discontinuance of the drug, also has been reported in less than 0.1% of patients receiving paroxetine. Although manifestations of withdrawal generally have been mild, transient and self-limiting, abrupt discontinuance of the drug should be avoided. Some evidence suggests that the risk of withdrawal effects may be somewhat greater with paroxetine than sertraline; fluoxetine appears to be associated with the fewest withdrawal effects, possibly because of its prolonged elimination half-life. Additional clinical experience is necessary to confirm these findings. (See Chronic Toxicity.)

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. Patients, therefore, should be appropriately monitored and closely observed for clinical worsening, suicidality, and unusual changes in behavior, particularly during initiation of paroxetine therapy (i.e., the first few months) and during periods of dosage adjustments. (See Cautions: Precautions and Contraindications, Cautions: Pediatric Precautions, and Acute Toxicity.)

■ **GI Effects** Like other SSRIs (e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline), paroxetine therapy is associated with a relatively high incidence of GI disturbances, principally nausea, dry mouth, and bowel abnormalities. The most frequent adverse effect associated with paroxetine therapy is nausea, which occurred in about 26% of patients receiving the drug in controlled clinical trials. Nausea generally is mild to moderate in severity and usually subsides after a few weeks of continued therapy with the drug. The incidence of nausea appears to be dose related. In clinical trials, nausea required discontinuance of paroxetine in about 3% of patients and was the most frequent adverse effect requiring discontinuance of the drug. Overall, adverse GI effects, principally nausea, required discontinuance of paroxetine therapy in about 6% of patients receiving the drug in clinical trials. While the mechanism(s) of paroxetine-induced GI effects has not been fully elucidated, they appear to arise at least in part because of increased serotonergic activity in the GI tract (which may result in stimulation of small intestine motility and inhibition of gastric and large intestine motility) and possibly because of the drug's effect on central serotonergic type 3 ($5\text{-}HT_3$) receptors.

Dry mouth occurred in about 18%, constipation in about 14%, diarrhea in about 12%, and decreased appetite in about 6% of patients receiving paroxetine in short-term controlled clinical trials. Other adverse GI effects associated with paroxetine therapy include flatulence, which occurred in 4%, and vomiting, which occurred in about 2% of patients receiving the drug in short-term controlled clinical trials. Vomiting generally is mild to moderate in severity and required discontinuance of the drug in about 1% of patients receiving the drug in controlled trials. Oropharyngeal disorders (principally lump or tightness in the throat), taste perversion, and dyspepsia were reported in about 2% and abdominal pain and increased appetite were reported in at least 1% of patients receiving paroxetine. The incidence of constipation, anorexia, decreased appetite, and dry mouth appear to be dose related.

Although a causal relationship to paroxetine has not been established, bruxism, colitis, dysphagia, eructation, gastroenteritis, gingivitis, glossitis, increased salivation, rectal hemorrhage, and ulcerative stomatitis have been reported in up to 1% of patients receiving the drug. Aphthous stomatitis, stomatitis, esophagitis, duodenitis, enteritis, peptic or gastric ulcer, ileus, peritonitis, hematemesis, bloody diarrhea, intestinal obstruction, fecal impaction or incontinence, melena, bulimia, cholelithiasis, tongue discoloration, tongue edema, mouth ulceration, loss of taste, gingival hemorrhage, salivary gland enlargement, and dental caries have been reported in less than 0.1% of patients receiving paroxetine. In addition, laryngismus has been reported during postmarketing surveillance. However, these adverse effects have not been definitely attributed to the drug.

Epidemiologic case-control and cohort design studies have suggested that SSRIs 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 SSRIs 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 drugs was found to substantially increase the risk of GI bleeding in patients receiving SSRIs in 2 of these studies. Although these studies focused on upper GI bleeding, there is 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, which may be maculopapular or vesiculobullous, has been reported in about 2% of patients receiving paroxetine in short-term controlled clinical trials. Pruritus has been reported in at least 1% of patients receiving the drug. In addition, allergic reactions have been reported in up to 1% of patients in clinical trials, and allergic alveolitis and anaphylaxis have been reported during postmarketing surveillance. However, these adverse effects have not been definitely attributed to paroxetine.

Adverse dermatologic effects reported in up to 1% of patients receiving paroxetine include acne, alopecia, contact dermatitis, dry skin, eczema, herpes simplex, photosensitivity, and urticaria; however, these adverse effects have not been definitely attributed to the drug. Angioedema, erythema nodosum, erythema multiforme, exfoliative dermatitis, fungal dermatitis, furunculosis, herpes zoster, hirsutism, maculopapular rash, seborrhea, skin discoloration, skin hypertrophy, decreased sweating, and skin ulcer have been reported in less than 0.1% of patients receiving the drug. In addition, toxic epidermal necrolysis has been reported rarely.

Sweating occurred in about 11–12% of patients receiving paroxetine in short- or long-term controlled clinical trials and required discontinuance of therapy in approximately 1% of patients. The incidence of sweating appears to be dose related.

■ **Metabolic and Endocrine Effects** Weight gain occurred in at least 1% of patients receiving paroxetine in controlled clinical trials. While clinically important weight loss may occur in some patients, only minimal weight loss (averaging 0.45 kg) generally occurred in up to 17% of patients receiving paroxetine in controlled clinical trials. In addition, while decreased appetite was reported in about 6% of patients receiving paroxetine in short-term clinical trials, the drug, unlike fluoxetine, does not appear to exhibit clinically important anorectic effects.

Ketosis and increased LDH concentrations have also been reported in less than 1% of paroxetine-treated patients, although a causal relationship to the drug has not been established. Thirst has been reported in up to 1% of patients receiving paroxetine, although a causal relationship to the drug has not been established. Adverse effects reported in less than 0.1% of patients receiving the drug include gout, hypercholesterolemia, hyperglycemia, hypoglycemia, and increased creatine kinase (CK, creatine phosphokinase, CPK), gamma globulin and nonprotein nitrogen concentrations; however, these adverse effects also have not been definitely attributed to paroxetine.

Diabetes mellitus, goiter, hyperthyroidism, hypothyroidism, thyroiditis, and symptoms suggestive of prolactinemia and galactorrhea have been reported in less than 0.1% of patients receiving paroxetine; however, these adverse effects have not been definitely attributed to the drug.

■ **Ocular and Otic Effects** Blurred vision, which appears to be dose related, occurred in about 4% of patients receiving paroxetine in controlled clinical trials. Adverse ocular effects reported in up to 1% of patients receiving paroxetine include abnormality of accommodation, conjunctivitis, ocular pain, mydriasis, and keratoconjunctivitis. Although a causal relationship to paroxetine has not been established, amblyopia, blepharitis, diplopia, cataract, conjunctival edema, corneal ulcer, exophthalmos, ocular hemorrhage, glaucoma, photophobia, night blindness, ptosis, retinal hemorrhage, and visual field defect, have been reported in less than 0.1% of patients receiving the drug. Anisocoria and optic neuritis also have been reported in at least one paroxetine-treated patient; these adverse effects have not been definitely attributed to the drug.

Tinnitus occurred in at least 1% of patients receiving paroxetine in controlled clinical trials. Otic pain or otitis media has been reported in up to 1% of patients receiving paroxetine. Deafness, hyperacusis, otitis externa, and parosmia have been reported in less than 0.1% of patients.

■ **Cardiovascular Effects** Paroxetine does not exhibit clinically important anticholinergic activity, and current evidence suggests that paroxetine is less cardiotoxic than most older antidepressant agents (e.g., tricyclic antidepressants, monoamine oxidase inhibitors).

No clinically important changes in vital signs (systolic and diastolic blood

pressure, heart rate) were observed in patients receiving paroxetine in controlled trials. 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 have not been reported during controlled clinical trials in paroxetine-treated patients. However, small but statistically significant QRS widening was reported with paroxetine relative to placebo in one study, and ECG changes occasionally have been reported in healthy individuals and patients receiving the drug. In addition, the relative safety of paroxetine in patients with underlying cardiac disease remains to be more fully elucidated.

Palpitation and vasodilation each have been reported in about 3% of patients receiving paroxetine in short-term controlled clinical trials. Unlike tricyclic antidepressants, paroxetine has been associated with hypotension (e.g., orthostatic) infrequently; in short-term controlled clinical trials, orthostatic hypotension occurred in at least 1% of patients receiving the drug. Chest pain also occurred in about 1–2% of patients in such trials. Hypertension, syncope, and tachycardia also have been reported in at least 1% of patients receiving paroxetine. Bradycardia and generalized peripheral and facial edema have been reported in up to 1% of patients receiving the drug, although a definite causal relationship to paroxetine has not been established. Angina pectoris, myocardial ischemia, myocardial infarction, cerebral ischemia, cerebrovascular accident, pallor, congestive heart failure, low cardiac output, arrhythmia nodal, supraventricular or ventricular extrasystoles, atrial fibrillation, heart block, bundle-branch block, pulmonary embolus, thrombosis, phlebitis, and varicose veins have been reported in less than 0.1% of patients receiving paroxetine; these adverse effects have not been definitely attributed to the drug.

In addition, ventricular fibrillation, ventricular tachycardia (including torsades de pointes), and pulmonary hypertension have been reported during postmarketing surveillance; however, these adverse effects have not been definitely attributed to paroxetine.

■ **Musculoskeletal Effects** Myopathy or myalgia occurred in about 2% of patients receiving paroxetine in short-term controlled clinical trials. In addition, arthralgia has been reported in at least 1% of patients receiving the drug. Myasthenia or back pain was reported in about 1% of patients receiving the drug in such trials. Arthritis or neck pain has been reported in up to 1% of patients receiving paroxetine, although a causal relationship to the drug has not been established. Arthrosis, bursitis, myositis, neck rigidity, osteoporosis, generalized spasm, tenosynovitis, and tetany have been reported in less than 0.1% of patients receiving paroxetine; these adverse effects have not been definitely attributed to the drug.

■ **Hematologic Effects** Anemia, eosinophilia, leukocytosis, leukopenia, ecchymosis, and purpura have been reported in up to 1% of patients receiving paroxetine, although a causal relationship to the drug has not been established. Altered platelet function and abnormal bleeding also have been reported. The manufacturers state that there have been several cases of abnormal bleeding (mostly ecchymosis and purpura) and a case of impaired platelet aggregation in patients receiving paroxetine to date. In one woman, widespread bruising developed on the arms, legs, and hips 15 days after paroxetine therapy was begun; the bruising subsided following discontinuance of the drug. In another female patient, spontaneous bruising of the arms and legs and excessive menstrual blood loss developed 2 weeks after starting paroxetine therapy; addition of ascorbic acid 500 mg daily improved the bleeding after 3 weeks but subsequent discontinuance of ascorbic acid led to a gradual recurrence of these symptoms. Similar reactions have been reported in several patients receiving other SSRIs (e.g., fluoxetine, fluvoxamine, sertraline). Although the precise mechanism for these reactions has not been established, it has been suggested that impaired platelet aggregation caused by platelet serotonin depletion and/or increased capillary fragility may contribute to these cases. (See Cautions: GI Effects and see also Drug Interactions: Drugs Affecting Hemostasis.)

Although a causal relationship to the drug has not been established, hemolytic anemia, impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis), porphyria, and thrombocytopenia have been reported during postmarketing surveillance in patients receiving paroxetine. Abnormal erythrocytes or lymphocytes; prolonged bleeding time; hypochromic anemia, iron-deficiency anemia, microcytic anemia, or normocytic anemia; eosinophilia, leukoeytosis, lymphocytosis, and monocytosis each have been reported in less than 0.1% of patients receiving paroxetine; these adverse effects have not been definitely attributed to the drug.

■ **Respiratory Effects** Respiratory disorders (principally cold symptoms and upper respiratory infections), pharyngitis and other oropharyngeal disorders (sensation of having a lump or tightness in the throat), increased cough, rhinitis, and sinusitis have been reported in at least 1% of patients receiving paroxetine in short-term controlled clinical trials. Yawning occurred in about 4% of patients receiving the drug.

Adverse effects reported in up to 1% of patients receiving paroxetine include asthma, dyspnea, epistaxis, hyperventilation, bronchitis, pneumonia, and respiratory influenza; however, a causal relationship to the drug has not been established. Other adverse respiratory effects reported in less than 0.1% of patients receiving paroxetine include emphysema, hemoptysis, hiccups, lung fibrosis, pulmonary edema, increased sputum production, stridor, and voice alteration; these adverse effects have not been definitely attributed to the drug. Pulmonary alveolitis has been reported rarely.

■ **Renal, Electrolyte, and Genitourinary Effects** ***Sexual Dysfunction*** Like other SSRIs, adverse effects on sexual function have been reported in both men and women receiving paroxetine. 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 paroxetine 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 SSRIs describe some form of sexual dysfunction during treatment and the actual incidence may be even higher. Results of some (but not all) studies in men and women suggest that paroxetine may be associated with a higher incidence of sexual dysfunction than some other currently available SSRIs.

Ejaculatory disturbances (principally ejaculatory delay), which appear to be dose related, are the most common adverse urogenital effects associated with paroxetine in males, reported by the manufacturer as occurring in about 13–28% of male patients receiving the drug compared with 0–2% of patients receiving placebo in controlled clinical studies for the treatment of depression, obsessive-compulsive disorder, panic disorder, social phobia, generalized anxiety disorder, or posttraumatic stress disorder. Abnormal ejaculation was a reason for drug discontinuance in up to about 5% of patients in these controlled clinical studies. However, the adverse effect of ejaculatory delay has been used for therapeutic benefit in the treatment of premature ejaculation. (See Uses: Premature Ejaculation.)

Decreased libido was reported in 6–15% of male patients receiving paroxetine in controlled clinical studies for the treatment of depression, obsessive-compulsive disorder, panic disorder, social phobia, generalized anxiety disorder, or PTSD compared with 0–5% of males receiving placebo. In these studies, impotence was reported in 2–9% of male patients receiving paroxetine compared with 0–3% of males receiving placebo.

In female patients receiving paroxetine in controlled clinical studies for the treatment of depression, obsessive-compulsive disorder, panic disorder, social phobia, generalized anxiety disorder, or PTSD, decreased libido was reported in 0–9% of those receiving paroxetine compared with 0–2% of women receiving placebo. In these studies, orgasmic disturbances were reported in 2–9% of female patients receiving the drug compared with 0–1% of female patients receiving placebo.

Increased libido has been reported in up to 1% of patients receiving paroxetine. Other reported adverse sexual effects include anorgasmia, erectile difficulties, and delayed orgasm. Priapism also has been reported in male patients receiving the drug.

Results of some (but not all) studies in men and women suggest that paroxetine may be associated with a higher incidence of sexual dysfunction than some other currently available SSRIs, including citalopram and sertraline. Since it is difficult to know the precise risk of sexual dysfunction associated with serotonin-reuptake inhibitors, clinicians should routinely inquire about such possible adverse effects in patients receiving these drugs.

Management of sexual dysfunction caused by SSRI 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 SSRIs 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.

Other Renal, Electrolyte, and Genitourinary Effects Treatment with SSRIs, including paroxetine, 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 the SSRI or SNRI was discontinued. Cases with serum sodium concentrations lower than 110 mEq/L have been reported. Hyponatremia has been reported following paroxetine overdosage in a geriatric patient. Hyponatremia and SIADH in patients receiving SSRIs usually develop an average of 2 weeks after initiating therapy (range: 3–120 days). 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 paroxetine 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 paroxetine 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.

Hyperkalemia, hypercalcemia, hyperphosphatemia, dehydration, increased BUN, hypocalcemia, and hypokalemia have been reported in less than 0.1% of patients receiving the drug; however, these adverse effects have not been definitely attributed to paroxetine.

Urinary frequency and urinary disorders (principally difficulty with micturition or urinary hesitancy) have been reported in about 3% of patients receiving paroxetine in short-term controlled clinical trials. Although a definite

causal relationship to paroxetine has not been established, amenorrhea, breast pain, menorrhagia, cystitis, urinary tract infection, dysuria, hematuria, nocturia, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, and vaginitis have been reported in up to 1% of patients receiving the drug. In addition, spontaneous abortion, breast atrophy, vaginal hemorrhage, metrorrhagia, uterine spasm, oliguria, urethritis, salpingitis, urinary casts, renal calculus, renal pain, nephritis, vaginal candidiasis, female lactation, fibrocystic breast, mastitis, and epididymitis have been reported in less than 0.1% of patients receiving paroxetine; however, these adverse effects have not been definitely attributed to paroxetine. Breast enlargement also has been reported in some women receiving chronic therapy with paroxetine or other selective serotonin-reuptake inhibitors. In one study, approximately 40% of patients receiving either selective serotonin-reuptake inhibitors or venlafaxine reported some degree of breast enlargement; most patients with breast enlargement also experienced weight gain, and serum prolactin concentrations were increased in the paroxetine-treated women in this study.

In addition, acute renal failure and eclampsia also have been reported during postmarketing surveillance in patients receiving paroxetine; however, these adverse effects have not been definitely attributed to the drug.

■ **Hepatic Effects** Abnormal liver function test results, including elevations in serum ALT (SGOT) and AST (SGPT) concentrations, have been reported in up to 1% of patients receiving paroxetine, and rarely have been a reason for drug discontinuance. Elevated serum alkaline phosphatase concentrations, bilirubinemia, hepatitis, ascites, and jaundice have been reported in less than 0.1% of patients receiving the drug. In addition, death resulting from liver necrosis and substantially elevated serum aminotransferase (transaminase) concentrations associated with severe liver dysfunction have been reported rarely.

■ **Other Adverse Effects** Fever, influenza-like symptoms, infections, and trauma occurred in at least 2% of patients receiving paroxetine. In addition, chills, influenza, lymphadenopathy, and malaise have been reported in up to 1% of patients receiving the drug. Adrenergic syndrome, cellulitis, lymphedema, moniliasis, pelvic pain, and sepsis have been reported in less than 0.1% of patients receiving the drug, but a definite causal relationship to paroxetine has not been established. Pancreatitis also has been reported during postmarketing surveillance in association with paroxetine; however, a causal relationship to the drug has not been clearly established.

■ **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 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 is currently 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. If a decision is made to discontinue therapy, paroxetine dosage should be tapered as rapidly as is feasible but with recognition of the risks of abrupt discontinuance. (See Dosage and Administration: Dosage.) 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 paroxetine, 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. Manifestations 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 paroxetine should be monitored for the development of serotonin syndrome or NMS-like signs and symptoms.

Concurrent or recent (i.e., within 2 weeks) therapy with MAO inhibitors used for treatment of depression is contraindicated in patients receiving paroxetine. If concurrent therapy with paroxetine 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 paroxetine and serotonin precursors (e.g., tryptophan) is not recommended. If signs and symptoms of serotonin syndrome or NMS develop during therapy, treatment with paroxetine 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 paroxetine in patients with concurrent systemic disease, including cardiovascular disease, hepatic impairment, or renal impairment, is limited, caution should be exercised when paroxetine 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.)

Because paroxetine may cause mydriasis, the drug should be used with caution in patients with angle-closure glaucoma.

Paroxetine should be used with caution in patients with severe renal or hepatic impairment, since increased plasma concentrations of the drug may occur in such patients. (See Pharmacokinetics: Elimination and see Dosage and Administration: Dosage in Renal and Hepatic Impairment.)

Although current evidence suggests that paroxetine is less cardiotoxic than most older antidepressant agents (see Cautions: Cardiovascular Effects), the safety of paroxetine in patients with a recent history of myocardial infarction or unstable cardiovascular disease has not been adequately evaluated to date.

Because of the potential for adverse drug interactions, the manufacturers recommend that patients receiving paroxetine 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 preparations. Although paroxetine has not been shown to potentiate the impairment of mental and motor skills caused by alcohol, the manufacturers recommend that patients be advised to avoid alcohol while receiving the drug.

Paroxetine generally is less sedating than most other currently available antidepressants and does not appear to produce substantial impairment of cognitive or psychomotor function nor to potentiate psychomotor impairment induced by other CNS depressants. However, patients should be cautioned that paroxetine may impair their ability to perform activities requiring mental alertness or physical coordination (e.g., operating machinery, driving a motor vehicle), particularly at dosages of 40 mg or more daily, and to avoid such activities until they experience how the drug affects them. In addition, the possibility that paroxetine may potentiate other (i.e., nonpsychomotor) adverse nervous system effects of CNS depressants should be considered.

The manufacturers recommend that patients receiving paroxetine be advised that while they may notice improvement within 1–4 weeks after starting therapy, they should continue therapy with the drug as directed by their physician.

Seizures have been reported in patients receiving therapeutic dosages of paroxetine. Because of limited experience with paroxetine in patients with a history of seizures, the drug should be used with caution in such patients and should be discontinued if seizures occur.

Activation of mania and hypomania has occurred in patients receiving therapeutic dosages of paroxetine. The drug should be used with caution in patients with a history of mania. (See Cautions: Nervous System Effects.)

Paroxetine and other SSRIs have been associated with the development of akathisia, which is characterized by an inner sense of restlessness and psychomotor agitation such as an inability to sit or stand still usually associated with subjective distress. Akathisia is most likely to occur within the first few weeks of therapy with these drugs.

Treatment with SSRIs, including paroxetine, 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 paroxetine 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 paroxetine 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.)

The manufacturers state that there have been several cases of abnormal bleeding (mostly ecchymosis and purpura) and a case of impaired platelet aggregation in patients receiving paroxetine. (See Cautions: Hematologic Effects.)

Because paroxetine is the active moiety in both paroxetine mesylate conventional tablets (Pexeva®) and commercially available paroxetine hydrochloride preparations (e.g., Paxil®, nonproprietary [generic] preparations), concurrent administration of paroxetine hydrochloride and paroxetine mesylate should be avoided.

Paroxetine is contraindicated in patients concurrently receiving pimozide. (See Drug Interactions: Pimozide.)

Paroxetine is contraindicated in patients concomitantly receiving thioridazine. (See Drugs Metabolized by Cytochrome P-450 [CYP] 2D6 under Drug Interactions: Drugs Undergoing Hepatic Metabolism or Affecting Hepatic Microsomal Enzymes.)

Paroxetine hydrochloride is contraindicated in patients concurrently receiving linezolid. (See Monoamine Oxidase Inhibitors under Drug Interactions: Serotonergic Drugs.)

Paroxetine also is contraindicated in patients hypersensitive to the drug or any ingredient in the formulation.

■ **Pediatric Precautions** Safety and efficacy of paroxetine in children younger than 18 years of age have not been established.

Paroxetine has not demonstrated efficacy in several placebo-controlled trials in 752 children and adolescents with major depressive disorder. Adverse effects reported in at least 2% of the paroxetine-treated pediatric patients in these trials and that occurred at least twice as frequently as in pediatric patients receiving placebo included emotional lability (including self-harm, suicidal thoughts, attempted suicide, crying, and mood fluctuations), hostility, decreased appetite, tremor, sweating, hyperkinesias, and agitation. Upon discontinuance of paroxetine in these pediatric trials following a taper phase regimen, adverse events that occurred in at least 2% of the paroxetine-treated pediatric patients and occurred at least twice as frequently as in pediatric patients receiving placebo included emotional lability (including suicidal ideation, suicide attempt, mood changes, and tearfulness), nervousness, dizziness, nausea, and abdominal pain.

In June 2003, the United Kingdom (UK) regulatory agency warned clinicians to avoid the off-label use of paroxetine for the treatment of depression in children younger than 18 years of age. This action was taken in response to concern about a possible association between selective serotonin-reuptake inhibitors and suicidal behavior, which includes a broad range of symptoms ranging from episodes of self-harm to attempted suicide. Proprietary data examined by the UK regulatory agency showed a slight increase in suicidal behavior among patients who were randomly assigned to selective serotonin-reuptake inhibitor treatment, as compared with subjects who received placebo.

The US Food and Drug Administration (FDA) determined that the available data at that time were not sufficient either to establish or to rule out an association between the use of these drugs and increased suicidal thoughts or actions by pediatric patients. However, following the results of independent classification and analysis of the suicidal events and behaviors observed in controlled studies, 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. 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., paroxetine, bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, 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 the 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 paroxetine discontinued). *Patients should not discontinue use of paroxetine without first consulting their clinician; it is very important that paroxetine not be abruptly discontinued (see Dosage and Administration: Dosage), as withdrawal effects may occur.*

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

■ **Geriatric Precautions** While safety and efficacy of paroxetine in geriatric patients have not been established specifically, 17% of patients (approximately 700) receiving the drug for depression in clinical trials were 65 years of age or older. Although no overall differences in efficacy or the adverse effect profile of paroxetine were observed between geriatric and younger patients and other clinical experience revealed no evidence of age-related differences, pharmacokinetic studies have revealed a decreased clearance of paroxetine in geriatric patients. (See Pharmacokinetics: Elimination.) For this reason, the manufacturers and some clinicians recommend initiating paroxetine therapy in patients 65 years of age or older at a lower dosage than in younger patients. (See Dosage and Administration: Dosage in Geriatric or Debilitated Patients.)

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

In studies comparing paroxetine and various tricyclic antidepressants, including amitriptyline, clomipramine, and doxepin, in geriatric patients, paroxetine was at least as effective and as well tolerated as or better tolerated than tricyclic antidepressants. In addition, serum anticholinergicity of paroxetine was found to be substantially lower than that of nortriptyline in geriatric depressed patients; complaints of dry mouth and tachycardia also occurred more frequently in nortriptyline-treated patients than in those receiving paroxetine. These findings indicate that, at therapeutic plasma concentrations, paroxetine has approximately 20% the anticholinergic potential of nortriptyline in older patients. Overall, paroxetine was less frequently associated with dry mouth, somnolence, constipation, tachycardia, or confusion than tricyclic antidepressants, although certain adverse effects (e.g., nausea, diarrhea, headache) were more common with paroxetine. In geriatric patients with depression, paroxetine appears to be at least as effective as fluoxetine.

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.)

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 selective serotonin-reuptake inhibitors (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 to be at increased risk of falls and appropriate measures should be taken.

■ **Mutagenicity and Carcinogenicity** Paroxetine was not mutagenic in several in vitro tests including the bacterial mutation assay, mouse lymphoma mutation assay, and unscheduled DNA synthesis assay. The drug also was not mutagenic in tests for cytogenetic aberrations in vivo in mouse bone marrow, in vitro in human lymphocytes, and in a dominant lethal test in rats.

Studies to determine the carcinogenic potential of paroxetine were performed in mice receiving oral dosages of 1, 5, and 25 mg/kg daily and in rats receiving dosages of 1, 5, and 20 mg/kg daily for 2 years. In mice, the maximum dosage was up to approximately 2.4 times the maximum human dose for depression, social anxiety disorder, generalized anxiety disorder, and PTSD on a mg/m^2 basis. In rats, the maximum dosage was up to approximately 3.9 times the maximum human dose for depression on a mg/m^2 basis. Because the maximum recommended human dosage for depression, social anxiety disorder, generalized anxiety disorder, and PTSD is slightly lower than that for obses-

sive-compulsive disorder (50 versus 60 mg daily, respectively), the dosages used in these carcinogenicity studies were only about 2 and 3.2 times the maximum recommended human dosage for obsessive-compulsive disorder in mice and rats, respectively. A substantially greater number of male rats in the high-dose group had reticulum cell sarcomas (1/100, 0/50, 0/50, and 4/50 for control, low-, middle-, and high-dose groups, respectively), and a substantially increased linear trend across dose groups was evident for the occurrence of lymphoreticular tumors in male rats. Female rats were not affected. Although there was a dose-related increase in the number of tumors in mice, there was no drug-related increase in the number of mice with tumors. The relationship of these findings to human exposure to paroxetine is not known.

■ **Pregnancy, Fertility, and Lactation** Some neonates exposed to paroxetine 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 occasionally have 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 for 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 paroxetine 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 paroxetine therapy in the third trimester prior to delivery if the drug is administered during pregnancy. (See Dosage: Treatment of Pregnant Women during the Third Trimester in Dosage and Administration.)

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, compared 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. Persistent pulmonary hypertension of the newborn 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 persistent pulmonary hypertension of the newborn and 836 women whose infants were born healthy, the risk for developing persistent pulmonary hypertension of the newborn 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 persistent pulmonary hypertension of the newborn associated with individual SSRIs, and the findings have not been confirmed. Although the risk of persistent pulmonary hypertension of the newborn 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.

Reproduction studies in rats receiving oral paroxetine dosages of 50 mg/kg daily and in rabbits receiving 6 mg/kg daily during organogenesis have been conducted. These dosages correspond to approximately 9.7 and 2.2 times the maximum recommended human dose for depression, social anxiety disorder, generalized anxiety disorder, and PTSD and approximately 8.1 and 1.9 times the maximum recommended human dose for obsessive-compulsive disorder on a mg/m^2 basis in rats and rabbits, respectively. Although these studies have not revealed evidence of teratogenicity, an increase in pup deaths was observed in rats during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation. This effect occurred at a dose of 1 mg/kg daily, which corresponds to 0.19 times the maximum recommended human dose for depression, social anxiety disorder, generalized anxiety disorder, and PTSD and 0.16 times the maximum recommended human dose for obsessive-compulsive disorder on a mg/m^2 basis. The no-effect dose for rat pup mortality has not been determined and the cause of these deaths is not known.

Preliminary analyses from 2 epidemiologic studies have shown that infants born to women exposed to paroxetine during the first trimester of pregnancy had an increased risk of cardiovascular malformations, principally ventricular and atrial septal defects. In one of these studies using Swedish national registry data, infants born to 6896 women exposed to antidepressants during the first trimester of pregnancy were evaluated; 5175 of the infants born to 5123 of these women were exposed to SSRIs, including 822 infants born to 815 women reporting first trimester use of paroxetine. An analysis of these data indicated that infants exposed to paroxetine during early pregnancy had an increased risk of cardiovascular malformations (principally ventricular and atrial septal defects) compared to the entire registry population. The rate of cardiovascular malformations following early pregnancy exposure to paroxetine was approximately 2% compared with 1% in the entire registry population. An analysis of the data from the same paroxetine-exposed infants revealed no increase in the overall risk of congenital malformations.

A separate retrospective cohort epidemiologic study using U.S. United Healthcare data evaluated 5956 infants born to women dispensed paroxetine (822 infants born to 815 women) or other antidepressants during the first trimester of pregnancy showed a trend toward an increased risk for cardiovascular malformations for paroxetine compared with other antidepressants. The prevalence of cardiovascular malformations following first trimester dispensing was 1.5% for paroxetine compared with 1% for other antidepressants; most of the observed cardiovascular malformations (in 9 out of 12 paroxetine-exposed infants) were ventricular septal defects. This study also demonstrated an increased risk of overall major congenital malformations (inclusive of cardiovascular malformations) for paroxetine compared with other antidepressants; the prevalence of all congenital malformations following first trimester exposure was 4% for paroxetine compared with 2% for other antidepressants.

In addition, a smaller study examining pregnancy outcomes in pregnant women exposed to paroxetine or fluoxetine who contacted two teratogen information services in Israel and Italy reported a higher overall rate of congenital malformations in infants exposed to paroxetine in the first trimester compared with infants in the control group with exposures to drugs not known to be teratogenic (5.1% and 2.6%, respectively). A higher rate of cardiovascular anomalies was also observed in the paroxetine group (1.9%) compared with the control group (0.6%) in this study. Similar trends were reported in the fluoxetine group but these did not achieve statistical significance.

Previous epidemiologic studies of pregnancy outcome following first trimester exposure to SSRIs, including paroxetine, had not revealed evidence of an increased risk of major congenital malformations. In a prospective, controlled, multicenter study, maternal use of SSRIs (paroxetine, fluvoxamine, sertraline) 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 addition, an increased risk of major congenital malformations was not observed in infants in 2 small, case-control studies based on prospectively gathered epidemiologic data collected in women exposed to paroxetine during the first trimester of pregnancy. In another small study based on medical records review, the incidence of congenital anomalies reported in infants born to women who were treated with paroxetine and other SSRIs during pregnancy was comparable to that observed in the general population.

Based on the conflicting preliminary findings reported to date from the available studies, the manufacturer of paroxetine hydrochloride states that it is unclear whether a causal relationship exists between these congenital malformations and maternal paroxetine exposure. However, the available data indicates that the individual risk of a mother having an infant with a cardiovascular malformation following first trimester paroxetine exposure is approximately 1/50, compared with an expected rate for such defects of approximately 1/100 infants in the general population. In general, septal defects range from those that are symptomatic and require surgical intervention to those that are asymptomatic and may resolve spontaneously. The final results of recent studies and additional data relating to the use of paroxetine during pregnancy will be analyzed further once they become available to better characterize the risk for congenital malformations with paroxetine.

The manufacturers of paroxetine state that if a woman becomes pregnant while receiving paroxetine, she should be informed of the potential hazard to the fetus. Unless the potential benefits to the mother justify continuing treatment, consideration should be given to either discontinuing paroxetine therapy or switching to another antidepressant. For women who intend to become pregnant or are in their first trimester of pregnancy, the manufacturer of paroxetine hydrochloride states that paroxetine should only be initiated after consideration of the other available treatment options.

The effect of paroxetine on labor and delivery is not known. However, there have been postmarketing reports of premature births in pregnant women who have received paroxetine or other selective serotonin-reuptake inhibitors.

Reproduction studies in rats receiving paroxetine dosages of 15 mg/kg daily, which corresponds to 2.9 times the highest recommended human daily dose for depression, social anxiety disorder, generalized anxiety disorder, and PTSD and 2.4 times the highest recommended human daily dose for obsessive-compulsive disorder on a mg/m^2 basis, revealed evidence of a reduced pregnancy rate. In toxicity studies performed for 2–52 weeks in male rats receiving paroxetine, irreversible lesions in the reproductive tract were reported. These lesions consisted of vacuolation of epididymal tubular epithelium in male rats receiving paroxetine dosages of 50 mg/kg daily (9.8 times the highest recommended human daily dose in major depressive disorder, social anxiety disorder, and generalized anxiety disorder and 8.2 times the highest recommended hu-

man daily dose in obsessive-compulsive disorder and panic disorder on a mg/m^2 basis). In male rats receiving paroxetine dosages of 25 mg/kg daily (4.9 times the highest recommended human daily dose in major depressive disorder, social anxiety disorder, and generalized anxiety disorder and 4.1 times the highest recommended human daily dose in obsessive-compulsive disorder and panic disorder on a mg/m^2 basis), atrophic changes in the seminiferous tubules of the testes with arrested spermatogenesis were observed.

Paroxetine is distributed into human milk. (See Pharmacokinetics: Distribution.) Paroxetine should be used with caution in nursing women, and women should be advised to notify their clinician if they plan to breast-feed.

Drug Interactions

■ **Serotonergic Drugs** Use of selective serotonin-reuptake inhibitors (SSRIs) such as paroxetine concurrently or in close succession with other drugs that affect serotonergic neurotransmission may result in serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions. Manifestations 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. Serotonin syndrome also has been reported when paroxetine was given together with another drug that impairs the hepatic metabolism of paroxetine. 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 several cases of serotonin syndrome.

The combination of SSRIs and MAO inhibitors may result in serotonin syndrome or NMS-like reactions. Such reactions also have been reported in patients receiving SSRIs concomitantly with tryptophan, lithium, dextromethorphan, sumatriptan, dihydroergotamine, or antipsychotics or other dopamine antagonists. In rare cases, 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, fentanyl, 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 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, drugs that affect serotonergic neurotransmission should be used cautiously in combination and such combinations should be 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 agent. 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 paroxetine and any concurrently administered serotonergic or antidopaminergic agents, including antipsychotic agents, should be discontinued immediately and supportive and symptomatic treatment should be initiated.

For further information on serotonin syndrome, including manifestations and treatment, see Serotonin Syndrome under Drug Interactions: Serotonergic Drugs, in Fluoxetine Hydrochloride 28:16.04.20.

Monoamine Oxidase Inhibitors Potentially serious, sometimes fatal serotonin syndrome or NMS-like reactions have been reported in patients receiving SSRIs in combination with an MAO inhibitor. Such reactions also have been reported in patients who recently have discontinued an SSRI and have been started on an MAO inhibitor. While there are no human data to date demonstrating such interactions with paroxetine, limited data from animal studies evaluating the effects of concomitant use of paroxetine and an MAO inhibitor suggest that these drugs may act synergistically to elevate blood pressure and produce behavioral excitation.

Because of the potential risk of serotonin syndrome or NMS-like reactions, concomitant use of paroxetine and MAO inhibitors is contraindicated. At least 2 weeks should elapse between discontinuance of MAO inhibitor therapy and initiation of paroxetine therapy and vice versa.

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. The manufacturer of paroxetine mesylate states that the drug should be used with caution in patients receiving linezolid, and some manufacturers of paroxetine hydrochloride state that concurrent administration with linezolid is contraindicated. 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 (not commercially available in the US), a selective and reversible MAO-A inhibitor, 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 SSRI citalopram or with clomipramine. Pending further experience with such combinations, some clinicians recommend that concurrent therapy with moclobemide and SSRIs be used only with extreme caution and that these drugs 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, has been reported to cause serotonin syndrome when used concomitantly with SSRIs (e.g., 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 SSRI therapy. In addition, the manufacturer of selegiline recommends that at least 2 weeks elapse between discontinuance of selegiline and initiation of SSRI 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 conjunction with SSRI therapy (such as paroxetine) or other serotonergic agents.

Other Selective Serotonin-reuptake Inhibitors and Selective Serotonin- and Norepinephrine-reuptake Inhibitors Concomitant administration of paroxetine 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 paroxetine rarely may result in potentially serious, sometimes fatal serotonin syndrome or NMS-like reactions. If signs and symptoms of serotonin syndrome or NMS occur, treatment with paroxetine and any concurrently administered antidopaminergic or serotonergic agents should be immediately discontinued and supportive and symptomatic treatment initiated. (See Drugs Metabolized by Cytochrome P-450 [CYP] 2D6 under Drug Interactions: Drugs Undergoing Hepatic Metabolism or Affecting Hepatic Microsomal Enzymes and see Drug Interactions: Clozapine and see Drug Interactions: Pimozide.)

Tryptophan and Other Serotonin Precursors As with other serotonin-reuptake inhibitors, an interaction between paroxetine and tryptophan, a serotonin precursor, may occur during concurrent use. Adverse reactions reported to date during concomitant therapy resembled serotonin syndrome and have consisted principally of headache, nausea, sweating, and dizziness. 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 paroxetine.

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 paroxetine.

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., citalopram, escitalopram, fluoxetine, 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 paroxetine 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 SSRI or SNRI therapy should be informed of the possibility of serotonin syndrome or NMS-like reactions and advised to immediately seek medical attention if they experience signs or symptoms of these syndromes.

Fentanyl Because cases of serotonin syndrome have been reported in patients concurrently receiving fentanyl and SSRIs, including paroxetine, clinicians should be aware of this potential interaction and monitor patients receiving these drugs in combination for possible signs and symptoms of serotonin syndrome.

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

■ **Drugs Undergoing Hepatic Metabolism or Affecting Hepatic Microsomal Enzymes** The metabolism and pharmacokinetics of paroxetine may be affected by a number of drugs that induce (e.g., phenobarbital) or inhibit (e.g., cimetidine, tricyclic antidepressants), drug-metabolizing enzymes.

Drugs Metabolized by Cytochrome P-450 (CYP) 2D6 Paroxetine, like many other antidepressants (e.g., other SSRIs, 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, paroxetine inhibits the activity of CYP2D6 and potentially may increase plasma concentrations of concomitantly administered drugs that also are metabolized by this isoenzyme. Although similar interactions are possible with other SSRIs, 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. In most patients (greater than 90%), the CYP2D6 isoenzyme is saturated early during paroxetine therapy. At steady state when the CYP2D6 pathway is essentially saturated, paroxetine is cleared by alternative cytochrome P-450 isoenzymes which, unlike CYP2D6, show no evidence of saturation.

Concomitant administration of paroxetine with risperidone, a CYP2D6 substrate, was evaluated in one study. In 10 patients with schizophrenia or schizoaffective disorder stabilized on risperidone therapy (4–8 mg daily) who also received paroxetine (20 mg daily) for 4 weeks, mean plasma concentrations of risperidone increased approximately fourfold, mean plasma concentrations of 9-hydroxyrisperidone (the active metabolite of risperidone) decreased by approximately 10%, and concentrations of the active moiety (the sum of the plasma concentrations of risperidone and 9-hydroxyrisperidone) increased by approximately 1.4 fold. These drugs were generally well tolerated when administered concurrently, with the exception of one patient who developed parkinsonian symptoms. Although the precise mechanism for this interaction remains to be fully established, it appears that paroxetine may impair the elimination of risperidone, principally by inhibiting CYP2D6-mediated 9-hydroxylation and, to a lesser extent, by simultaneously affecting the further metabolism of 9-hydroxyrisperidone or other pathways of risperidone biotransformation. Pending further accumulation of data, some clinicians recommend careful clinical observation and possible monitoring of plasma risperidone concentrations when paroxetine and risperidone are given concurrently. Consideration also should be given to using a lower initial dosage of paroxetine (10–20 mg daily) since the inhibitory effect of paroxetine on CYP2D6 is concentration dependent.

The steady-state pharmacokinetics of atomoxetine were altered when the drug was administered at a dosage of 20 mg twice daily concurrently with paroxetine 20 mg daily in healthy adults who were extensive CYP2D6 metabolizers. Concurrent administration with paroxetine increased maximum plasma atomoxetine concentrations threefold to fourfold and steady-state area under the plasma concentration curve was increased sixfold to eightfold compared with administration of atomoxetine alone. The pharmacokinetics of paroxetine were not altered. The manufacturers of paroxetine and atomoxetine recommend that atomoxetine be administered at a reduced dosage when the drugs are administered concurrently.

Concomitant use of paroxetine 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), risperidone, and some phenothiazines (e.g., perphenazine, thioridazine).

In one study, chronic dosing of paroxetine (20 mg once daily) under steady-state conditions increased single-dose desipramine (100 mg) peak plasma concentrations, AUC, and elimination half-life by an average of approximately two-, five-, and threefold, respectively. (See Drug Interactions: Tricyclic and Other Antidepressants.)

Administration of perphenazine in patients receiving paroxetine 20 mg daily for 10 days increased plasma concentrations and the adverse CNS effects of perphenazine. This interaction appears to result principally from paroxetine-induced inhibition of the CYP2D6 isoenzyme. Pending further experience with combined therapy, a reduction in perphenazine dosage may be necessary to prevent adverse CNS effects in patients receiving paroxetine.

For information on a potential interaction between paroxetine and metoprolol, see Drug Interactions: β-Adrenergic Blocking Agents.

Concurrent use of paroxetine with other drugs metabolized by CYP2D6, including certain antidepressants (e.g., nortriptyline, amitriptyline, imipramine, desipramine, fluoxetine), phenothiazines (e.g., perphenazine), and class IC antiarrhythmics, or drugs that inhibit CYP2D6 should be approached with caution. Because concomitant use of paroxetine and thioridazine may result in increased plasma concentrations of the phenothiazine and increase the risk of serious, potentially fatal, adverse cardiac effects (e.g., ventricular arrhythmias, sudden death), thioridazine should not be used concomitantly with paroxetine (see Cautions: Precautions and Contraindications). The manufacturer of paroxetine states that concurrent use of a drug metabolized by CYP2D6 may necessitate the administration of dosages of the other drugs that are lower than those usually prescribed. Furthermore, whenever paroxetine therapy is discontinued (and plasma concentrations of the drug are decreased) during concurrent therapy with another drug metabolized by CYP2D6, an increased dosage of the concurrently administered drug may be necessary.

Drugs Metabolized by Cytochrome P-450 (CYP) 3A4 Although paroxetine 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 an in vivo drug interaction study, concomitant administration of paroxetine and the cytochrome P-450 3A4 substrate, terfenadine (no longer commercially available in the US), had no effect on the pharmacokinetics of terfenadine. In another in vivo interaction study, ketoconazole, which is a potent inhibitor of CYP3A4 activity, was found to be at least 100 times more potent than paroxetine as an inhibitor of the metabolism of several substrates for this enzyme, including terfenadine, astemizole (no longer commercially available in the US), cisapride, triazolam, and cyclosporine. Based on the assumption that the relationship between paroxetine's inhibitory activity in vitro and its lack of effect on terfenadine's clearance in vivo predicts its effect on other CYP3A4 substrates, the manufacturer states that these data suggest that the extent of paroxetine's inhibition of CYP3A4 activity is unlikely to be of clinical importance.

Drugs Metabolized by Other Cytochrome P-450 Isoenzymes Unlike fluvoxamine, in vitro data indicate that paroxetine does not substantially inhibit the CYP1A2 isoenzyme, which is responsible for the metabolism of caffeine and numerous other substances.

Cimetidine Cimetidine is known to inhibit many cytochrome P-450 oxidative enzymes and can affect the pharmacokinetics of paroxetine. In a study in which oral paroxetine (30 mg once daily) was given for 4 weeks, steady-state plasma paroxetine concentrations were increased by approximately 50% during concomitant use of oral cimetidine (300 mg 3 times daily) for the final week. The possible effects of paroxetine on the pharmacokinetics of cimetidine have not been studied. If paroxetine and cimetidine are used concurrently, dosage adjustment of paroxetine after the initial 20-mg dose should be guided by clinical effect.

Phenobarbital Phenobarbital is known to induce many cytochrome P-450 oxidative enzymes and can affect the pharmacokinetics of paroxetine. Following administration of a single 30-mg oral dose of paroxetine in individuals who had achieved steady-state serum phenobarbital concentrations (100 mg of phenobarbital daily for 14 days), the AUC and elimination half-life of paroxetine were reduced by an average of 25 and 38%, respectively, compared with administration of paroxetine alone. The influence of paroxetine on the pharmacokinetics of phenobarbital has not been studied to date. Since paroxetine exhibits nonlinear pharmacokinetics, the results of this study may not apply in situations in which both drugs are administered chronically. The manufacturer of paroxetine states that initial dosage adjustment of paroxetine is not considered necessary in patients receiving phenobarbital, and any subsequent dosage adjustment should be guided by clinical effect.

■ **Tricyclic and Other Antidepressants** The extent to which SSRI interactions with tricyclic antidepressants may pose clinical problems depends on the degree of inhibition and the pharmacokinetics of the serotonin-reuptake inhibitor involved. In one study, daily dosing of paroxetine (20 mg once daily) under steady-state conditions increased single-dose desipramine (100 mg) peak plasma concentrations, AUC, and elimination half-life by an average of approximately 2-, 5-, and 3-fold, respectively. This interaction appears to result from paroxetine-induced inhibition of CYP2D6. Thus, the manufacturers recommend that caution be exercised during concomitant use of tricyclics with

paroxetine since paroxetine may inhibit the metabolism of the tricyclic antidepressant. In addition, plasma tricyclic concentrations may need to be monitored and the dosage of the tricyclic reduced during concomitant use. (See Drugs Metabolized by Cytochrome P-450 [CYP] 2D6 under Drug Interactions: Drugs Undergoing Hepatic Metabolism or Affecting Hepatic Microsomal Enzymes.)

Clinical experience regarding the optimal timing of switching from other antidepressants to paroxetine therapy is limited. Therefore, care and prudent medical judgment should be exercised when switching from other antidepressants to paroxetine. (See Dosage and Administration: Dosage and see also Drug Interactions: Serotonergic Drugs.)

■ **Lithium** In a multiple-dose study, there was no evidence of a pharmacokinetic or pharmacodynamic interaction between lithium and paroxetine. However, because there is little clinical experience with combined therapy and because lithium may enhance the serotonergic effects of paroxetine, potentially resulting in serotonin syndrome or NMS-like reactions, concurrent use of lithium and paroxetine should be undertaken with caution. (See Drug Interactions: Serotonergic Drugs.)

■ **Protein-bound Drugs** Because paroxetine 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 or digitoxin (no longer commercially available in the US). In vitro studies to date have shown that paroxetine has no effect on the protein binding of 2 highly protein-bound drugs, phenytoin and warfarin; however, preliminary data suggest that there may be a pharmacodynamic interaction between paroxetine and warfarin. Pending further accumulation of data, patients receiving paroxetine concomitantly with any highly protein-bound drug should be observed for potential adverse effects associated with combined therapy. (See Warfarin under Drug Interactions: Drugs Affecting Hemostasis.)

■ **Drugs Affecting Hemostasis** ***Warfarin*** In vitro data have shown that paroxetine has no effect on the protein binding of warfarin. However, preliminary data suggest that there may be a pharmacodynamic interaction between these drugs that causes an increased bleeding diathesis while the prothrombin time remains unchanged. An increase in mild but clinically important bleeding was observed in healthy individuals receiving paroxetine and warfarin for several days. Because of limited clinical experience to date, the concurrent use of paroxetine and warfarin should be undertaken with caution. (See Drug Interactions: Protein-bound Drugs.)

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 drugs 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 hemostasis, and selective serotonin-reuptake inhibitors decrease serotonin uptake from the blood by platelets, thereby decreasing the amount of serotonin in platelets. Patients receiving paroxetine should be cautioned about the concomitant use of drugs that interfere with hemostasis, including aspirin and other nonsteroidal anti-inflammatory agents.

■ **Digoxin** The steady-state pharmacokinetics of paroxetine were not altered when administered concurrently with digoxin at steady state. The mean AUC of digoxin at steady state decreased by 15% in the presence of paroxetine. Because there is limited clinical experience to date, the manufacturers state that combined therapy with paroxetine and digoxin should be undertaken with caution.

■ **Alcohol** Paroxetine has not been shown to potentiate the impairment of mental and motor skills caused 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 paroxetine and alcohol within the CNS. The manufacturers recommend that patients be advised to avoid alcohol while receiving paroxetine.

■ **Benzodiazepines** Under steady-state conditions, diazepam does not appear to affect the pharmacokinetics of paroxetine. The effect of paroxetine on diazepam pharmacokinetics has not been evaluated to date. Paroxetine does not appear to potentiate the CNS depressant effects of diazepam, lorazepam, or oxazepam.

■ **Clozapine** Concomitant use of SSRIs such as paroxetine in patients receiving clozapine can increase plasma concentrations of the antipsychotic agent. In a study in schizophrenic patients receiving clozapine under steady-state conditions, initiation of paroxetine therapy resulted in only minor changes in plasma concentrations of clozapine and its metabolites; however, initiation of fluvoxamine therapy resulted in increases that were threefold compared with baseline. In other published reports, concomitant use of clozapine and SSRIs (fluvoxamine, paroxetine, sertraline) resulted in modest increases (less than twofold) in clozapine and metabolite concentrations. The manufacturer of clozapine states that caution should be exercised and patients closely monitored if clozapine is used in patients receiving SSRIs, and a reduction in clozapine dosage should be considered. (See Antipsychotic Agents and Other Dopamine Antagonists under Drug Interactions: Serotonergic Drugs.)

■ **Pimozide** In a controlled study, concurrent administration of a single 2-mg dose of pimozide in healthy individuals receiving paroxetine (dosage titrated up to 60 mg daily) was associated with mean increases in the AUC and peak plasma concentrations of pimozide of 151 and 62%, respectively, compared with pimozide given alone. Because of the narrow therapeutic index of pimozide and its known ability to prolong the QT interval, concurrent administration of paroxetine and pimozide is contraindicated. (See Antipsychotic Agents and Other Dopamine Antagonists under Drug Interactions: Serotonergic Drugs.)

■ **Electroconvulsive Therapy** The effects of paroxetine in conjunction with electroconvulsive therapy (ECT) have not been systematically evaluated to date in clinical studies.

■ **β-Adrenergic Blocking Agents** In a study in which propranolol (80 mg twice daily) was given orally for 18 days, the steady-state plasma concentrations of propranolol were not affected when paroxetine (30 mg once daily) was used concurrently during the last 10 days. The manufacturers state that the effect(s) of propranolol on paroxetine have not been systematically evaluated.

Severe hypotension has been reported following the initiation of paroxetine therapy in a patient who had been receiving chronic metoprolol therapy. Metoprolol is metabolized by the CYP2D6 isoenzyme and paroxetine is known to potently inhibit this enzyme. Pending further experience with this combination, caution should be exercised when paroxetine and metoprolol are used concomitantly.

■ **Phenytoin** In vitro studies to date have shown that paroxetine has no effect on the protein binding of phenytoin. When a single 30-mg oral dose of paroxetine was administered in individuals in whom steady-state plasma phenytoin concentrations (300 mg once daily for 14 days) had been achieved, the AUC and elimination half-life of paroxetine were reduced by an average of 50 and 35%, respectively, compared with paroxetine administered alone. In another study, when a single 300-mg oral dose of phenytoin was administered to individuals in whom steady-state plasma paroxetine concentrations (30 mg once daily for 14 days) had been achieved, the AUC of phenytoin was slightly reduced (by an average of 12%) compared with phenytoin administered alone. However, because both paroxetine and phenytoin exhibit nonlinear pharmacokinetics, these studies may not address the case in which both drugs are given chronically. Elevated plasma phenytoin concentration has been reported in one patient 4 weeks after concurrent therapy with paroxetine and phenytoin. Pending further experience, the manufacturers state that initial dosage adjustments are not considered necessary during concurrent use and that any subsequent adjustments in dosage should be guided by clinical effects.

■ **Theophylline** Elevated serum theophylline concentrations associated with paroxetine therapy have been reported. Although this interaction has not been systematically studied to date, the manufacturers recommend that serum concentrations of theophylline be monitored during concomitant paroxetine therapy.

■ **Procyclidine** Multiple oral doses of paroxetine (30 mg once daily) have increased the steady-state AUC, peak concentrations, and trough concentrations of procyclidine (5 mg once daily) by 35, 37, and 67%, respectively, compared with procyclidine alone at steady state. If anticholinergic effects are observed in patients receiving concurrent therapy with these drugs, the manufacturers recommend that the procyclidine dosage be reduced.

■ **Antacids** Limited data indicate that antacids do not substantially interfere with the absorption of paroxetine following oral administration.

■ **Fosamprenavir and Ritonavir** Concurrent administration of fosamprenavir and ritonavir with paroxetine substantially decreased plasma paroxetine concentrations. The manufacturers recommend that dosage adjustments in patients receiving these drugs concurrently be guided by clinical effect (tolerability and efficacy).

Acute Toxicity

Limited information is available on the acute toxicity of paroxetine.

■ **Pathogenesis** The acute lethal dose of paroxetine in humans is not known.

■ **Manifestations** In general, overdosage of paroxetine may be expected to produce effects that are extensions of the drug's pharmacologic and adverse effects. Overdosages of paroxetine may result in somnolence, coma, nausea, tremor, tachycardia, confusion, vomiting, and dizziness. Other signs and symptoms observed in patients who received overdosages of paroxetine alone or in combination with other substances include mydriasis, convulsions (including status epilepticus), ventricular arrhythmias (including torsades de pointes), hypertension, aggressive reactions, syncope, hypotension, stupor, bradycardia, dystonia, rhabdomyolysis, symptoms of hepatic dysfunction (including hepatic failure, hepatic necrosis, jaundice, hepatitis, and hepatic steatosis), serotonin syndrome, manic reactions, myoclonus, acute renal failure, and urinary retention.

The manufacturers state that, since introduction of paroxetine in the US, 48 fatalities involving overdosages of paroxetine alone or in combination with other substances have been reported worldwide. In 145 nonfatal overdosages, most patients recovered without sequelae. One patient recovered after ingesting 2 g of paroxetine (33 times the maximum recommended daily dosage).

In a geriatric woman who ingested 360 mg of paroxetine, the initial sign

of overdosage was excessive vomiting; hyponatremia developed 5 days later and was associated with somnolence, confusion, muscle spasms, dehydration, and slow reflexes. Ecchymoses and myxedema also were observed in this patient.

In 28 children aged 10.5 months to 17 years of age who ingested an overdosage of paroxetine alone, less sedation and fewer adverse cardiovascular effects were observed when compared with tricyclic antidepressant overdosage. In children 5 years of age and younger, ingestions of 120 mg or less of paroxetine were treated with GI evacuation and minimal supportive care with favorable outcomes. In children 12 years of age and younger who ingested 600–800 mg of the drug alone, most of the patients remained asymptomatic.

■ **Treatment** Because fatalities and severe toxicity have been reported following paroxetine overdosage, particularly in large overdosage and when taken with other drugs or alcohol, some clinicians recommend that any overdosage involving the drug be managed aggressively. Because suicidal ingestion often involves more than one drug, clinicians treating paroxetine overdosage should be alert to possible manifestations caused by drugs other than paroxetine. The manufacturers specifically caution about patients who are currently receiving or recently have taken paroxetine who might ingest either accidentally or intentionally excessive quantities of a tricyclic antidepressant. In such cases, accumulation of both the tricyclic and its active metabolite may increase the possibility of clinically important sequelae and lengthen the time needed for close medical supervision. (See Drug Interactions: Tricyclic and Other Antidepressants.)

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 paroxetine 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 paroxetine overdosage generally involves symptomatic and supportive care. A patent airway should be established and maintained, and adequate oxygenation and ventilation should be ensured. An ECG should be taken and monitoring of cardiac function should be instituted if there is any evidence of abnormality. Frequent vital sign monitoring and close observation of the patient is necessary. There is no specific antidote for paroxetine intoxication.

Following recent (i.e., within 4 hours) ingestion of a potentially toxic amount of paroxetine 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) may be as or more effective than induction of emesis or gastric lavage, its use has been recommended either in the initial management of paroxetine overdosage or following induction of emesis or gastric lavage in patients who have ingested a potentially toxic quantity of the drug. In the past, the manufacturer of paroxetine hydrochloride suggested that 20–30 g of activated charcoal be administered following gastric evacuation every 4–6 hours during the first 24–48 hours following ingestion.

Because of the large volume of distribution of paroxetine and its principal metabolite, peritoneal dialysis, forced diuresis, hemoperfusion, and/or exchange transfusion are unlikely to be effective in removing substantial amounts of paroxetine from the body.

Clinicians should consult a poison control center for additional information on the management of paroxetine overdosage.

Chronic Toxicity

Paroxetine has not been studied systematically in animals or humans to determine whether therapy with the drug is associated with abuse, tolerance, or physical dependence.

The clinical trials conducted with paroxetine did not reveal any tendency for drug-seeking behavior. However, withdrawal syndrome, manifested as dizziness, sensory disturbances, blurred vision, sweating, nausea, insomnia, tremor, confusion, lethargy, insomnia, nervousness or anxiety, headache, paresthesias, hypermanic-like symptoms (including hyperactivity, decreased need for sleep, irritability, agitation, aggressiveness, volatility, explosive vocal and temper outbursts), and egodystonic impulsive behavior (including shoplifting, homicidal impulses, suicidal impulses and gestures), has been reported following discontinuance of paroxetine therapy. Such reactions may emerge after abrupt discontinuance or intermittent noncompliance with therapy and, less frequently, when the dosage is reduced. Although manifestations of withdrawal generally have been mild, transient, and self-limiting, patients should be carefully monitored when paroxetine therapy is discontinued and abrupt discontinuance of the drug should be avoided. (See Dosage and Administration: Dosage:)

Some evidence suggests that the risk of withdrawal effects may be somewhat greater with paroxetine than with sertraline; fluoxetine appears to associated with the fewest withdrawal effects, possibly due at least in part to its prolonged elimination half-life. Additional clinical experience is necessary to confirm these findings.

Experience with paroxetine and with other serotonin-reuptake inhibitors suggests that a withdrawal syndrome may occur within several days following abrupt discontinuance of these drugs. The most commonly observed manifestations are those that resemble influenza, such as fatigue, GI complaints (e.g., nausea), dizziness or lightheadedness, tremor, anxiety, insomnia, chills, sweating, and incoordination. Other reported manifestations include memory impairment, paresthesia, shock-like sensations, headache, palpitations, agitation, and aggression. Although the mechanism(s) for such withdrawal reactions is not fully understood, it has been suggested that they may be caused by a sudden decrease in serotonin availability at the synapse or cholinergic rebound; other neurotransmitters (e.g., dopamine, norepinephrine, GABA) also may be involved. These manifestations may in some cases be mistaken for physical illness or relapse into depression, but generally appear to be self-limiting and improve over one to several weeks. Manifestations of withdrawal also may be improved by restarting therapy with paroxetine or another antidepressant with a similar pharmacologic profile. Paroxetine therapy should be discontinued gradually (e.g., over a period of several weeks) to prevent the possible development of withdrawal reactions.

As with other CNS-active drugs, clinicians should carefully evaluate patients for a history of substance abuse prior to initiating paroxetine therapy. If paroxetine 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).

Pharmacology

The pharmacology of paroxetine is complex and in many ways resembles that of other antidepressant agents, particularly those agents (e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline, clomipramine, trazodone) that predominantly potentiate the pharmacologic effects of serotonin (5-HT). Like other selective serotonin-reuptake inhibitors (SSRIs), paroxetine 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 paroxetine is unclear, but the drug has been shown to selectively inhibit the reuptake of serotonin at the presynaptic neuronal membrane. Paroxetine-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 SSRIs (e.g., citalopram, fluoxetine, fluvoxamine, sertraline), paroxetine appears to have only very weak effects on the reuptake of norepinephrine or dopamine and does not exhibit clinically important anticholinergic, antihistaminic, or adrenergic (α_1, α_2, β) 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., serotonin, norepinephrine) 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 mainly 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 are commonly referred to as "down regulation". However, in an animal study, long-term administration of paroxetine was not shown to downregulate noradrenergic receptors in the CNS as has been observed with many other clinically effective antidepressants. In addition, some antidepressants (e.g., amitriptyline) reportedly decrease the number of serotonergic (5-HT) binding sites following chronic administration.

The precise mechanism of action that is responsible for the efficacy of paroxetine in the treatment of obsessive-compulsive disorder is unclear. However, because of the potency of clomipramine and SSRIs (e.g., citalopram, fluoxetine, fluvoxamine, sertraline) in inhibiting serotonin reuptake and their efficacy in the treatment of obsessive-compulsive disorder, a serotonin 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 paroxetine 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.

The exact mechanism of action of paroxetine in panic disorder, social phobia, or generalized anxiety disorder has not been fully elucidated but appears to involve inhibition of reuptake of serotonin at the presynaptic membrane.

Animal data indicate that serotonergic mechanisms also appear to be involved at least in part in a number of other pharmacologic effects associated with SSRIs, such as decreased food intake and altered food selection as well as decreased alcohol intake.

Serotonergic Effects Paroxetine is a highly selective inhibitor of serotonin reuptake at the presynaptic neuronal membrane. Paroxetine-induced inhibition of serotonin reuptake causes increased synaptic concentrations of the neurotransmitter, resulting in numerous functional changes associated with enhanced serotonergic neurotransmission.

Data from in vitro studies suggest that paroxetine is more potent than citalopram, clomipramine, fluoxetine, fluvoxamine, and sertraline as a serotonin-reuptake inhibitor. Unlike some other serotonin-reuptake inhibitors, the metabolites of paroxetine have been shown to possess no more than 2% of the potency

of the parent compound as inhibitors of serotonin reuptake; therefore, they are unlikely to contribute to the clinical activity of the drug.

At therapeutic dosages in humans, paroxetine has been shown to inhibit the reuptake of serotonin into platelets.

Effects on Other Neurotransmitters Like other serotonin-reuptake inhibitors, paroxetine has been shown to have little or no activity in inhibiting the reuptake of norepinephrine. Paroxetine appears to have only very weak activity on neuronal reuptake of dopamine. In addition, paroxetine does not inhibit monoamine oxidase (MAO).

Unlike tricyclic and some other antidepressants, paroxetine does not exhibit clinically important anticholinergic, α- or β-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-adrenergic receptors (e.g., orthostatic hypotension), and histamine H_1- and H_2-receptors (e.g., sedation) is lower in paroxetine-treated patients than tricyclic-treated patients. In vitro studies have demonstrated that paroxetine does not possess clinically important affinity for α_1- or α_2-adrenergic, β- adrenergic, histaminergic (H_1-, GABA, benzodiazepine, or dopamine D_2-receptors.

Although paroxetine has demonstrated weak affinity for muscarinic cholinergic receptors in vitro and has caused mydriasis in vivo, these effects generally occurred only at dosages greatly exceeding those required for increasing serotonergic activity in the CNS. Limited data indicate that mydriasis may also be serotonergically mediated. In addition, serum anticholinergicity of paroxetine was found to be substantially lower than that of nortriptyline in depressed geriatric patients in one study; complaints of dry mouth and tachycardia also occurred more frequently in the nortriptyline-treated patients than in those treated with paroxetine. These findings indicate that, at therapeutic plasma concentrations, paroxetine has approximately 20% the anticholinergic potential of nortriptyline in older patients. Therefore, it appears unlikely that paroxetine will produce adverse anticholinergic events when given in the usual recommended dosage.

Effects on Sleep Like tricyclic and most other antidepressants, paroxetine suppresses rapid eye movement (REM) sleep. Some evidence suggests that the drug may suppress REM sleep in a dose-dependent manner. 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. While the precise mechanism has not been fully elucidated, results of animal studies indicate that paroxetine's effects on REM sleep may be serotonergically mediated.

In some studies, paroxetine prolonged REM latency, increased awakenings, increased stage 1 sleep, and/or reduced actual sleep time and sleep efficiency. In one study, administration of single, 40-mg doses of paroxetine in the morning increased sleep latency; however, the drug did not affect sleep latency when given at bedtime. In addition, sleep maintenance parameters (such as nocturnal wake time, total sleep time, and sleep efficiency) deteriorated in a dose-dependent manner both when a single dose of the drug was given in the morning and when given as a single 30-mg dose at bedtime. Overall, the changes in sleep observed with paroxetine are relatively small and are unlikely to be of clinical importance during prolonged administration. In addition, the changes noted with paroxetine are similar to those reported with other SSRIs and suggest an alerting effect on sleep that has not been shown to adversely affect sleep quality.

Effects on EEG Limited data currently are available regarding the effects of paroxetine on the EEG. In animals, EEG studies have revealed an activating effect associated with slight behavioral arousal and weak locomotor stimulation at dosages higher than those required to inhibit serotonin reuptake in the CNS. EEG changes in healthy individuals receiving single, 70-mg oral doses of paroxetine revealed a decrease in delta and theta activity and an increase in beta activity; these changes were still evident after 72 hours. Overall, available data in humans suggest that paroxetine generally does not produce clinically relevant changes on the EEG.

Effects on Psychomotor Function Paroxetine generally does not appear to cause clinically important sedation and generally does not interfere with psychomotor performance. Controlled studies in healthy young individuals and in patients with major depression did not demonstrate any adverse effects on psychomotor performance in those receiving 20-mg doses of the drug. No adverse effects on psychomotor performance or cognitive function were observed in healthy men older than 60 years of age who received single and repeated doses of paroxetine 20 mg in a controlled study; in some tests (e.g., critical flicker fusion thresholds), paroxetine improved information processing ability. In a controlled study evaluating the effects of paroxetine (20 or 40 mg administered daily for 8 days) on psychomotor performance and car driving in healthy males, the 20-mg dosage was found to have no effect while the 40-mg dosage was not found to affect road tracking but slightly impaired performance in some psychomotor tests in a persistent manner. Further study is needed to clarify whether paroxetine may adversely affect psychomotor performance at dosages of 40 mg daily or more.

■ **Cardiovascular Effects** No clinically important changes in vital signs (systolic and diastolic blood pressure, heart rate, temperature) were observed in patients receiving paroxetine in controlled trials. Paroxetine also appears to have little effect on the ECG. In controlled studies, paroxetine did not produce clinically important changes in heart rate, cardiac conduction, or other ECG parameters in patients receiving the drug. In depressed patients with stable ischemic heart disease, paroxetine did not substantially affect blood pressure or conduction intervals and did not produce sustained effects on heart rate, heart rhythm, or indexes of heart rate variability. However, a small but statistically significant QRS widening relative to placebo was reported in one study, and ECG changes occasionally have been reported in healthy individuals and patients receiving the drug. In addition, the relative safety of paroxetine in patients with underlying cardiac disease, particularly those with severe cardiovascular disease and immediately following a myocardial infarction, remains to be more fully elucidated.

Paroxetine did not demonstrate any substantial change in cardiovascular autonomic function tests (such as heart rate variability) in a limited number of depressed patients receiving the drug for 14 days. On the other hand, paroxetine has been shown to increase heart rate variability in a limited number of patients with panic disorder, a condition associated with decreased heart rate variability and consequently an increased risk of serious cardiovascular problems including sudden cardiac death.

■ **Effects on Appetite and Body Weight** Paroxetine appears to possess some anorexigenic activity, although to a lesser degree than certain other serotonergic agents (e.g., fenfluramine [no longer commercially available in the US], fluoxetine, sertraline, zimelidine). Limited data from animal studies suggest that fenfluramine is the most effective inhibitor of food intake followed by fluoxetine, then sertraline, and then paroxetine. Although the precise mechanism has not been clearly established, results from animal studies indicate that the appetite-inhibiting action of these antidepressants may result at least in part from serotonin-reuptake blockade and enhancement of serotonin release thereby increasing serotonin availability at the neuronal synapse.

While clinically important weight loss may occur in some patients receiving paroxetine, only minimal weight loss (averaging 0.45 kg) generally occurred in patients receiving the drug in controlled clinical trials. In addition, while decreased appetite was reported in about 6% of patients receiving paroxetine in short-term clinical trials, the drug, unlike fluoxetine, does not appear to exhibit clinically important anorectic effects. (See Cautions: Metabolic and Endocrine Effects.)

■ **Neuroendocrine Effects** Limited data currently are available regarding the effects of paroxetine on the endocrine system. Elevated serum prolactin concentrations have been reported in some women receiving chronic paroxetine therapy.

Pharmacokinetics

Paroxetine is commercially available in the US as paroxetine hydrochloride (e.g., Paxil®, Paxil CR®) and as paroxetine mesylate (i.e., Pexeva®). Conventional tablets of Paxil® and Pexeva® are *not* bioequivalent. The U.S. 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.

In all human studies described in the Pharmacokinetics section, paroxetine was administered as either the hydrochloride or the mesylate salt; dosages and concentrations are expressed in terms of paroxetine.

■ **Absorption** Paroxetine hydrochloride appears to be slowly but well absorbed from the GI tract following oral administration. Although the oral bioavailability of paroxetine hydrochloride in humans has not been fully elucidated to date, the manufacturer states that paroxetine is completely absorbed after oral dosing of a solution of the hydrochloride salt. However, the relative proportion of an oral dose that reaches systemic circulation unchanged appears to be relatively small because paroxetine undergoes extensive first-pass metabolism. The oral tablets and suspension of paroxetine hydrochloride reportedly are bioequivalent.

Paroxetine mesylate is completely absorbed following oral administration of the tablets.

Food does not substantially affect the absorption of paroxetine. In one study, no substantial differences in pharmacokinetic parameters were noted when paroxetine hydrochloride was administered under fasting and nonfasting conditions or with a low- or high-fat diet, milk, water, or antacids. In another study, administration of a single dose of paroxetine hydrochloride with food resulted in a 6% increase in the area under the concentration-time curve (AUC), a 29% increase in peak plasma concentrations of the drug, and a decrease in the time to peak plasma concentrations from 6.4 to 4.9 hours.

In healthy males receiving one 30-mg tablet of paroxetine (administered as paroxetine hydrochloride) once daily for 30 days, steady-state plasma paroxetine concentrations were achieved after approximately 10 days in most patients, although achievement of steady-state concentrations may take substantially longer in some patients. At steady-state, mean peak plasma paroxetine concentrations of 61.7 ng/mL occurred after an average of 5.2 hours following oral administration; corresponding mean trough concentrations of 30.7 ng/mL were reported. However, wide interindividual variation in peak plasma concentrations of paroxetine has been observed in both single- and multiple-dose studies. In geriatric individuals receiving multiple daily doses of 20–40 mg daily of paroxetine (administered as paroxetine hydrochloride), trough plasma concentrations were 70–80% higher than trough concentrations in nongeriatric

individuals. In another multiple-dose study, mean steady-state trough concentrations were approximately 3 times higher in geriatric individuals than in younger adults receiving paroxetine (administered as paroxetine hydrochloride) 20 mg daily, although there was considerable overlap between the 2 groups. Therefore, the manufacturers and some clinicians recommend that paroxetine be administered in a reduced dosage (i.e., 10 mg daily) initially in geriatric patients. (See Cautions: Geriatric Precautions and see Dosage and Administration: Dosage in Geriatric and Debilitated Patients.)

In healthy males receiving one 30-mg tablet of paroxetine (administered as paroxetine mesylate) once daily for 24 days, steady-state plasma paroxetine concentrations were achieved after approximately 13 days in most patients, although achievement of steady-state concentrations may take substantially longer in some patients. At steady-state, mean peak plasma paroxetine concentrations of 81.3 ng/mL occurred after an average of 8.1 hours following oral administration of paroxetine mesylate tablets; corresponding mean trough concentrations of 43.2 ng/mL were reported.

When compared with administration of a single dose of paroxetine hydrochloride, steady-state peak and trough paroxetine concentrations following multiple dosing were approximately 6 and 14 times higher than would be expected from single-dose values. In addition, steady-state drug exposure based on AUC (0–24 hour) was about 8 times greater than would have been predicted based on the single-dose data in these individuals. When compared with administration of a single dose of paroxetine mesylate, steady-state peak and trough paroxetine concentrations following multiple dosing were approximately 7 and 10 times higher than would be expected from single-dose values. In addition, steady-state drug exposure based on AUC (0–24 hour) was about 8 and 10 times greater than would have been predicted based on the single-dose data in these individuals receiving the hydrochloride and mesylate salts of paroxetine, respectively. The manufacturers attributed this excess accumulation to the fact that one of the enzymes that metabolizes paroxetine, the cytochrome P-450 isoenzyme CYP2D6, is saturable.

In steady-state, dose-proportionality studies involving geriatric and nongeriatric patients receiving 20–40 and 20–50 mg daily of paroxetine (administered as paroxetine hydrochloride), respectively, some nonlinearity was observed in both groups, which also suggests a saturable metabolic pathway. When compared with trough paroxetine concentrations after 20 mg of the drug daily, trough concentrations after 40 mg daily were approximately 2–3 times higher than doubled.

As with other serotonin-reuptake inhibitors, the relationship between plasma paroxetine concentrations and the therapeutic and/or toxic effects of the drug has not been clearly established.

■ **Distribution** Distribution of paroxetine and its metabolites into human body tissues and fluids has not been fully characterized. However, limited pharmacokinetic data suggest that the parent drug, which is highly lipophilic, and some of its metabolites are widely distributed throughout body tissues, including the CNS. Only 1% of paroxetine remains in plasma.

Although the apparent volume of distribution of paroxetine has not been determined in humans, values ranging from 3.1–28 L/kg have been reported in animal studies. The drug crosses the blood-brain barrier in humans and animals.

In vitro, approximately 95 and 93% of paroxetine is bound to plasma proteins at plasma concentrations of 100 and 400 ng/mL, respectively. Under usual clinical conditions, plasma paroxetine concentrations would be less than 400 ng/mL. In vitro, paroxetine does not alter the plasma protein binding of 2 other highly protein-bound drugs, phenytoin and warfarin.

Paroxetine is distributed into human milk. In one lactating woman receiving paroxetine (administered as paroxetine hydrochloride) 20 mg daily for 1 week, the concentration of paroxetine in breast milk was 7.6 ng/mL 4 hours after the daily dose; no adverse effects were observed in the infant during lactation. Based on an estimated weight-adjusted dose to the infant of 0.34% of the maternal dose, the exposure of infants during breastfeeding appears to be lower for paroxetine and fluvoxamine than for fluoxetine; however, further study is needed to clarify the clinical importance of these findings.

■ **Elimination** The elimination half-life of paroxetine when administered as paroxetine hydrochloride averages approximately 21–24 hours, although there is wide interpatient variation with half-lives (ranging from 7–65 hours in one study). In healthy males receiving one 30-mg tablet of paroxetine (administered as paroxetine mesylate) once daily for 24 days, the mean paroxetine half-life was 33.2 hours. In geriatric individuals, elimination half-life of paroxetine (administered as paroxetine hydrochloride) may be increased (e.g., to about 36 hours).

The exact metabolic fate of paroxetine has not been fully elucidated; however, paroxetine is extensively metabolized, probably in the liver. The principal metabolites are polar and conjugated products of oxidation and methylation, which are readily cleared by the body. Conjugates with glucuronic acid and sulfate predominate, and the principal metabolites have been isolated and identified. The metabolites of paroxetine have been shown to possess no more than 2% of the potency of the parent compound as inhibitors of serotonin reuptake; therefore, they are essentially inactive.

Like some other serotonin-reuptake inhibitors, paroxetine is partially metabolized by the drug metabolizing isoenzyme CYP2D6 (a cytochrome P-450 isoenzyme implicated in sparteine/debrisoquine polymorphism). Saturation of this enzyme at dosages used clinically appears to account for the nonlinearity of paroxetine kinetics observed with increasing dosage and duration of treatment. The role of the CYP2D6 enzyme in paroxetine metabolism also suggests potential drug-drug interactions. (See Drug Interactions: Drugs Undergoing Hepatic Metabolism or Affecting Hepatic Microsomal Enzymes.)

Following oral administration, paroxetine and its metabolites are excreted in both urine and feces. Following oral administration of a single, 30-mg dose of paroxetine (administered as paroxetine hydrochloride) as an oral solution (not commercially available), approximately 64% of the dose was excreted in the urine within 10 days; unchanged paroxetine accounted for 2% of the dose and metabolites accounted for the remaining 62% of the dose. During the same period, approximately 36% of the dose was eliminated in feces (probably via the bile), mostly as metabolites and less than 1% as the parent drug.

The effect of age on the elimination of paroxetine has not been fully elucidated. In healthy geriatric adults, hepatic clearance of paroxetine was mildly impaired leading to slower elimination and increased plasma concentrations of the drug. (See Pharmacokinetics: Absorption.) Studies in depressed, geriatric patients confirm these findings with higher steady-state concentrations and longer elimination half-lives reported compared with younger individuals. These results suggest that older patients may be more susceptible to saturation of hepatic metabolic activity resulting in nonlinear kinetics and higher plasma concentrations occurring at lower dosages of paroxetine. Therefore, the manufacturers and some clinicians recommend that paroxetine initially be administered in a reduced dosage in geriatric patients. (See Cautions: Geriatric Precautions and see Dosage and Administration: Dosage in Geriatric and Debilitated Patients.)

Because paroxetine is extensively metabolized by the liver, hepatic impairment can affect the elimination of the drug. In cirrhotic patients with moderate hepatic impairment who received a single 20-mg dose of paroxetine (administered as paroxetine hydrochloride), no significant difference in plasma paroxetine concentrations and pharmacokinetic parameters was observed when compared with corresponding data in healthy individuals. However, accumulation potentially may occur in patients receiving multiple daily doses of paroxetine. The manufacturers state that patients with impaired hepatic function have approximately twofold higher peak plasma concentrations and AUC values. Therefore, the manufacturers recommend that paroxetine be administered in a reduced dosage initially in patients with severe hepatic impairment; caution also should be exercised when increasing the dosage of paroxetine in such patients. (See Cautions: Precautions and Contraindications and see Dosage and Administration: Dosage in Renal and Hepatic Impairment.)

The effect of renal impairment on the pharmacokinetics of paroxetine has not been fully evaluated to date. Following oral administration of multiple daily doses of paroxetine as paroxetine hydrochloride in patients with creatinine clearances less than 30 mL/minute, mean plasma concentrations of paroxetine were approximately 4 times greater than those seen in healthy individuals. In patients with creatinine clearances of 30–60 mL/minute, peak plasma concentrations and AUC values were approximately twofold higher when compared with healthy individuals. The influence of renal impairment in patients receiving multiple daily doses of paroxetine has not been evaluated to date. Pending further accumulation of data, the manufacturers and some clinicians recommend that paroxetine be administered in a reduced dosage initially in patients with severe renal impairment. (See Cautions: Precautions and Contraindications and see Dosage and Administration: Dosage in Renal and Hepatic Impairment.)

Because of the large volume of distribution of paroxetine and its principal metabolite, peritoneal dialysis, forced diuresis, hemoperfusion, and/or exchange transfusion are unlikely to be effective in removing substantial amounts of paroxetine from the body.

Chemistry and Stability

■ **Chemistry** Paroxetine, a selective serotonin-reuptake inhibitor (SSRI) antidepressant agent, is a phenylpiperidine-derivative. Paroxetine differs structurally from other SSRIs (e.g., citalopram, fluoxetine, sertraline) and also differs structurally and pharmacologically from other currently available antidepressants (e.g., tricyclic antidepressants, monoamine oxidase inhibitors).

Paroxetine is commercially available in the US as the hydrochloride and mesylate salts. Paroxetine hydrochloride occurs as an odorless, off-white powder and has a solubility of 5.4 mg/mL in water. The drug has a pK_a of approximately 9.9. Paroxetine mesylate also occurs as an odorless, off-white powder but has a solubility of more than 1 g/mL in water.

The commercially available extended-release tablets of paroxetine hydrochloride contain the drug in a biodegradable polymeric delivery system, consisting of a hydrophilic core surrounded by a biodegradable barrier layer. This delivery system is designed to release the drug gradually over a period of 4–5 hours after ingestion; in addition, an enteric coating delays the release of drug until after the extended-release tablet has left the stomach.

■ **Stability** Paroxetine hydrochloride conventional tablets should be stored at 15–30°C. The oral suspension and extended-release tablets of paroxetine hydrochloride should be stored at or below 25°C. When stored as directed, paroxetine hydrochloride conventional tablets and oral suspension have an expiration date of 3 and 2 years following the date of manufacture, respectively.

Paroxetine mesylate conventional tablets should be stored at a temperature of 25°C but may be exposed to temperatures ranging from 15–30°C; the tablets should be protected from humidity.

Preparations

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

Paroxetine Hydrochloride

Oral		
Suspension	10 mg (of paroxetine) per 5 mL	Paxil®, GlaxoSmithKline
Tablets, extended-release, film-coated	12.5 mg (of paroxetine)	Paxil CR®, GlaxoSmithKline
	25 mg (of paroxetine)	Paxil CR®, GlaxoSmithKline
	37.5 mg (of paroxetine)	Paxil CR®, GlaxoSmithKline
Tablets, film-coated	10 mg (of paroxetine)*	Paroxetine Hydrochloride Film-coated Tablets
		Paxil® (scored), GlaxoSmithKline
	20 mg (of paroxetine)*	Paroxetine Hydrochloride Film-coated Tablets
		Paxil® (scored), GlaxoSmithKline
	30 mg (of paroxetine)*	Paroxetine Hydrochloride Film-coated Tablets
		Paxil®, GlaxoSmithKline
	40 mg (of paroxetine)*	Paroxetine Hydrochloride Film-coated Tablets
		Paxil®, GlaxoSmithKline

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

Paroxetine Mesylate

Oral		
Tablets, film-coated	10 mg (of paroxetine)	Pexeva®, JDS Pharmaceuticals
	20 mg (of paroxetine)	Pexeva® (scored), JDS Pharmaceuticals
	30 mg (of paroxetine)	Pexeva®, JDS Pharmaceuticals
	40 mg (of paroxetine)	Pexeva®, JDS Pharmaceuticals

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

Sertraline Hydrochloride

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

Uses

■ **Major Depressive Disorder** Sertraline is used in the treatment of major depressive disorder. 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, Drug Interactions: Tricyclic and Other Antidepressants, and Drug Interactions: Lithium.)

The efficacy of sertraline for the acute treatment of major depression has been established by 2 placebo-controlled studies in adult outpatients who met DSM-III criteria for major depression. In the first study of 8 weeks' duration, sertraline was administered with flexible dosing in a range of 50–200 mg daily; the mean daily dosage for patients completing the study was 145 mg daily. In the second study of 6 weeks' duration, sertraline was administered in fixed doses of 50, 100, and 200 mg daily. Overall, these 2 studies demonstrated that sertraline was superior to placebo in improving scores on the Hamilton Depression Rating Scale and the Clinical Global Impression Severity and Improvement Scales. However, the second study was not readily interpretable regarding whether there was a dose-response relationship for the drug's efficacy.

In a third study, depressed outpatients who had responded by the end of an initial 8-week open treatment phase to sertraline 50–200 mg daily were randomized to continue sertraline in the same dosage range or placebo for 44 weeks in a double-blind manner. The mean daily dosage of sertraline in those who completed this long-term study was 70 mg daily, and the relapse rate in the sertraline-treated patients was substantially lower than in those who received placebo.

An analysis of these 3 controlled studies for possible gender-related effects on treatment outcome did not suggest any difference in efficacy based on the gender of the patient.

While the optimum duration of sertraline therapy has not been established, many experts state that acute depressive episodes require several months or longer of sustained antidepressant therapy. In addition, some clinicians recommend that long-term antidepressant therapy be considered in certain patients at risk for recurrence of depressive episodes (such as those with highly recurrent unipolar depression). The efficacy of sertraline in maintaining an antidepressant response for up to 1 year without increased toxicity has been demonstrated in a controlled setting. The manufacturers state that the usefulness of the drug in patients receiving prolonged therapy should be reevaluated periodically. (See Dosage and Administration: Dosage.)

The manufacturers state that the drug's antidepressant efficacy in hospital settings has not been adequately studied to date.

As with certain other antidepressants, the possibility that sertraline may precipitate hypomanic or manic attacks in patients with bipolar or other major affective disorder should be considered. Sertraline is *not* approved for use in treating bipolar depression in adults.

Considerations in Choosing an Antidepressant A variety of antidepressant drugs is 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 sertraline in patients with depression is greater than that of placebo and comparable to that of usual dosages of tricyclic antidepressants (e.g., amitriptyline), other SSRIs (e.g., fluoxetine), and other antidepressants (e.g., nefazodone). In geriatric patients with major depression, sertraline appears to be as effective as amitriptyline. The onset of action of sertraline appears to be comparable to that of tricyclic antidepressants.