sion 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 currently is unknown whether the suicidality risk extends to longer-term use (i.e., beyond several months); however, there is substantial evidence from placebo-controlled maintenance trials in adults with major depressive disorder that antidepressants can delay the recurrence of depression.

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

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

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).

Patients should be warned that trazodone may impair their ability to perform activities requiring mental alertness or physical coordination (e.g., operating machinery, driving a motor vehicle). Patients also should be warned that trazodone may enhance their response to alcohol, barbiturates, or other CNS depressants. Since the risk of dizziness or lightheadedness may be increased during fasting conditions, patients should be advised to take trazodone shortly after a meal or light snack. In addition, total drug absorption may be up to 20% greater when the drug is taken with food rather than on an empty stomach. Because priapism has been associated with trazodone therapy, patients should be instructed to discontinue the drug and consult a physician if prolonged or inappropriate penile erection occurs.

Until additional clinical experience on the safety of trazodone in patients with cardiovascular disease is obtained, it is recommended that these patients be closely monitored, particularly for arrhythmias, while receiving the drug. (See Cautions: Cardiovascular Effects.) It is also recommended that trazodone *not* be used during the initial recovery phase of myocardial infarction.

Leukocyte and differential counts should be performed in patients who develop fever and sore throat or other signs of infection while receiving trazodone. The drug should be discontinued in patients whose leukocyte or absolute neutrophil count decreases to less than normal levels. (See Cautions: Hematologic Effects.)

Trazodone is contraindicated in patients who are hypersensitive to the drug.

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

FDA warns that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder and other psychiatric disorders. The risk of suicidality for these drugs was identified in a pooled analysis of data from a total of 24 short-term (4–16 weeks), placebo-controlled studies of 9 antidepressants (i.e., bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, venlafaxine) in over 4400 children and adolescents with major depressive disorder, obsessive-compulsive disorder (OCD), or other psychiatric disorders. The analysis revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in pediatric patients receiving antidepressants than in those receiving placebo. The average risk of such events was 4% among children and adolescents receiving these drugs, twice the risk (2%) that was observed among those receiving placebo. However, a more recent meta-analysis of 27 placebo-controlled trials of 9 antidepressants (SSRIs and others) in patients younger than 19 years of age with major depressive disorder, OCD, or non-OCD anxiety disorders suggests that the benefits of antidepressant therapy in treating these conditions may outweigh the risks of suicidal behavior or suicidal ideation. No suicides occurred in these pediatric trials.

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

As a result of this analysis and public discussion of the issue, FDA has directed manufacturers of all antidepressants to add a boxed warning to the labeling of their products to alert clinicians of this suicidality risk in children and adolescents and to recommend appropriate monitoring and close observation of patients receiving these agents. (See Cautions: Precautions and Contraindications.) The drugs that are the focus of the revised labeling are all drugs included in the general class of antidepressants, including those that have not been studied in controlled clinical trials in pediatric patients, since the available data are not adequate to exclude any single antidepressant from an increased risk of suicidality. 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.

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

■ **Mutagenicity and Carcinogenicity** In vitro tests have *not* shown trazodone to be mutagenic. No evidence of carcinogenesis was seen in animals receiving oral trazodone dosages up to 300 mg/kg daily for 18 months.

■ **Pregnancy, Fertility, and Lactation** Trazodone has been shown to be teratogenic in rats and rabbits when given at dosages 15–50 times the maximum human dosage. The drug also caused increased fetal resorption and other adverse fetal effects in rats when given at dosages approximately 30–50 times the suggested maximum human dosage. There are no adequate and controlled studies to date using trazodone in pregnant women, and the drug should be used during pregnancy only when the potential benefits justify the possible risks to the fetus.

The effect of trazodone on fertility in humans is not known. Impotence, retrograde ejaculation, and decreased or increased libido have occurred in some individuals during trazodone therapy. Reproduction studies in male and female rats using trazodone dosages up to 150 times the usual human dosage have not revealed evidence of impaired fertility.

Because trazodone is distributed into milk, the drug should be used with caution in nursing women.

Drug Interactions

■ **Drugs Affecting Hepatic Microsomal Enzymes** Results of in vitro studies indicate that metabolism of trazodone is mediated by the cytochrome P-450 (CYP) 3A4 isoenzyme, and the possibility exists that drugs that inhibit or induce this isoenzyme may affect the pharmacokinetics of trazodone. Other metabolic pathways that may be involved in the metabolism of trazodone have not been well characterized.

Concomitant use of trazodone with inhibitors of CYP3A4 can result in substantially increased plasma concentrations of trazodone and increase the potential for adverse effects. In one study, concomitant use of ritonavir (200 mg twice daily for 2 days) and trazodone (a single 50-mg dose) in healthy individuals increased maximum plasma concentrations and decreased clearance of trazodone by 34 and 52%, respectively, and increased area under the plasma concentration-time curve (AUC) and half-life of trazodone by greater than twofold. Adverse effects (e.g., nausea, hypotension, syncope) also were observed with concomitant use of trazodone and ritonavir. The manufacturers of trazodone state that a reduction in trazodone dosage should be considered in patients receiving a potent inhibitor of the CYP3A4 isoenzyme (e.g., indinavir, itraconazole, ketoconazole, nefazodone, ritonavir) concomitantly with trazodone.

Concomitant use of trazodone (100–300 mg daily) with carbamazepine (400 mg daily), an inducer of CYP3A4, decreased plasma concentrations of trazodone and an active metabolite, *m*-chlorophenylpiperazine, by 76 and 60%, respectively. Patients receiving trazodone and carbamazepine concomitantly should be closely monitored and dosage of trazodone increased if necessary.

■ **Serotonergic Agents** ***Fluoxetine*** Elevated plasma trazodone concentrations and adverse effects possibly associated with trazodone toxicity have been reported occasionally during concomitant trazodone and fluoxetine therapy. Although the exact mechanism has not been established, it has been suggested that fluoxetine may inhibit the hepatic metabolism of many antidepressant agents, including trazodone. In addition, both trazodone and fluoxetine possess serotonergic activity; therefore, the possibility of serotonin syndrome also should be considered in patients receiving trazodone and fluoxetine or other selective serotonin-reuptake inhibitor therapy concurrently. For detailed