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: Drugs Associated with Serotonin Syndrome, see Drug Interactions: Tricyclic and Other Antidepressants, and see Drug Interactions: Lithium.)

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

Considerations in Choosing Antidepressants A variety of antidepressant drugs are available for the treatment of major depressive disorder, including selective serotonin-reuptake inhibitors (e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline), 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, duloxetine, maprotiline, nefazodone, trazodone, venlafaxine). Most clinical studies have shown that the antidepressant effect of usual dosages of fluoxetine in patients with moderate to severe depression is greater than that of placebo and comparable to that of usual dosages of tricyclic antidepressants, maprotiline, other selective serotonin-reuptake inhibitors (e.g., paroxetine, sertraline), and other antidepressants (e.g., trazodone). Fluoxetine appears to be as effective as tricyclic antidepressants in reducing most of the signs and symptoms associated with major depressive disorder, including depression, anxiety, cognitive disturbances, and somatic symptoms. However, in some studies, the drug did not appear to be as effective as tricyclic antidepressants or trazodone in reducing sleep disturbances associated with depression. In geriatric patients with major depressive disorder, fluoxetine appears to be as effective as and to cause fewer overall adverse effects than doxepin. The onset of action of fluoxetine appears to be comparable to that of tricyclic antidepressants, although the onset of action has been variably reported to be somewhat faster or slower than that of tricyclic antidepressants in some studies.

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

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

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

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

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

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

Geriatric Considerations. The response to antidepressants in geriatric patients 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, selective serotonin-reuptake inhibitors appear to be as effective as tricyclic antidepressants (e.g., amitriptyline) but may cause fewer overall adverse effects than these other agents. Geriatric patients appear to be especially sensitive to anticholinergic (e.g., dry mouth, constipation, vision disturbance), cardiovascular, orthostatic hypotensive, and sedative effects of tricyclic antidepressants. The low incidence of anticholinergic effects associated with fluoxetine compared with tricyclic antidepressants also 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. Some clinicians state that selective serotonin-reuptake inhibitors including fluoxetine may be preferred for treating depression in geriatric patients in whom the orthostatic hypotension associated with many antidepressants (e.g., tricyclics) potentially may result in injuries (such as severe falls). However, despite the fewer cardiovascular and anticholinergic effects associated with selective serotonin-reuptake inhibitors, 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 selective serotonin-reuptake inhibitors 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.