ance of the suspect drug; in other cases hyperglycemia resolved with discontinuance of the antipsychotic.

Various experts have developed additional recommendations for the management of diabetes risks in patients receiving atypical antipsychotics; these include initial screening measures and regular monitoring (e.g., determination of diabetes risk factors; BMI determination using weight and height; waist circumference; blood pressure; fasting blood glucose; hemoglobin A_{1c} [HbA_{1c}]; fasting lipid profile), as well as provision of patient education and referral to clinicians experienced in the treatment of diabetes, when appropriate. Although some clinicians state that a switch from one atypical antipsychotic agent to another that has not been associated with substantial weight gain or diabetes should be considered in patients who experience weight gain (equal to or exceeding 5% of baseline body weight) or develop worsening glycemia or dyslipidemia at any time during therapy, such recommendations are controversial because differences in risk of developing diabetes associated with use of the different atypical antipsychotics remain to be fully established. Many clinicians consider antipsychotic efficacy the most important factor when making treatment decisions and suggest that detrimental effects of switching from a beneficial treatment regimen also should be considered in addition to any potential for exacerbation or development of medical conditions (e.g., diabetes). Decisions to alter drug therapy should be made on an individual basis, weighing the potential risks and benefits of the particular drug in each patient.

Cardiovascular Effects Clozapine should be used with caution in patients with cardiovascular and/or pulmonary disease because the drug may cause tachycardia, hypotension, and cardiac and/or respiratory arrest. In such patients, the recommendation for gradual dosage titration following a low initial dose should be observed carefully. (See Dosage and Administration: Dosage.)

Analyses of postmarketing surveillance data suggest that clozapine is associated with an increased risk of potentially fatal myocarditis, particularly during the first month of therapy. Immediate discontinuance of the drug is recommended in cases of suspected myocarditis. (See Myocarditis under Cautions: Cardiovascular Effects.)

Fatal pulmonary embolism has been reported with clozapine therapy. The possibility of pulmonary embolism should be considered in patients presenting with deep-vein thrombosis, acute dyspnea, chest pain, or other respiratory signs and symptoms.

Because cardiomyopathy has been reported in patients treated with clozapine, signs and symptoms suggestive of cardiomyopathy, particularly exertional dyspnea, fatigue, orthopnea, paroxysmal nocturnal dyspnea, and peripheral edema, should alert the clinician to perform further investigations. If the diagnosis of cardiomyopathy is confirmed, the drug should be discontinued unless the benefit to the patient clearly outweighs the risk.

Orthostatic hypotension with and without syncope can occur with clozapine therapy and may represent a continuing risk in some patients. Orthostatic hypotension is more likely to occur during initial titration of the drug in association with rapid dose escalation, but may even occur with the first dose at clozapine doses as low as 12.5 mg. Rarely, severe hypotension or orthostatic collapse can be profound and be accompanied by respiratory and/or cardiac arrest. Such adverse cardiovascular effects have occurred during initial treatment with the drug alone or in combination with benzodiazepines or other psychotropic agents. (See Drug Interactions: CNS Depressants.) Temporary reduction in dose or interruption of clozapine therapy may be required. Severe hypotensive effects also may be alleviated with standard measures (e.g., IV fluids, placing patient in Trendelenburg's position) and, if required, by the administration of norepinephrine or phenylephrine; epinephrine should *not* be used since a further lowering of blood pressure may occur. (See Drug Interactions: Hypotensive Agents.) Patients should be informed of the risk of orthostatic hypotension associated with use of clozapine, especially during the period of initial dosage titration. In addition, if clozapine therapy has been discontinued for more than 2 days, patients should be advised to contact their clinician for dosing instructions. (See Reinitiation of Therapy under Dosage: Psychotic Disorders, in Dosage and Administration.)

Seizures Clozapine is contraindicated in patients with uncontrolled seizure disorders.

Generalized tonic-clonic (grand mal) seizures have occurred in patients receiving clozapine, particularly in patients receiving high dosages (greater than 600 mg daily) and/or in whom plasma clozapine concentrations were elevated. (See Seizures under Cautions: Nervous System Effects.) Clozapine should be administered with extreme caution to patients having a history of seizure disorder or other factors possibly predisposing to seizure (e.g., abnormal EEG without a history of epilepsy, preexisting CNS pathology, history of electroconvulsive therapy or of perinatal or birth difficulties, family history of seizure or febrile convulsion). Because of the substantial risk of seizures associated with clozapine use, patients should be advised not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others (e.g., operating heavy machinery, driving an automobile, swimming, climbing). In addition, the manufacturers recommend that general anesthesia be administered with caution in patients receiving clozapine therapy because of this and other adverse CNS effects associated with the drug. An anesthesiologist should be consulted regarding continuation of clozapine therapy in patients undergoing surgery involving general anesthesia.

Hematotoxicity Because of the substantial risk of agranulocytosis, a potentially life-threatening adverse event, clozapine therapy should be reserved for use in the treatment of severely ill schizophrenic patients who fail to respond to adequate courses of standard antipsychotic therapy or for suicide risk reduction in patients with schizophrenia or schizoaffective disorder who are judged to be at risk for recurrent suicidal behavior. Patients should be warned of this risk and informed that clozapine is available only through distribution systems that ensure baseline and periodic monitoring of leukocyte counts according to a prescribed schedule prior to delivery of the next supply of medication. (See Cautions: Hematologic Effects.) In addition, patients should be advised to report immediately the development of lethargy, malaise, weakness, fever, sore throat, mucous membrane ulceration, or any other potential manifestation of infection. Particular attention should be paid to any flu-like symptoms or other complaints that might suggest infection. Patients who develop agranulocytosis or severe leukopenia/granulocytopenia (leukocyte less than 2000/$mm^3$and ANC less than 1000/mm^3) while receiving clozapine should *not* be rechallenged with the drug. Although it is not known whether the risk of agranulocytosis is increased, clozapine generally should be avoided or used with caution in patients with a history of agranulocytosis induced by other drugs.

Clozapine is contraindicated in patients with myeloproliferative disorders, preexisting bone marrow depression, or a history of clozapine-induced agranulocytosis or severe granulocytopenia. The drug also is contraindicated in patients receiving other agents that may cause agranulocytosis or suppress bone marrow function and in those with severe CNS depression or comatose states from any cause. Although the manufacturers do not mention it as a specific contraindication to clozapine therapy, the American Psychiatric Association recommends that clozapine therapy be avoided in schizophrenic patients who are unable or unwilling to comply with the close monitoring that is necessary to detect possible adverse hematologic effects associated with the drug.

Other Precautions and Contraindications Clozapine is contraindicated in patients with a history of hypersensitivity to the drug or any ingredient in the formulation.

■ **Pediatric Precautions** Safety and efficacy of clozapine in children and adolescents younger than 16 years of age have not been established. However, clozapine has been used in a limited number of children and adolescents with treatment-refractory schizophrenia (see Pediatric Considerations under Psychotic Disorders: Schizophrenia, in Uses) and results of at least one randomized, double-blind clinical study indicate that adverse hematologic effects were a major concern for children and adolescents receiving clozapine†. Although no cases of agranulocytosis occurred in this study, 24% of these children and adolescents experienced mild to moderate neutropenia during 2 years of follow-up compared with an estimated cumulative risk of 1.5–2% of developing neutropenia in adults. The precise mechanism by which clozapine induces agranulocytosis is not known, but a higher concentration of the metabolite norclozapine, which has been associated with hematopoietic toxicity in children and adolescents receiving clozapine, has been suggested as a possible reason for the increased risk in this age group.

In addition to adverse hematologic effects, clinically important seizure activity (e.g., epileptiform spikes, myoclonus, tonic-clonic seizures) also has been reported in children and adolescents with no previous history of epilepsy who received clozapine. In some cases, EEG abnormalities were associated with clinical deterioration (i.e., increased aggression, psychosis, irritability). Because some children and adolescents responded behaviorally to reduced dosages of clozapine and the addition of an anticonvulsant (e.g., valproate), it has been suggested that the EEG may be a sensitive indicator of clozapine toxicity in children as well as in adults.

■ **Geriatric Precautions** Clinical studies of clozapine did not include sufficient numbers of patients 65 years of age and older to determine whether geriatric patients respond differently than younger patients. Because geriatric patients may be at increased risk for certain cardiovascular (e.g., orthostatic hypotension, tachycardia) and anticholinergic effects of the drug (e.g., constipation, urinary retention in the presence of prostatic hypertrophy), clozapine should be used cautiously in this age group. In addition, geriatric patients generally are more sensitive than younger patients to drugs that affect the CNS; data from clinical studies indicate that the incidence of tardive dyskinesia appears to be highest among geriatric patients, especially women. In general, dosage should be titrated carefully in geriatric patients, usually initiating therapy at the low end of the dosage range; the greater frequency of decreased hepatic, renal, and/or cardiac function and of concomitant disease and drug therapy observed in the elderly also should be considered.

Geriatric patients with dementia-related psychosis treated with atypical antipsychotic drugs appear to be at an increased risk of death compared with that among patients receiving placebo. Analyses of 17 placebo-controlled trials (average duration of 10 weeks) revealed an approximate 1.6- to 1.7- fold increase in mortality among geriatric patients receiving atypical antipsychotic drugs (i.e., aripiprazole, olanzapine, quetiapine, risperidone) compared with that in patients receiving placebo. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5% compared with a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Clozapine is not approved for the treatment of dementia-related psychosis.

■ **Mutagenicity and Carcinogenicity** Clozapine did not exhibit carcinogenic potential in long-term studies in mice and rats receiving dosages approximately 7 times (on a mg/kg basis) the usual human dosage. Clozapine