phenones, phenothiazines) and has been referred to as an atypical or second-generation antipsychotic agent. The exact mechanism of action of aripiprazole in schizophrenia, bipolar mania, major depressive disorder, and agitation associated with schizophrenia or bipolar mania has not been fully elucidated but, like that of other drugs with efficacy in these conditions (e.g., olanzapine, risperidone, ziprasidone), may involve the drug's activity at dopamine D_2 and serotonin type 1 ($5\text{-}HT_{1A}$) and type 2 ($5\text{-}HT_{2A}$) receptors. However, aripiprazole appears to differ from other atypical antipsychotic agents because the drug demonstrates partial agonist activity at D_2 and $5\text{-}HT_{1A}$ receptors and antagonist activity at $5\text{-}HT_{2A}$ receptors. Antagonism at other receptors (e.g., α_1-adrenergic receptors, histamine H_1 receptors) may contribute to other therapeutic and adverse effects (e.g., orthostatic hypotension, somnolence) observed with aripiprazole.

Aripiprazole is extensively metabolized in the liver principally via dehydrogenation, hydroxylation, and *N*-dealkylation by the cytochrome P-450 (CYP) 2D6 and 3A4 isoenzymes. The major active metabolite of aripiprazole, dehydro-aripiprazole, exhibits affinity for D_2 receptors similar to that of the parent compound and represents approximately 40% of aripiprazole area under the concentration-time curve (AUC) in plasma. Steady-state plasma concentrations of both aripiprazole and dehydro-aripiprazole are achieved within 14 days. The elimination half-lives of aripiprazole and dehydro-aripiprazole are approximately 75 and 94 hours, respectively. Approximately 18% and less than 1% of aripiprazole is excreted unchanged in feces and urine, respectively.

Advice to Patients

Importance of providing copy of written patient information (medication guide) each time aripiprazole is dispensed. Importance of advising patients to read the patient information before taking aripiprazole and each time the prescription is refilled.

Increased mortality in geriatric patients with dementia-related psychosis; importance of advising patients and caregivers that geriatric patients with dementia-related psychosis treated with antipsychotic agents are at an increased risk of death. Patients and caregivers should also be informed that aripiprazole is *not* approved for treating geriatric patients with dementia-related psychosis.

Risk of suicidality; importance of patients, family, and caregivers being alert to and immediately reporting emergence of suicidality, worsening depression, or unusual changes in behavior, especially during the first few months of therapy or during periods of dosage adjustment.

Because somnolence and impairment of judgment, thinking, or motor skills may be associated with aripiprazole, avoid driving, operating machinery, or performing hazardous tasks while taking aripiprazole until the drug's effects on the individual are known. Importance of avoiding alcohol during aripiprazole therapy.

Risk of neuroleptic malignant syndrome (NMS), a rare but life-threatening syndrome that can cause high fever, stiff muscles, sweating, fast or irregular heart beat, change in blood pressure, confusion, and kidney damage. Importance of informing patients to immediately contact a healthcare professional if such symptoms develop.

Importance of clinicians informing patients in whom chronic aripiprazole use is contemplated of risk of tardive dyskinesia. Importance of informing patients to report any muscle movements that cannot be stopped to a healthcare professional.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs, as well as any concomitant illnesses (e.g., diabetes mellitus).

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

Importance of avoiding overheating or dehydration.

For patients taking aripiprazole orally disintegrating tablets, importance of not removing a tablet from the blister package until just before administering a dose; importance of peeling blister open with dry hands and placing tablet on tongue to dissolve and be swallowed with saliva.

Importance of informing patients with phenylketonuria that aripiprazole orally disintegrating 10- and 15-mg tablets contain 1.12 and 1.68 mg of phenylalanine, respectively.

Importance of being aware that aripiprazole oral solution contains 400 mg of sucrose and 200 mg of fructose per mL.

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

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

Preparations

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

Aripiprazole

Oral		
Solution	5 mg/5 mL	Abilify* Oral Solution, Otsuka (also promoted by Bristol-Myers Squibb)
Tablets	2 mg	Abilify*, Otsuka (also promoted by Bristol-Myers Squibb)
	5 mg	Abilify*, Otsuka (also promoted by Bristol-Myers Squibb)
	10 mg	Abilify*, Otsuka (also promoted by Bristol-Myers Squibb)
	15 mg	Abilify*, Otsuka (also promoted by Bristol-Myers Squibb)
	20 mg	Abilify*, Otsuka (also promoted by Bristol-Myers Squibb)
	30 mg	Abilify*, Otsuka (also promoted by Bristol-Myers Squibb)
Tablets, orally disintegrating	10 mg	Abilify* Discmelt*, Otsuka (also promoted by Bristol-Myers Squibb)
	15 mg	Abilify* Discmelt*, Otsuka (also promoted by Bristol-Myers Squibb)
Parenteral		
Injection, for IM use only	7.5 mg/mL (9.75 mg)	Abilify*, Otsuka (also promoted by Bristol-Myers Squibb)

Clozapine

■ Clozapine has been referred to as an atypical or second-generation antipsychotic agent.

Uses

■ **Psychotic Disorders** Clozapine is used for the symptomatic management of psychotic disorders (e.g., schizophrenia). Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to sustain symptom remission or control and to minimize the risk of relapse. Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia and generally are effective in all subtypes of the disorder and subgroups of patients. Patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.

Clozapine has been shown to be an effective, relatively rapid-acting, broad-spectrum antipsychotic agent in both uncontrolled and controlled studies of patients with schizophrenia. In these studies, improvement in manifestations of schizophrenia was based on the results of various psychiatric rating scales, principally the Brief Psychiatric Rating Scale (BPRS) that assesses factors such as anergy, thought disturbance, activation, hostility/suspiciousness, and anxiety/depression. In clinical studies, clozapine improved both positive (florid symptomatology such as hallucinations, conceptual disorganization, and suspiciousness) and negative ("deficit" symptomatology such as emotional withdrawal, motor retardation, blunted affect, and disorientation) manifestations of schizophrenia; conventional (typical) antipsychotic agents appear to have lesser effects on negative manifestations of the disorder. In comparative studies, clozapine was at least as effective as, or more effective than several conventional antipsychotic agents, including chlorpromazine, haloperidol, perphenazine, or trifluoperazine.

Unlike conventional antipsychotic agents, however, clozapine generally does not induce extrapyramidal effects and has not been clearly implicated as a causative agent in tardive dyskinesia.

While the risks of adverse neurologic effects with long-term clozapine therapy remain to be fully elucidated, other adverse effects, including some potentially serious effects (e.g., agranulocytosis, seizures), may occur more frequently with clozapine therapy. Consequently, the manufacturers and most clinicians currently state that use of clozapine should be reserved for patients with severe disease that fails to respond adequately to conventional antipsychotic therapy, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs. What constitutes an adequate trial of standard antipsychotic therapy, however, varies widely. The manufacturers and some clinicians recommend that a patient be given an adequate trial of at least 2 different antipsychotic agents from at least 2 different chemical classes (e.g., phenothiazines, butyrophenones, thioxanthenes) before the patient is considered a candidate for clozapine therapy. The American Psychiatric Association (APA), however, currently recommends that a trial of clozapine be considered in patients who fail to respond to adequate trials of at least one antipsychotic agent unless therapy with the drug is specifically contraindicated (e.g., patients with myeloproliferative disorders, preexisting bone marrow depression, or a history of clozapine-induced agranulocytosis or severe granulocytopenia) or patients are unable or unwilling to comply with monitoring requirements. The APA also recommends that clo-

zapine should be considered in patients with a history of chronic and persistent suicidal ideation and behavior and in patients with persistent hostility and aggression.

Schizophrenia Clozapine is used for the symptomatic management of schizophrenia in severely ill patients whose disease fails to respond adequately to other antipsychotic therapy. Schizophrenia is a major psychotic disorder that frequently has devastating effects on various aspects of the patient's life and carries a high risk of suicide and other life-threatening behaviors. Manifestations of schizophrenia involve multiple psychologic processes, including perception (e.g., hallucinations), ideation, reality testing (e.g., delusions), emotion (e.g., flatness, inappropriate affect), thought processes (e.g., loose associations), behavior (e.g., catatonia, disorganization), attention, concentration, motivation (e.g., avolition, impaired intention and planning), and judgment. The principal manifestations of this disorder usually are described in terms of positive and negative (deficit) symptoms, and more recently, disorganized symptoms. Positive symptoms include hallucinations, delusions, bizarre behavior, hostility, uncooperativeness, and paranoid ideation, while negative symptoms include restricted range and intensity of emotional expression (affective flattening), reduced thought and speech productivity (alogia), anhedonia, apathy, and decreased initiation of goal-directed behavior (avolition). Disorganized symptoms include disorganized speech (thought disorder) and behavior and poor attention.

Evidence from both retrospective and controlled prospective studies indicates that clozapine is effective in many patients who fail to respond adequately to other antipsychotic therapy and/or in whom such therapy produces intolerable adverse effects. In a controlled, comparative study in patients with at least moderately severe schizophrenia whose disease was refractory to at least 3 antipsychotic agents from at least 2 different chemical classes during the past 5 years, an adequate clinical response (a 20% or greater decrease in total BPRS score and either a posttreatment Clinical Global Impressions [CGI] scale rating of mildly ill or a posttreatment BPRS score of 35 or less) was noted after 1–6 weeks of therapy in 30% of patients receiving clozapine (mean maximum dosage exceeding 600 mg daily) compared with 4% of patients receiving chlorpromazine (mean maximum dosage exceeding 1200 mg daily) plus benztropine. In addition, clozapine was substantially more effective than chlorpromazine plus benztropine in improving both positive and negative manifestations of schizophrenia. In this study, resistance to antipsychotic treatment prior to entry into the clozapine/chlorpromazine comparative phase was confirmed by a 6-week trial of haloperidol (mean dosage of 61 mg daily) combined with benztropine. This study provides evidence from both categorical and continuous measures not only of clozapine's efficacy as an antipsychotic agent but also of its superiority over conventional antipsychotic drug therapy in a well-defined group of antipsychotic-resistant patients. Similar 6-week response rates in treatment-resistant schizophrenia have been reported in other studies with the drug. Clinically important improvement in quality of life and social functioning, including deinstitutionalization, interpersonal relationships, and ability to hold a job or attend school, also have been reported following initiation of clozapine therapy in patients with antipsychotic-resistant schizophrenia.

For additional information on the symptomatic management of schizophrenia, including treatment recommendations and results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, see Schizophrenia and Other Psychotic Disorders under Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

Pediatric Considerations. Although the safety and efficacy of clozapine in children and adolescents younger than 16 years of age have not been established, the drug has been successfully used for the management of childhood-onset schizophrenia in a limited number of treatment-resistant children and adolescents†. While the lower risk of extrapyramidal adverse effects and tardive dyskinesia during treatment with atypical antipsychotic agents such as clozapine compared with conventional antipsychotic agents represents an advantage in the treatment of childhood-onset schizophrenia, concerns regarding serious adverse effects (e.g., neutropenia; seizures) associated with clozapine limit its use in clinical practice. (See Cautions: Pediatric Precautions.) Therefore, the American Academy of Child and Adolescent Psychiatry (AACAP) states that clozapine is not considered a first-line agent, and the drug is recommended only in patients who have failed to respond to adequate therapeutic trials (i.e., use of sufficient dosages over a period of 4–6 weeks) of at least 2 other antipsychotic agents (at least one of which is an atypical antipsychotic) and/or have experienced substantial adverse effects (e.g., tardive dyskinesia) while receiving other antipsychotic agents. For additional information on the symptomatic management of childhood-onset schizophrenia, see Pediatric Considerations under Psychotic Disorders: Schizophrenia, in Uses in the Phenothiazines General Statement 28:16.08.24.

In one randomized, double-blind, clinical study conducted by the National Institute of Mental Health (NIMH), a limited number of children and adolescents (mean: 14 years of age) with childhood-onset schizophrenia (i.e., development of the disorder by 12 years of age or younger) who were intolerant and/or nonresponsive to at least 2 different antipsychotic agents were treated with either clozapine (up to a 525 mg daily; mean final dosage 176 mg daily) or haloperidol (up to 27 mg daily; mean final dosage 16 mg daily) for 6 weeks. In this study, children and adolescents receiving clozapine had substantially greater reductions in both positive and negative symptoms of schizophrenia than those receiving haloperidol. Additional follow-up of these patients over a 2-year period indicated that, as reported in adults, maximal antipsychotic effects in schizophrenic children and adolescents may not be evident until after 6–9 months of clozapine therapy. For most children and adolescents in the study, clozapine improved interpersonal functioning and enabled a return to a less restrictive setting. However, mild to moderate neutropenia occurred in 24% of the patients, and 29% required therapy with an anticonvulsant.

Suicide Risk Reduction in Schizophrenia and Schizoaffective Disorder Clozapine is used to reduce the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at chronic risk for such behavior, based on history and recent clinical state. Efficacy of clozapine for this indication has been established in a multicenter, randomized, open-label clinical study (the International Suicide Prevention Trial [Inter SePT]) of 2 years' duration comparing clozapine and olanzapine in patients with schizophrenia (62%) or schizoaffective disorder (38%) who were judged to be at risk for recurrent suicidal behavior. These patients either had attempted suicide or had been hospitalized to prevent a suicide attempt within the 3 years prior to their baseline evaluation or had demonstrated moderate-to-severe suicidal ideation with a depressive component or command hallucinations to do self-harm within 1 week prior to their baseline evaluation. Treatment resistance (i.e., resistance to standard antipsychotic drug therapies) was not a requirement for inclusion in this study, and only 27% of the total patient population was identified as being treatment resistant at baseline.

In the Inter SePT study, patients who received flexible dosages of clozapine (mean dosage: 274.2 mg daily) for approximately 2 years had a 26% reduction in their risk for suicide attempts or hospitalization to prevent suicide compared with those who received flexible dosages of olanzapine (mean dosage: 16.6 mg daily); the treatment-resistant status of patients was not predictive of response to clozapine or olanzapine. The cumulative probability of experiencing a suicide attempt, including a completed suicide, or hospitalization due to imminent suicide risk (including increased level of surveillance for suicidal behavior for patients already hospitalized) also was lower for patients receiving clozapine (24%) than for those receiving olanzapine (32%) at year 2. In addition, patients receiving clozapine had a statistically significant longer delay in the time to recurrent suicidal behavior than those receiving olanzapine. These results, however, may have been confounded by extensive use of other treatments to reduce the suicide risk, including concomitant psychotropic agents (84% with antipsychotics; 65% with anxiolytics; 53% with antidepressants, 28% with mood stabilizers), hospitalization and psychotherapy, the contributions of which to clozapine's efficacy are unknown.

Some clinicians state that methodologic problems (e.g., lack of actively suicidal patients in the study, possible bias and unblinding of suicide monitoring board members during the study, use of concomitant psychotropic agents) associated with the Inter SePT study limit definitive conclusions about the efficacy of clozapine for prevention of suicide in patients with schizophrenia or schizoaffective disorder. The US Food and Drug Administration (FDA) currently is advising clinicians to interpret the results of the Inter SePT study only as evidence of the efficacy of clozapine in delaying time to recurrent suicidal behavior, and not as efficacy of the drug for treatment of suicidal behaviors or as a demonstration of the superior efficacy of clozapine over olanzapine. However, the APA states that, based on the available evidence from the Inter SePT study, clozapine should be preferentially considered for schizophrenia patients with a history of chronic and persistent suicidal ideation and behaviors. Decisions to initiate clozapine therapy or switch patients from other antipsychotics to clozapine, therefore, should be individualized. In addition, safety and efficacy of clozapine in actively suicidal patients have yet to be determined.

■ **Parkinsonian Syndrome** Clozapine has been used in a limited number of patients with advanced, idiopathic parkinsonian syndrome for the management of dopaminomimetic psychosis† associated with antiparkinsonian drug therapy, but adverse effects such as sedation, confusion, and increased parkinsonian manifestations may limit the benefit of clozapine therapy in these patients. Attempts to relieve antiparkinsonian drug-induced delusions, paranoia, and hallucinations by reduction of antiparkinsonian drug dosage or administration of typical antipsychotic agents often aggravate parkinsonian symptoms. Limited data suggest that administration of clozapine in dosages of 6.25–400 mg daily can improve psychotic symptoms within a few days, reportedly without exacerbating parkinsonian manifestations. However, in a controlled study in a limited number of patients receiving clozapine dosages up to 250 mg daily, exacerbation of parkinsonian manifestations and development of delirium occurred frequently despite prevention of antiparkinsonian drug-induced deterioration of psychosis; it has been suggested that rapid clozapine dosage escalation may have contributed to the observed negative effect on parkinsonian manifestations and delirium. Clozapine dosages of 100–250 mg daily reportedly have been associated with hypersalivation, hypophonia, bradykinesia, and considerable sedation in patients with idiopathic parkinsonian syndrome, and withdrawal of clozapine therapy or a decrease in dosage also has exacerbated parkinsonian manifestations. Some clinicians suggest that the dosage of clozapine required to treat drug-induced dopaminomimetic psychosis may be substantially less than that required for treatment of psychosis in young, otherwise healthy individuals and that clozapine therapy should be initiated at low dosages (e.g., 6.25–50 mg daily) with cautious upward titration (e.g., to a maximum of 100–200 mg daily). Other clinicians have suggested that clozapine be used only as a last resort in patients with drug-induced dopaminomimetic psychosis.

Dosage and Administration

■ **Administration** Because of the risk of potentially life-threatening agranulocytosis, clozapine is available only through distribution systems that ensure baseline and periodic blood tests prior to delivery of the next supply of medication; dispensing is contingent on the results of the white blood cell (WBC) count and the absolute neutrophil count (ANC). (See Granulocytopenia and Agranulocytosis under Cautions: Hematologic Effects.) Although the amount of clozapine dispensed usually should not exceed a weekly supply, the manufacturers state that additional amounts (up to a 1-week supply) of the drug may be dispensed in exceptional circumstances (e.g., weather, holidays). In addition, patients may receive a supply sufficient for therapy for a period of time equal to that of the monitoring period; patients monitored weekly may receive a 1-week (7 day) supply of medication, patients monitored biweekly may receive a 2-week (14 day) supply, and patients eligible for monitoring every 4 weeks may receive a 28-day supply of medication, depending on WBC count and ANC results.

While availability of clozapine previously was exclusively through Novartis' Clozaril® Patient Monitoring System (CPMS), run jointly with CareMark and Roche Biomedical Laboratories, other distribution systems currently are in place; the individual manufacturers should be contacted for additional information on current mechanisms for obtaining the drug. Before initiating clozapine therapy in any patient, clinicians should check with the Clozaril® National Registry (phone number: [800]448-5938) to ensure that the patient does not have a history of clozapine-induced agranulocytosis or severe leukopenia/granulocytopenia; clozapine should *not* be administered to patients with such a history. (See Cautions: Hematologic Effects.)

Clozapine is administered orally, without regard to meals. Clozapine also has been administered IM†, but a parenteral preparation currently is not commercially available in the US.

Patients receiving clozapine orally disintegrating tablets should be instructed not to remove a tablet from the blister until just prior to dosing. The tablet should not be pushed through the foil; instead, the blister backing should be peeled completely off the blister. The tablet should then be gently removed and immediately placed on the tongue, where it rapidly disintegrates in saliva, and then subsequently swallowed with or without liquid. When clozapine orally disintegrating tablets are divided, the remaining half of the tablet that is not taken should be destroyed.

■ **Dosage** Dosage of clozapine should be carefully adjusted according to individual requirements and response using the lowest possible effective dosage.

Cautious dosage titration and administration of clozapine in divided doses are necessary to minimize the risk of certain adverse effects such as hypotension, seizures, and sedation. (See Cautions: Nervous System Effects and also see Cautions: Cardiovascular Effects.) The sedative effects of the drug may necessitate administration of most or all of the daily dose at bedtime, but some clinicians recommend that doses exceeding 500 mg generally be divided (e.g., a portion in the evening and the remainder at bedtime). Some clinicians also suggest that administration of clozapine in the morning be avoided, particularly in outpatients, at least until the patient has developed tolerance to the sedative effects of the drug.

Schizophrenia **Adult Dosage.** For the management of schizophrenia, the usual initial adult dosage of clozapine is 12.5 mg (one-half of a 25-mg tablet) once or twice daily. (If therapy is initiated with orally disintegrating tablets, the remaining half tablet should be destroyed.) Some clinicians advise that, if practical, consideration should be given to administering the first dose in a setting where facilities for cardiopulmonary resuscitation are available for at least a few hours after the first dose. If the drug is well tolerated, dosage may be increased by 25–50 mg daily over a 2-week period until a dosage of 300–450 mg daily is achieved. Subsequent dosage increases should be made no more frequently than once or twice weekly, in increments not exceeding 50–100 mg. The manufacturers state that cautious titration is necessary to minimize the risks of hypotension, myoclonic jerks, generalized seizures, and sedation. (See Cautions: Nervous System Effects.) If myoclonic jerks or generalized seizures occur, dosage of clozapine should be reduced and, if necessary, anticonvulsant therapy initiated.

Daily administration of clozapine in divided doses should continue until an effective and tolerable dosage is reached, usually within 2–5 weeks. Although many patients may respond adequately to dosages between 200–600 mg daily, a dosage of 600–900 mg daily may be required in some patients. In the multicenter study that provides the principal support for the effectiveness of clozapine in patients resistant to standard antipsychotic therapy, the maximum dosage of clozapine ranged from 100–900 mg daily, which was given in 3 divided doses. The mean and median clozapine dosages in this study both were approximately 600 mg daily. Although some clinicians suggest that dosages exceeding 450–500 mg daily have not been shown to be associated with increased therapeutic benefit, others state that added response is observed at higher dosages in some patients and stress the need for individualized therapy. The manufacturers and most clinicians recommend that the maximum daily dosage of clozapine not exceed 900 mg. Because of the possibility that high dosages of clozapine may be associated with an increased risk of adverse reactions, particularly seizures, patients generally should be given adequate time to respond to a given dosage before dosage escalation is considered.

Pediatric Dosage. The dosage of clozapine for the management of schizophrenia in children and adolescents† has not been established. However, the National Institute of Mental Health (NIMH) protocol used an initial dosage of 6.25–25 mg daily depending on the patient's weight. Dosages could be increased in this study every 3–4 days by 1–2 times the initial dose on an individual basis up to a maximum of 525 mg daily.

Duration of Therapy. The optimum duration of clozapine therapy for the management of schizophrenia currently is not known. While some clinicians state that clozapine therapy should be continued for longer than 6 weeks only in patients who exhibit substantial benefit within this period, others state that even less than substantial degrees of benefit may warrant continued therapy and that an adequate trial of clozapine may require at least 12 weeks (e.g., at 200–600 mg daily) or possibly 5–9 months or longer unless clinical deterioration or intolerable or potentially serious toxicity precludes it. The manufacturers currently recommend that patients who respond continue to receive clozapine therapy but at the lowest dosage needed to maintain remission of symptoms; following effective control of symptoms, dosage may be reduced gradually to determine the minimum therapeutic maintenance dose. In addition, patients should be reassessed periodically to determine the need for continued therapy with the drug. Extended therapy in patients failing to show an acceptable response to clozapine generally should be avoided because of the substantial, continuing risks of agranulocytosis and seizures. (See Cautions: Hematologic Effects and also see Seizures under Cautions: Nervous System Effects.)

Suicide Risk Reduction For suicide risk reduction in schizophrenia and schizoaffective disorder, the usual initial adult dosage of clozapine is 12.5 mg once or twice daily. If the drug is well tolerated, dosage may be increased by 25–50 mg daily over a 2-week period until a dosage of 300–450 mg daily is achieved. Subsequent dosage increases should be made no more frequently than once or twice weekly, in increments not exceeding 50–100 mg. In the multicenter Inter SePT study that provides the principal support for the effectiveness of clozapine for suicide risk reduction, mean dosage was about 300 mg daily (range: 12.5–900 mg daily).

Because efficacy of clozapine for this indication was demonstrated over a 2-year treatment period in this study, clozapine therapy to reduce the risk of suicidal behavior should be continued for at least 2 years. After 2 years, it is recommended that the patient's risk of suicidal behavior be reassessed. If the clinician's assessment indicates that a clinically important risk for suicidal behavior is still present, clozapine therapy should be continued. Thereafter, the need to continue therapy with the drug should be reevaluated at regular intervals, based on thorough assessments of the patient's risk for suicidal behavior during treatment. If the clinician determines that the patient is no longer at risk for suicidal behavior, clozapine therapy may be discontinued gradually (see Dosage: Discontinuance of Therapy) and treatment of the underlying disorder with an antipsychotic agent to which the patient has previously responded may be resumed.

Discontinuance of Therapy In the event of planned termination of clozapine therapy, gradual reduction in dosage over a 1- to 2-week period is recommended. However, should abrupt discontinuance of therapy be required (e.g., because of leukopenia or agranulocytosis), the patient should be observed carefully for recurrence of psychotic symptoms and symptoms related to cholinergic rebound such as headache, nausea, vomiting, and diarrhea. Sudden withdrawal from clozapine therapy can lead to rapid decompensation and rebound psychosis. (See Other Nervous System Effects under Cautions: Nervous System Effects.)

Reinitiation of Therapy If clozapine therapy is restarted in patients who have had even brief interruptions (i.e., 2 days or more) in therapy, dosage generally should be titrated as with initial therapy (i.e., 12.5 mg once or twice daily). If this dosage is well tolerated, dosage may be titrated back to the therapeutic dosage more quickly than during initial treatment. The manufacturers state that clozapine therapy should be reinstituted with extreme caution, even following brief interruptions of only 24 hours, in patients who have previously experienced respiratory or cardiac arrest during initial dosing but subsequently were titrated to a therapeutic dosage.

Because the mechanisms underlying clozapine-induced adverse reactions are unknown and it is conceivable that reexposure might enhance the risk of an adverse effect and/or increase its severity (e.g., when immune-mediated mechanisms are involved), the manufacturers advise additional caution during reinitiation of therapy. When reinitiating therapy, consider WBC count and ANC monitoring recommendations. (See Table 2: WBC and ANC Monitoring for Clozapine Reinitiation under Cautions.)

Patients in whom clozapine therapy is discontinued because of leukocyte counts less than 2000/mm^3 or an ANC less than 1000/ mm^3 must *not* be restarted on the drug. (See Cautions: Hematologic Effects.)

Cautions

Although clozapine differs chemically from the phenothiazines, the drug may be capable of producing many of the toxic manifestations of phenothiazine derivatives. Not all adverse effects of the phenothiazines have been reported with clozapine, but the possibility that they may occur should be considered. Adverse effects of clozapine and the phenothiazines are numerous and may involve nearly all organ systems. Although these effects usually are reversible when dosage is reduced or the drug is discontinued, some effects may be irreversible and, rarely, fatal. In some patients, unexpected death associated with

antipsychotic therapy has been attributed to cardiac arrest or asphyxia resulting from failure of the gag reflex. (See Cautions: Cardiovascular Effects.) In other cases, the cause of death could not be determined or definitely attributed to antipsychotic drug therapy. An increased risk of death has been observed in geriatric patients with dementia-related psychoses receiving atypical antipsychotics. (See Cautions: Geriatric Precautions.)

The most frequent adverse effects of clozapine involve the central and autonomic nervous systems (e.g., drowsiness or sedation, hypersalivation) and the cardiovascular system (e.g., tachycardia, hypotension). While the frequency and severity of some adverse effects (e.g., extrapyramidal reactions, tardive dyskinesia) appear to be less with clozapine than with other antipsychotic agents, other potentially serious adverse effects (e.g., agranulocytosis, seizures) may occur more frequently with clozapine therapy, and the potential risks and benefits should be evaluated carefully whenever therapy with the drug is considered. Because of the substantial risk of clozapine-associated agranulocytosis, which may persist over an extended period of time and be life-threatening or fatal if not detected early and therapy interrupted, clozapine is available for use only through patient-management systems that ensure baseline and periodic blood tests prior to delivery of the next supply of medication; dispensing is contingent on the results of the white blood cell (WBC) count and absolute neutrophil count (ANC). Before initiating clozapine therapy in any patient, clinicians should check with the Clozaril® National Registry to ensure that the patient has no history of clozapine-induced agranulocytosis or severe leukopenia/granulocytopenia; clozapine should *not* be administered to patients with such a history. (See Cautions: Hematologic Effects.)

■ **Hematologic Effects** ***Granulocytopenia and Agranulocytosis***

Agranulocytosis, defined as an absolute neutrophil count (ANC) less than 500/mm³ and characterized by leukopenia (WBC count less than 2000/mm³) and relative lymphopenia, has an estimated cumulative incidence of 1–2% after 1 year of clozapine therapy, as compared with an estimated incidence of 0.1–1% for phenothiazine-induced agranulocytosis. The rate of clozapine-induced agranulocytosis is based on the occurrence of 15 cases out of 1743 patients who received clozapine during clinical trials in the US. Some evidence suggests that the incidence of clozapine-induced agranulocytosis is at least 10 times greater than that of other antipsychotic agents, although it also has been suggested that the incidence of clozapine-induced agranulocytosis may be no higher than that associated with phenothiazines. Of the 149 cases of clozapine-induced agranulocytosis reported worldwide as of December 31, 1989, 32% were fatal. Few of these fatalities have occurred since 1977 when the knowledge of clozapine-induced agranulocytosis became widespread and close monitoring of WBC count became widely practiced. In the US, under a weekly leukocyte monitoring system in premarketing studies and in postmarketing experience with clozapine, 585 cases of agranulocytosis, including 19 fatalities, had occurred as of August 21, 1997; one patient receiving concomitant therapy with carbamazepine and clozapine died following development of an unusual hypoplastic anemia with agranulocytosis, a pancytopenic condition not usually characteristic of clozapine-induced hematologic effects. Based on analysis of data pooled from a confidential national master file of information (the Clozaril® National Registry), the incidence of agranulocytosis appears to rise steeply during the first 2 months of therapy and peaks in the third month. The incidence gradually declines with continued therapy and reaches a rate of 3 per 1000 person-years by 6 months of therapy. After 6 months, the incidence of agranulocytosis declines still further. However, the manufacturer of Clozaril® cautions that a reduction in the frequency of leukocyte monitoring may result in an increase in incidence of agranulocytosis.

The precise mechanism by which clozapine induces agranulocytosis is not known, but both immunologic and toxic mechanisms (including a direct myelotoxic effect of the drug and/or its metabolites) have been implicated. Some evidence suggests that granulocyte antibodies may be involved. Except for the evidence of marked bone marrow depression during initial clozapine therapy and a disproportionate number of females, there are no established risk factors, based on worldwide experience, for developing clozapine-induced agranulocytosis. However, a disproportionate number of US cases have occurred in patients of Eastern European Jewish heritage compared with the overall proportion of such patients exposed to clozapine during domestic trials. Results of genetic typing indicate that genetic factors marked by a major histocompatibility complex haplotype (HLA-B38, DR4, DQw3) may be associated with the susceptibility of certain Jewish patients with schizophrenia to develop agranulocytosis when treated with clozapine; the incidence of some phenotypes common among Ashkenazi Jews has been found to be greatly increased in patients with clozapine-induced agranulocytosis.

Most cases of clozapine-induced agranulocytosis in the US have occurred within 4–16 weeks of exposure to the drug. Although no patient characteristics predictive of an increased risk of agranulocytosis with clozapine have been identified conclusively, agranulocytosis associated with the use of other antipsychotic agents has been reported to occur more frequently in women, geriatric patients, and patients who are cachectic or have serious underlying medical conditions (e.g., immunocompromised patients, patients with human immunodeficiency virus [HIV] infection); such patients also may be at increased risk for developing agranuloeytosis with clozapine therapy.

Investigation of 16 cases of clozapine-associated granuloeytopenia occurring within a 2-month period in 1975 in southwest Finland, including 13 cases of agranulocytosis, revealed characteristics similar to those of phenothiazine-induced agranulocytosis. In all of these cases, the reaction occurred during first exposure to the drug and followed a latent period of 17–109 days at a cumulative dose of 4.5–42 g; reduced values for hemoglobin and peripheral erythrocyte and thrombocyte counts were found infrequently, and granulopoiesis in sternal marrow usually was severely depressed or absent. Erythropoiesis was below normal in only one case, and thrombopoiesis was normal or even increased. Hematologic values returned to baseline within 1–3 weeks after withdrawal of clozapine. All fatalities were attributed to secondary infection in patients in whom granulocytopenia was not diagnosed early or clozapine discontinued promptly. In patients who died, the clinical course typically consisted of fever with tonsillitis, which progressed to pneumonia and septicemia; the immediate cause of death usually was renal or cardiac failure. The frequency of clozapine-induced agranulocytosis or granulocytopenia in the Finnish experience was 7.1 per thousand—approximately 21 times higher than that reported in other countries. Although it has been suggested that a local genetic or environmental factor or factors may have been involved in the Finnish cases, the existence of such a factor has not been documented.

The most likely time of occurrence of granulocytopenia appears to be 4–16 weeks after initiation of treatment with clozapine. However, neither dose nor duration of therapy is a reliable predictor of agranulocytosis. Most patients develop agranulocytosis within the first 10 weeks of therapy, but a latent period of up to 1 year or longer also has been reported. Within the first 18 weeks of therapy, 77–90% of all cases of granulocytopeniu and agranuloeytosis have been reported and 85% of fatalities secondary to agranulocytosis have occurred. The latent period between the fall in leukocyte count and the development of a secondary infection usually is moderately long. Leukooyte count usually declines gradually (e.g., over a period of weeks), but it also may decline precipitously. Patients receiving clozapine may have a transient and benign reduction in leukocyte count without progression to agranulocytosis, and may or may not develop manifestations of infection (e.g., fever, sore throat).

Patients in whom granulocytopenia is diagnosed and clozapine therapy discontinued before the occurrence of infection generally have a favorable prognosis. Early diagnosis of granulocytopenia and appropriate medical management can forestall serious consequences and reduce morbidity and mortality substantially since the condition generally is reversible if clozapine is discontinued promptly. In contrast, agranulocytosis is more likely to be fatal in patients in whom clozapine therapy is not halted before the development of infection.

Because of the substantial, persistent risk of agranulocytosis associated with clozapine use, patients must have a WBC count and ANC performed before initiation of therapy with the drug. Clozapine therapy should not be initiated if the baseline WBC count is less than 3500/mm³ or the ANC is less than 2000/mm³. While some clinicians suggest that WBC counts be done weekly during the first 4–12 months of therapy and then less frequently (e.g., every 2 weeks or monthly) thereafter, other clinicians state that patients must have weekly WBC counts for the duration of therapy. However, the manufacturers suggest that the frequency of monitoring depends in part on the duration of therapy, adherence to therapy, and development of adverse hematologic effects. The manufacturers state that patients must have WBC counts and ANC monitored at least weekly for the first 6 months of continuous treatment and then every other week for the next 6 months if WBC counts and ANC remain acceptable (WBC count equal to or exceeding 3500/mm³, ANC equal to or exceeding 2000/mm³). After a further 6 months, if acceptable WBC counts and ANCs continue to be maintained, the frequency of monitoring may be reduced to every 4 weeks for the remainder of clozapine therapy. After discontinuance of therapy, continue to monitor WBC count and ANC weekly for at least 4 weeks from the day of discontinuance or until WBC count is equal to or exceeding 3500/mm³ and ANC is equal to or exceeding 2000/mm³. The current recommendations for WBC count and ANC monitoring based on the stage of therapy and the results from WBC and ANC monitoring are provided in Table 1 below. Dispensing of clozapine is contingent upon compliance with these *required* WBC and ANC tests. (See Dosage and Administration: Administration.)

Table 1. Frequency of Monitoring based on Stage of Therapy or Results from WBC and ANC Monitoring

Situation	Hematological Values	Frequency of WBC and ANC Monitoring
Initiation of therapy	WBC ≥3500/mm³ ANC ≥2000/mm³ Do not initiate in patients with a history of myeloproliferative disorder or clozapine-induced agranulocytosis or granulocytopenia.	Weekly for 6 months.
During 6–12 months of therapy	All results for WBC ≥3500/mm³ and ANC ≥2000/mm³	Every 2 weeks for 6 months.
After 12 months of therapy	All results for WBC ≥3500/mm³ and ANC ≥2000/mm³	Every 4 weeks thereafter.
Immature forms present	Not applicable	Repeat WBC and ANC.

Discontinuance of therapy	Not applicable	Weekly for at least 4 weeks from day of discontinuance or until WBC ≥3500/mm³ and ANC ≥2000/mm³.
Substantial decrease in WBC or ANC	Single decrease or cumulative decrease within 3 weeks of WBC≥3000/mm³ or ANC ≥1500/mm³	Repeat WBC and ANC. Carefully monitor for manifestations of infection.** If repeat values for WBC ≥3000/mm³ and ≤3500/mm³ and ANC <2000/mm³, monitor twice weekly.
Mild leukopenia/mild granulocytopenia	WBC ≥3000/mm³ but <3500/mm³ and/or ANC ≥1500/mm³ but <2000/mm³	Monitor twice weekly until WBC >3500/mm³ and ANC >2000/mm³, then resume previous monitoring frequency. Carefully monitor for manifestations of infection.**
Moderate leukopenia/moderate granulocytopenia	WBC ≥2000/mm³ but <3000/mm³ and/or ANC ≥1000/mm³ but <1500/mm³	Interrupt therapy and carefully monitor for manifestations of infection.** Monitor daily until WBC >3000/mm³ and ANC >1500/mm³, then monitor twice weekly until WBC >3500/mm³ and ANC >2000/mm³. May rechallenge when WBC >3500/mm³ and ANC >2000/mm³. If rechallenged, monitor weekly for 1 year before returning to the usual monitoring schedule of every 2 weeks for 6 months then every 4 weeks indefinitely.
Severe leukopenia/severe granulocytopenia	WBC <2000/mm³ and/or ANC <1000/mm³	Discontinue therapy and *do not rechallenge patient.** Carefully monitor for manifestations of infection.** Monitor until normal and for at least 4 weeks from day of discontinuance as follows: daily until WBC >3000/mm³ and ANC >1500/mm³, twice weekly until WBC >3500/mm³ and ANC >2000/mm³, then weekly after WBC >3500/mm³. Consider bone marrow aspiration to determine granulopoietic status; if granulopoiesis is deficient, protective isolation with close observation may be indicated. If infection develops, perform cultures and institute appropriate anti-infective therapy.
Agranulocytosis	ANC ≤500/mm³	Discontinue therapy and *do not rechallenge patient.** Carefully monitor for manifestations of infection.** Monitor until normal and for at least 4 weeks from day of discontinuance as follows: daily until WBC >3000/mm³ and ANC >1500/mm³, twice weekly until WBC >3500/mm³ and ANC >2000/mm³, then weekly after WBC >3500/mm³. Consider bone marrow aspiration to determine granulopoietic status; if granulopoiesis is deficient, protective isolation with close observation may be indicated. If infection develops, perform cultures and institute appropriate anti-infective therapy.

* Agranulocytosis develops upon rechallenge, often with a shorter latency. Patients who have experienced substantial bone marrow suppression during therapy are listed in a national master file. (See Dosage and Administration: Administration.)

** Carefully monitor for flu-like symptoms or other manifestations of infection; institute appropriate anti-infective therapy if necessary.

If clozapine therapy is reinitiated after interruption of therapy, WBC counts and ANC should be monitored after reinitiating therapy based on the duration of previous therapy, length of interruption of therapy, and previous WBC counts and ANC in the patient according to the schedule in Table 2 below:

Table 2. WBC and ANC Monitoring for Clozapine Reinitiation

Previous therapy duration <6 months, with no abnormal blood event (WBC ≥3500/mm³ and ANC ≥2000/mm³) and interruption in therapy ≥3 days but≤1 month	Continue with weekly WBC and ANC monitoring where left off in schedule; do not restart 6-month period. When 6-month period complete, may decrease monitoring frequency to every other week.
Previous therapy duration <6 months, with no abnormal blood event and interruption in therapy >1 month	Monitor WBC and ANC weekly for *additional* 6 months before decreasing to biweekly testing.
Previous therapy duration <6 months, *with* abnormal blood event (WBC <3500/mm³ or ANC <2000/mm³) but rechallengeable (i.e., WBC ≥2000/mm³ and ANC ≥1000/mm³ during previous therapy)	See Table 1.
Previous therapy duration 6–12 months, with no abnormal blood event and interruption in therapy ≥3 days but ≤1 month	Monitor WBC and ANC weekly for 6 weeks, then resume monitoring every other week for an additional 6 months.*
Previous therapy duration 6–12 months, with no abnormal blood event and interruption in therapy >1 month	Monitor WBC and ANC weekly for 6 months, then resume monitoring every other week for an additional 6 months.*
Previous therapy duration 6–12 months, *with* abnormal blood event (WBC <3500/mm³ or ANC <2000/mm³) but rechallengeable (i.e., WBC ≥2000/mm³ and ANC ≥1000/mm³ during previous therapy)	See Table 1.*
Previous therapy duration >12 months, with no abnormal blood event and interruption in therapy ≥3 days but ≤1 month	Monitor WBC and ANC weekly for 6 weeks, then resume monitoring every 4 weeks.*
Previous therapy duration >12 months, with no abnormal blood event and interruption in therapy >1 month	Monitor WBC and ANC weekly for 6 months, then resume monitoring every other week for an additional 6 months, then resume monitoring every 4 weeks.*
Previous therapy duration >12 months, *with* abnormal blood event (WBC <3500/mm³ or ANC <2000/mm³) but rechallengeable (i.e., WBC ≥2000/mm³ and ANC ≥1000/mm³ during previous therapy)	See Table 1.

*Transition to reduce frequency of monitoring only permitted if all WBC counts are equal to or exceeding 3500/mm³ and ANC values are equal to or exceeding 2000/mm³.

Although some clinicians suggest that body temperature be measured at least once daily for the first 18 weeks of clozapine therapy, others state that such monitoring is not an adequate means of assessing infection in clozapine-treated patients because of the drug's pharmacologic potential for causing temperature elevation. Patients receiving clozapine should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat, or any other potential manifestation of infection.

Supportive therapy with biosynthetic hematopoietic agents, including filgrastim, a recombinant human granulocyte colony-stimulating factor (G-CSF), and sargramostim, a recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF), has been effective in a limited number of patients with clozapine-induced neutropenia and agranulocytosis. Consultation with a hematologist and infectious disease expert is recommended.

When granulocytopenia is diagnosed and clozapine therapy is discontinued, patients usually recover in 7–28 days. Most of these patients require further antipsychotic therapy because of a recurrence of psychotic symptoms. (See Other Nervous System Effects under Cautions: Nervous System Effects.) Since there appears to be no cross-sensitivity between clozapine and other antipsychotics in terms of hematologic toxicity, other antipsychotic drugs generally may be used without causing further hematologic complications in patients who develop clozapine-induced agranulocytosis. However, patients who develop clozapine-induced agranulocytosis (or those in whom the total WBC count and ANC decrease to less than 2000/mm³ and less than 1000/mm³, respectively) should *not* be rechallenged with clozapine. Patients in whom clozapine therapy has been discontinued due to substantial leukocyte suppression have been found to develop agranulocytosis upon rechallenge with the drug, often with a shorter latency on reexposure. To reduce the chance of rechallenge in patients who

have experienced substantial bone marrow suppression with clozapine therapy, the manufacturer of Clozaril® maintains a confidential national master file of information (the Clozaril® National Registry) on all nonrechallengeable patients.

Eosinophilia Eosinophilia has been reported in approximately 1% of patients who received clozapine therapy in clinical trials. The manufacturers state that if the total eosinophil count exceeds 4000/mm³, clozapine therapy should be temporarily discontinued until the count falls below 3000/mm³.

Other Hematologic Effects Other hematologic effects reported with clozapine therapy include leukopenia, neutropenia, and thrombocytopenia, which have been reported in 1–3% of patients. Anemia, leukocytosis, and increased platelet count have been reported in less than 1% of patients receiving clozapine. Other clozapine-induced hematologic effects reportedly include basophilia, a substantial reduction in B cells, and an increase in hemoglobin concentration. Elevated erythrocyte sedimentation rate (ESR) and sepsis have been reported in patients receiving clozapine during postmarketing surveillance; however, a causal relationship to the drug has not been established.

■ **Nervous System Effects** ***Seizures*** Clozapine lowers the seizure threshold and can cause EEG changes, including the occurrence of spike and wave complexes. Seizures reportedly occurred in approximately 3.5% of patients exposed to the drug during clinical trials in the US (cumulative annual incidence of approximately 5%). In contrast, a seizure incidence of approximately 1% has been reported in patients treated with other antipsychotic agents. The risk of seizures with clozapine therapy appears to be related to dosage and/or plasma concentrations of the drug, with a reported incidence of approximately 0.6–2% at dosages less than 300 mg daily, 1.4–5% at 300–600 mg daily, and 5–14% at high dosages (600–900 mg daily). Clozapine-induced seizures may be associated with rapid dosage escalations, particularly in patients with preexisting epilepsy, and in those receiving concomitant therapy with drugs that may lead to increased plasma concentrations of clozapine. If myoclonic jerks or generalized seizures occur, clozapine dosage should be reduced and, if necessary, anticonvulsant treatment initiated.

One patient receiving clozapine experienced a generalized tonic-clonic (grand mal) seizure following accidental ingestion of an extra dose (total dose ingested within 24 hours: 1050 mg); the same patient had another seizure several weeks later, 2 hours after a usual 450-mg morning dose. Results of plasma clozapine determinations obtained at the time of the seizures revealed plasma clozapine concentrations of approximately 2000 ng/mL in each case. Another patient who had been taking clozapine for 27 months had a generalized tonic-clonic seizure following an apparent intentional overdosage (total dose ingested within 24 hours: approximately 3 g), after which the patient made an uneventful recovery. One hour after the seizure, the patient's plasma clozapine concentration was 1313 ng/mL.

Discontinuance of clozapine therapy, at least temporarily, should be seriously considered in patients who experience seizures while receiving the drug; however, some clinicians state that reduced clozapine dosage and/or, occasionally, addition of anticonvulsant therapy may adequately ameliorate this effect. If clozapine therapy is to be continued in such patients, many clinicians recommend obtaining additional informed consent from the patient. In patients in whom clozapine is withheld, it has been suggested that therapy with the drug can be reinitiated at one-half the previous dosage. Clozapine dosage may then be increased gradually, if clinically indicated, and the need for concomitant anticonvulsant therapy should be considered. Some clinicians recommend that patients who have experienced a clozapine-induced seizure *not* be given clozapine dosages exceeding 600 mg daily unless the results of an EEG performed prior to the anticipated dosage increase are normal; others suggest addition of anticonvulsant therapy and/or consultation with a neurologist in managing such patients. In patients with preexisting seizure disorders who are treated concomitantly with certain anticonvulsants and clozapine, the anticonvulsant dosage may need to be increased. However, clozapine should not be used concomitantly with anticonvulsants (e.g., carbamazepine) or other drugs that potentially may cause bone marrow suppression. (See Drug Interactions: Myelosuppressive Agents.)

Extrapyramidal Reactions In contrast to other antipsychotic agents, clozapine has a low potential for causing certain acute extrapyramidal effects (e.g., dystonias). Such effects, when they occur, have been limited principally to tremor, restlessness, rigidity, and akathisia; these manifestations generally are milder and less persistent than those produced by other antipsychotic drugs. In addition, marked or total remission of such manifestations induced by other antipsychotics has occurred during treatment with clozapine in some patients.

Neuroleptic malignant syndrome (NMS), a potentially fatal symptom complex, has been reported in patients receiving phenothiazines or other antipsychotic therapy. NMS attributable to clozapine therapy alone has been reported in a few patients, and there also have been several reports of NMS in patients treated concomitantly with clozapine and lithium or other CNS drugs; some clinicians suggest that NMS may be more likely to occur when clozapine or other antipsychotic agents are used concomitantly with lithium. Manifestations of NMS (e.g., muscle rigidity, hyperpyrexia, tachycardia, increased serum creatine kinase [CK, creatine phosphokinase, CPK], diaphoresis, somnolence), all of which may not occur in all patients with the condition, have occurred in a few patients treated with clozapine alone or combined with lithium or carbamazepine; resolution of the syndrome occurred following discontinuance of clozapine. However, clozapine also has been used successfully and apparently without recurrence of NMS in at least one patient who developed the syndrome while receiving chlorpromazine.

For additional information on NMS, see Extrapyramidal Reactions in Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Tardive Dyskinesia A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic agents. However, results of clinical trials in which clozapine was used have demonstrated a virtual absence of acute extrapyramidal reactions (e.g., dystonia), and there reportedly have been no confirmed cases of tardive dyskinesia associated with clozapine therapy alone. Nevertheless, a few cases of tardive dyskinesia have been reported in patients receiving clozapine who had been treated previously with other antipsychotic agents. Although current evidence suggests that clozapine may be less likely than other antipsychotic agents to cause tardive dyskinesia, it cannot yet be concluded, based on current limited experience, that the drug is incapable of causing this syndrome. The possibility of clozapine-induced tardive dyskinesia should be considered in patients receiving long-term therapy with the drug or in those starting clozapine therapy after discontinuance of conventional (typical) antipsychotic agents.

For additional information on tardive dyskinesia, see Tardive Dyskinesia in Cautions: Nervous System Effects in the Phenothiazines General Statement 28:16.08.24.

Other Nervous System Effects Drowsiness and/or sedation occur frequently in patients receiving clozapine. (See Effects on Sleep under Pharmacology: Nervous System Effects.) Somnolence reportedly occurred in 46% of patients receiving clozapine in the International Suicide Prevention Trial (InterSePT) compared with 25% of those receiving olanzapine. The sedative-hypnotic effect of clozapine is most pronounced initially, diminishes after 1–4 weeks, and then generally, but not always, disappears during continued therapy. Daytime sleepiness may be minimized by administration of clozapine at bedtime. (See Dosage and Administration: Dosage.)

Dizziness and vertigo, headache, syncope, disturbed sleep (e.g., insomnia) or nightmares, hypokinesia or akinesia, and agitation have been reported with clozapine therapy. In the International Suicide Prevention Trial (InterSePT), dizziness (excluding vertigo) and insomnia reportedly occurred in 27 and 20% of patients receiving clozapine, respectively, compared with 12 and 33% of those receiving olanzapine, respectively. Clozapine also may cause confusion or delirium, which may be related to central anticholinergic effects, and has been ameliorated in some cases by IV administration of physostigmine. Depression, fatigue, hyperkinesia, weakness or lethargy, and slurred speech also have been reported. Other adverse nervous system effects associated with clozapine therapy include ataxia, epileptiform movements or myoclonic jerks, and anxiety.

Adverse nervous system effects reported in less than 1% of clozapine-treated patients include loss of speech, amentia (deterioration in cognitive function), tics, poor coordination, delusions or hallucinations, stuttering, dysarthria, amnesia, histrionic movements, increased or decreased libido, paranoia, shakiness, parkinsonian syndrome, and irritability. Difficulty in writing, residual daytime effects such as impairment of mental performance, and periodic cataplexy, which is characterized by sudden episodes of dropping objects and may or may not be accompanied by knee buckling, also have been reported infrequently with clozapine therapy. Exacerbation of psychosis, myoclonus, paresthesia, and status epilepticus have been reported in patients receiving clozapine during postmarketing surveillance; however, a causal relationship to the drug has not been established.

Abrupt discontinuance of clozapine (e.g., because of leukopenia or agranulocytosis) may result in recurrence of psychotic symptoms or behavior, including autism, auditory hallucinations, suicide attempts, development of parkinsonian symptoms, anxiety, insomnia, delusions, and violent behavior. It has been suggested that this "rebound psychosis" may result, at least in part, from clozapine-induced supersensitivity of mesolimbic dopamine receptors (see Behavioral Effects in Animals under Pharmacology: Nervous System Effects) and that the essential feature of this phenomenon appears to be recurrence of positive symptoms of schizophrenia. Patients who develop rebound psychosis following discontinuance of clozapine may improve with initiation of other antipsychotic therapy; however, clozapine should *not* be reinstituted in patients in whom severe leukopenia/granulocytopenia or agranulocytosis has occurred. (See Cautions: Hematologic Effects.)

■ **Fever** Fever or transient temperature elevations exceeding 38°C generally have been reported in 5% or more of patients receiving clozapine. The peak incidence of fever occurs within the first 3 weeks of therapy, usually between days 5–20 of treatment. Fever generally is benign and self-limiting and usually diminishes within a few (4–8) days despite continued clozapine therapy; however, it may necessitate discontinuance of the drug. Fever occasionally may be associated with an increase or decrease in leukocyte count, in which case patients should be evaluated for underlying infection or development of agranulocytosis. (See Cautions: Hematologic Effects.) In the presence of high fever, the possibility of neuroleptic malignant syndrome also must be considered. (See Extrapyramidal Reactions under Cautions: Nervous System Effects.)

The mechanism of clozapine-induced fever (other than that occurring secondary to some other factor such as infection) is not yet known. It may result from the drug's pronounced anticholinergic activity (see Anticholinergic Effects under Pharmacology: Nervous System Effects) or a direct effect on the

hypothalamic thermoregulatory center. Clozapine-induced hyperthermia may be a hypersensitivity reaction, a common mechanism underlying drug fevers. It has been suggested that decreasing the dosage of clozapine and then gradually increasing it to the previous level may reverse the hyperthermia and not be accompanied by a recurrence of elevated temperature; however, recurrence is possible despite such dosage adjustment.

■ **Cardiovascular Effects** ***Myocarditis*** Myocarditis (sometimes fatal) has been reported during postmarketing surveillance in patients receiving clozapine. Postmarketing surveillance data from 4 countries employing hematologic monitoring of clozapine-treated patients indicated 30 cases of myocarditis in 205,493 clozapine-treated US patients as of August 2001, 7 cases of myocarditis in 15,600 such Canadian patients as of April 2001, 30 cases of myocarditis in 24,108 such United Kingdom patients as of August 2001, and 15 cases of myocarditis in 8000 such Australian patients as of March 1999, representing an incidence of approximately 5, 16, 43, and 97 cases/100,000 patient-years of clozapine therapy, respectively. Of these 82 cases of myocarditis identified through postmarketing surveillance, 38% resulted in death. Although the overall incidence of myocarditis in patients with schizophrenia receiving antipsychotic agents is unknown, the incidence of myocarditis or fatal myocarditis, respectively, in patients receiving clozapine appears to be 17–322 or 14–161 times greater than the incidence in general population.

These postmarketing surveillance data also suggest that the incidence of myocarditis, including fatal myocarditis, may be highest during the first month of therapy, with 62% of myocarditis cases occurring within the first month of clozapine therapy, 31% of cases occurring after the first month of therapy, and the onset unknown in 7% of cases. Therefore, the possibility of myocarditis should be considered in patients receiving clozapine who present with unexplained fatigue, dyspnea, tachypnea, fever, chest pain, palpitations, other signs or symptoms of heart failure, or ECG findings such as ST-T wave changes or arrhythmias.

It is not known whether eosinophilia is a reliable predictor of myocarditis. However, tachycardia, which has been associated with clozapine therapy, also may be a manifestation of myocarditis. Therefore, tachycardia occurring during the first month of clozapine therapy warrants close monitoring for other manifestations of myocarditis. If myocarditis is suspected, the drug should be discontinued promptly. Because myocarditis recurred in 3 of 5 patients rechallenged with the drug, patients who develop myocarditis while receiving clozapine should *not* be rechallenged with the drug.

Cardiomyopathy Cardiomyopathy has been reported in US patients treated with clozapine at a reporting rate of 8.9 cases/100,000 person-years, which was similar to an estimate of the cardiomyopathy incidence in the US general population derived from the 1999 National Hospital Discharge Survey data (9.7 cases/100,000 person-years). Approximately 80% of clozapine-treated patients in whom cardiomyopathy was reported were younger than 50 years of age; the duration of treatment with clozapine prior to cardiomyopathy diagnosis varied, but exceeded 6 months in 65% of the reports. Dilated cardiomyopathy was most frequently reported, although a large percentage of reports did not specify the type of cardiomyopathy. 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.

Thromboembolic Effects Deep-vein thrombosis and pulmonary embolism have been reported in patients receiving clozapine during postmarketing surveillance. As of December 31, 1993, 18 cases of fatal pulmonary embolism were reported in patients 10–54 years of age receiving clozapine therapy. Based on the extent of use observed in the Clozaril National Registry, the mortality rate associated with pulmonary embolism was 1 death per 3450 person-years of use; this incidence is approximately 27.5 times higher than that in the general population. Although a causal relationship between clozapine and these adverse cardiovascular effects has not been established, the possibility of pulmonary embolism should be considered in patients presenting with deep-vein thrombosis or respiratory symptomatology. (See Cautions: Precautions and Contraindications.

Blood Pressure Effects Hypotension and hypertension reportedly occur in less than 10% of patients receiving clozapine. When they occur, changes in blood pressure, principally reductions in systolic pressure, appear soon after initiation of clozapine therapy and may be associated with rapid dosage increases. A decrease in arterial blood pressure below 90 mm Hg was reported in 18% of male patients and 33% of female patients receiving clozapine in one retrospective study. Hypotension may result from clozapine's antiadrenergic effects (see Adrenergic Effects under Pharmacology: Nervous System Effects) and may pose a serious risk for individuals with compromised cardiac function. However, tolerance to the hypotensive effects of clozapine often develops with continued therapy.

Orthostatic hypotension, with or without syncope, has been reported, particularly during initial titration or rapid escalation of clozapine dosage; however, this effect may represent a continuing risk in some patients. Rarely (approximately 1 case per 3000 patients), orthostatic hypotension has been accompanied by profound collapse and respiratory and/or cardiac arrest in patients receiving initial doses as low as 12.5 mg. If clozapine therapy is temporarily discontinued (i.e., for 2 or more days), the manufacturers recommend that the drug be reinitiated at a lower dosage (12.5 mg once or twice daily). In some cases when collapse and cardiac and/or respiratory arrest developed during initial therapy, benzodiazepines or other psychotropic agents were used concomitantly, suggesting a possible adverse interaction between clozapine and these agents. (See Drug Interactions: Benzodiazepines.) Although the clinical importance of this interaction has not been fully established, the manufacturers state that clozapine should be initiated with caution in patients receiving benzodiazepines or other psychotropic agents. Collapse and respiratory and/or cardiac arrest also have been reported in patients receiving initial therapy with clozapine alone. The risk of orthostatic hypotension may be reduced by initiating therapy at lower dosages, followed by only gradual, modest increases as necessary. (See Dosage and Administration: Dosage.) In some cases, withholding the drug for 24 hours and then restarting at a lower dosage has been accomplished without recurrence of orthostatic hypotension.

Tachycardia Tachycardia, which may persist throughout therapy in some cases, reportedly has been observed in 25% of patients receiving clozapine. Patients who experience clozapine-induced tachycardia demonstrate an average increase in pulse rate of 10–15 beats per minute (bpm); with aggressive dosage increases, the mean increase in heart rate ranges from 20–25 bpm. Persistent tachycardia associated with clozapine therapy is not simply a reflex response to hypotension and is present in all positions monitored. Although this effect may lessen once a plateau dosage level is reached, tachycardia may pose a serious risk for individuals with compromised cardiac function.

ECG Effects Some clozapine-treated patients experience ECG repolarization changes, including ST-segment depression, shortening of the PQ interval, and/or flattening, depression, or inversion of T waves. These changes usually normalize after discontinuance of clozapine and are similar to those seen with other antipsychotic agents. The clinical importance of these changes currently is unclear, but some clinicians suggest that they occur infrequently and usually are not serious.

Other Cardiovascular Effects In clinical trials of clozapine, some patients experienced serious cardiovascular events, including ischemic changes, chest pain and angina, hypertension, myocardial infarction, nonfatal arrhythmias, or sudden, unexplained death. Causality assessment was difficult because of serious preexisting cardiac disease in many of the patients and plausible alternative causes.

In addition, postexercise decreases in left ventricular output, which may indicate left ventricular failure, have been reported in patients receiving the drug. Edema, palpitation, phlebitis or thrombophlebitis, cyanosis, ventricular premature complexes, and bradycardia have been reported in less than 1% of clozapine-treated patients. Although a causal relationship has not been established, atrial or ventricular fibrillation, congestive heart failure, pericarditis, and pericardial effusions also have been reported during postmarketing surveillance in patients receiving the drug.

Rare instances of sudden, unexplained death have been reported in psychiatric patients, with or without associated antipsychotic drug treatment, and the relationship between sudden death and antipsychotic drug use is unknown. Some autopsy results have suggested that clozapine-treated patients have died from cardiac arrest and uncompensated cardiac disease, or from other causes such as renal insufficiency or severe alcohol abuse. A causal relationship between clozapine use and sudden death has not been established. (See Cautions: Geriatric Precautions.)

■ **Autonomic Nervous System Effects** Adverse autonomic nervous system effects occur in more than 5% of patients receiving clozapine. Dry mouth occurs frequently, but hypersalivation, an apparently paradoxical effect considering the drug's potent anticholinergic activity, is more common. (See Cautions: GI Effects.)

Other autonomic nervous system effects of clozapine include hyperhidrosis, decreased sweating, visual disturbances, nasal congestion, and pallor. Numbness, polydipsia, hot flushes (flashes), dry throat, and mydriasis have been reported in less than 1% of clozapine-treated patients.

■ **Hepatic Effects** Transient increases in liver function test results, including serum aminotransferases (transaminases), LDH, and alkaline phosphatase, may occur with clozapine therapy, usually with no accompanying physical signs or symptoms. Clozapine-induced changes in liver function test results may be more pronounced than those with other tricyclic antipsychotic agents. Clozapine causes slight liver hyperplasia in rats; hyperplasia was reversible and no histologic changes were detectable. Clozapine occasionally causes slight elevations of bilirubin concentration. Cholestasis, hepatitis, and jaundice have been reported in patients receiving clozapine during postmarketing surveillance; however, a causal relationship to the drug has not been established.

■ **Endocrine and Metabolic Effects** Severe hyperglycemia, sometimes associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients receiving certain atypical antipsychotic agents, including clozapine. While confounding factors such as an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population make it difficult to establish with certainty the relationship between use of agents in this drug class and glucose abnormalities, epidemiologic studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotic agents included in the studies (e.g., clozapine, olanzapine, quetiapine, risperidone). (See Cautions: Precautions and Contraindications.)

Precise risk estimates for hyperglycemia-related adverse events in patients

treated with atypical antipsychotics currently are not available. While some evidence suggests that the risk for diabetes may be greater with some atypical antipsychotics (e.g., clozapine, olanzapine) than with others (e.g., quetiapine, risperidone) in the class, available data are conflicting and insufficient to provide reliuble estimates of relative risk assoeiated with use of the varions atypieal antipsychotics.

Clozapine causes only a brief, transient elevation of prolactin concentration. (See Pharmacology: Neuroendocrine Effects.) Because the drug's effects on prolactin are only minor, prolactin-dependent effects such as galactorrhea and amenorrheu usually are not associated with clozapine therapy. Breast pain or discomfort has been reported in less than 1% of clozapine-treated patients.

Clozapine may cause increased appetite, polyphagia, and weight gain in a substantial proportion (approximately one-third) of patients. Some clinicians suggest that the potential for weight gain with clozapine therapy may be similar to that with other antipsychotic therapy; others state that they have observed greater weight gain with clozapine in some patients. In the 2-year InterSePT trial, weight gain reportedly occurred in 31% of patients receiving clozapine compared with 56% of those receiving olanzapine. Some clozapine-treated patients reportedly have gained up to 1 kg weekly for 6 weeks. Weight gain may result from the drug's serotonergic-, histaminergic-, and adrenergic-blocking properties. Weight gain has been reported to be a problem for some patients during long-term therapy with clozapine and may be a major cause of outpatient noncompliance. Some clinicians suggest using exercise and active measures (e.g., dietary counseling) to control dietary intake in clozapine-treated patients.

Hyperuricemia, hyponatremia, weight loss, and decreased serum cholesterol concentrations also have been reported in patients receiving clozapine, although a causal relationship to the drug has not been established. In addition, hypercholesterolemia and hypertriglyceridemia have been reported very rarely during postmarketing experience with the drug.

Small decreases in protein-bound iodine or thyroxine concentrations have heen reported in some patients receiving clozapine, but these values remained within normal limits.

■ **GI Effects** Increased salivation may occur in approximately one-third of patients receiving clozapine; in some studies, hypersalivation was reported in up to 75–85% of clozapine-treated patients. In the InterSePT trial, increased salivation reportedly occurred in 48% of patients receiving clozapine compared with 6% of those receiving olanzapine. Salivation may be profuse, very fluid, and particularly troublesome during sleep because of decreased swallowing. Since clozapine exhibits intrinsic anticholinergic properties, hypersalivation is an unexpected paradoxieal effect. A muscle-relaxant effect of the drug may contribute to hypersalivation, but the cause has not been fully elucidated. Difficulty in swallowing has been reported in a few clozapine-treated patients, and it has been suggested that the drug may cause esophageal dysfunction, which may contribute to or exacerbate the nocturnal hypersalivation associated with clozapine therapy. Some clozapine-treated patients develop tolerance to increased salivation within a few weeks. Occasionally, hypersalivation may be ameliorated by reduction of clnzapine dosage or cautious use of a peripherally acting anticholinergic drug; however, some clinicians generally advise against the use of anticholinergic therapy for this adverse effect because of possible potentiation of clozapine's anticholinergic activity.

Other GI effeets associated with clozapine therapy include constipation, diarrhea, nausea and vomiting, dyspepsia or heartburn, abdominal discomfort, and anorexia; some of these effects have been reported in more than 5% of patients. Constipation, nausea, vomiting, and dyspepsia reportedly occurred in 14–25% of patients receiving clozapine in the InterSePT trial compared with 8–10% of those receiving olanzapine. Although some clinicians advocate the use of metoclopramide (e.g., in doses less than 30 mg daily) for the treatment of clozapine-induced nausea, nther clinicians suggest that metoclopramide or other dopamine antagonists not be used or be used with extreme caution for the treatment of clozapine-induced nausea because of their potential for causing parkinsonian manifestations and tardive dyskinesia.

Abdominal distention, gastroenteritis, rectal bleeding, nervous stomach, abnormal stools, hematemesis, gastric ulcer, bitter taste, and eructation have been reported in less than 1% of patients receiving clozapine. Although a causal relationship to the drug has not been established, salivary gland swelling and paralytic ileus also have been reported in patients receiving clozapine.

■ **Genitourinary Effects** Genitourinary effects reported with clozapine therapy include polyuria, incontinence, urinary urgency or frequency, urinary retention, or other urinary abnormalities; enuresis; impotence; abnormal ejaculation; dysmenorrhea; and vaginal itch or infection. Priapism and acute interstitial nephritis also have been reported with clozapine therapy, although a causal relationship to the drug has not been established.

■ **Respiratory Effects** Clozapine-induced respiratory effects include throat discomfort, dyspneu or shortness of breath, coughing, pneumonia or pneumonia-like symptoms, rhinorrhea, hyperventilation, wheezing, bronchitis, laryngitis, and sneezing. Although a causal relationship to the drug has not been established, aspiration and pleural effusion also have been reported with clozapine therapy during postmarketing surveillance.

Respiratory depression or failure, including arrest requiring resuscitation, also has been reported in patients receiving clozapine, usually at initiation of therapy and particularly in patients receiving concomitant benzodiazepine therapy or in those with a history of recent benzodiazepine use. Some evidence indicates that the incidence of respiratory arrest and vascular collapse is about 1–2% of patients receiving clozapine concomitantly with a benzodiazepine. For additional precautionary information about this potential effect, see Benzodiazepines under Drug Interactions: CNS Depressants.

■ **Dermatologic and Sensitivity Reactions** Rash has been reported in 2% of patients receiving clozapine. Pruritus, eczema, erythema, bruising, dermatitis, petechiae, and urticaria have occurred in less than 1% of patients.

Hypersensitivity reactions, including photosensitivity, vasculitis, erythema multiforme, and Stevens-Johnson syndrome, have been reported with clozapine during postmarketing surveillance; however, a causal relationship to the drug has not been established.

■ **Musculoskeletal Effects** Adverse musculoskeletal effects reported in 1% of clozapine-treated patients include muscular weakness (myasthenic syndrome); back, neck, and leg pain; and muscle ache or spasm. Muscle twitching and joint pain have been reported less frequently. Rhabdomyolysis has been reported with clozapine during postmarketing surveillance; however, a causal relationship to the drug has not been established.

■ **Other Adverse Effects** Numb or sore tongue, chills (with or without fever), malaise, ear or eyelid disorder, ocular hyperemia, epistaxis, and nystagmus have been reported in 1% or less of patients receiving clozapine. Periorbital edema and narrow angle glaucoma also have been reported in clozapine-treated patients, although a causal relationship to the drug has not been established.

■ **Precautions and Contraindications** Clozapine shares many of the toxic potentials of other antipsychotic agents (e.g., phenothiazines), and the usual precautions associated with therapy with these agents should be observed. (See Cautions, in the Phenothiazines General Statement 28:16.08.24.)

Sedative Effects Because of initial sedative effects of the drug, patients should be cautioned that clozapine may impair their ability to perform activities requiring mental alertness or physical coordination (e.g., operating machinery, driving a motor vehicle), especially during the first few days of therapy. The recommendation for gradual dosage escalation should be closely followed. (See Dosage and Administration.)

Febrile Reactions During clozapine therapy, patients also may experience transient temperature elevations exceeding 38°C, with the peak incidence within the first 3 weeks of therapy. (See Cautions: Fever.) While this fever generally is benign and self-limiting, it may necessitate discontinuance of therapy. Occasionally, there may be an associated increase or decrease in leukocyte count and patients with fever should be carefully monitored to rule out the possibility of infection or the development of agranulocytosis. In the presence of high fever, the possibility of neuroleptio malignant syndrome also must be considered. (See Extrapyramidal Reactions under Cautions: Nervous System Effects.)

Anticholinergic Effects and Paralytic Ileus Clinical experience with clozapine in patients with concomitant systemic diseases is limited. However, clozapine has potent anticholinergic activity and should therefore be used with caution in individuals whose condition may be aggravated by anticholinergic effects (e.g., patients with prostatic hyperplasia, urinary retention, angle-closure [obstructive, narrow-angle] glaucoma). Clozapine therapy has been associated with varying degrees of impairment of intestinal peristalsis, ranging from constipation to intestinal obstruction, fecal impaction, and paralytic ileus, that rarely have been fatal. The manufacturers state that constipation may be treated initially by maintaining adequate hydration and by using bulk-forming laxatives. Consultation with a gastroenterologist may be necessary in more severe cases. Clozapine is contraindicated in patients with paralytic ileus.

Hepatic Dysfunction Because there have been reports of hepatie dysfunction, including hepatitis, in patients reeeiving clozapine, the drug should be used with caution in patients with preexisting liver disease. Liver function tests should be performed immediately in patients who develop nausea, vomiting, and/or anorexia during clozapine therapy. The manufacturers state that clozapine therapy should be discontinued in patients with marked elevations in serum aminotransferase concentrations or in those presenting with manifestations of jaundice.

Individuals with Phenylketonuria Individuals with phenylketonuria (i.e., homozygous genetic deficiency of phenylalanine hydroxylase) and other individuals who must restrict their intake of phenylalanine should be warned that clozapine 25- or 100-mg orally disintegrating tablets contain aspartame, which is metabolized in the GI tract to provide about 1.74 or 6.96 mg of phenylalanine, respectively, following oral administration.

Hyperglycemia and Diabetes Mellitus Because severe hyperglycemia, sometimes associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients receiving certain atypical antipsychotic agents, including clozapine, the manufacturers state that patients with preexisting diabetes mellitus in whom therapy with an atypical antipsychotic is initiated should be closely monitored for worsening of glucose control; those with risk factors for diabetes (e.g., obesity, family history of diabetes) should undergo fasting blood glucose testing upon therapy initiation and periodically throughout treatment. Any patient who develops manifestations of hyperglycemia (e.g., polydipsia, polyphagia, polyuria, weakness) during treatment with an atypieal antipsychotic should undergo fasting blood glucose testing. In some cases, patients who developed hyperglycemia while receiving an atypical antipsychotic have required continuance of antidiabetie treatment despite discontinuance 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 also did not exhibit genotoxic or mutagenic effects when assayed in appropriate bacterial and mammalian tests.

■ **Pregnancy, Fertility, and Lactation** Reproduction studies in rats and rabbits using clozapine dosages approximately 2–4 times the usual human dosage have not revealed evidence of harm to the fetus. There are no adequate and controlled studies to date using clozapine in pregnant women, and the drug should be used during pregnancy only when clearly needed. Patients receiving clozapine should notify their physician if they become or plan to become pregnant during therapy.

Reproduction studies in rats and rabbits using clozapine dosages approximately 2–4 times the usual human dosage have not revealed impaired fertility.

Studies in animals suggest that clozapine may be distributed into milk. Because of the potential for serious adverse reactions to clozapine in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the woman.

Drug Interactions

The manufacturers state that the potential risks of using clozapine in combination with other drugs have not been evaluated systematically. However, clinical experience and/or theoretical considerations indicate that certain potential drug interactions exist.

■ **Myelosuppressive Agents** The mechanism of clozapine-induced agranulocytosis is unknown; however, the possibility that causative factors may interact synergistically to increase the risk and/or severity of bone marrow suppression warrants consideration. (See Cautions: Hematologic Effects.) Therefore, clozapine should not be used with other agents having a well-known potential to suppress bone marrow function. That clozapine may be directly myelotoxic has been suggested by in vitro study of the serum and bone marrow of a patient who died during multidrug therapy that included clozapine and carbamazepine.

■ **Drugs Affecting the Seizure Threshold** Clozapine may lower the seizure threshold and has caused seizures in some patients (see Seizures under Cautions: Nervous System Effects); therefore, concomitant therapy with other agents that lower the seizure threshold generally should be avoided if possible. If such combined therapy is required, caution should be exercised (e.g., using low initial dosages of clozapine with slow upward titration) and the possible need for anticonvulsant therapy considered.

■ **CNS Depressants** ***Benzodiazepines*** Severe hypotension (including absence of measurable blood pressure), respiratory or cardiac arrest, and loss of consciousness have been reported in several patients who received clozapine concomitantly with or following benzodiazepine (i.e., flurazepam, lorazepam, diazepam) therapy. Such effects occurred following administration of 12.5–150 mg of clozapine concurrently with or within 24 hours of the benzodiazepine, but patients generally have recovered within a few minutes to hours, usually spontaneously; the reactions usually developed on the first or second day of clozapine therapy. Although a causal relationship has not definitely been established and such effects also have been observed in clozapine-treated patients who were not receiving a benzodiazepine concomitantly (see Cautions: Cardiovascular Effects), death resulting from respiratory arrest reportedly has occurred in at least one patient receiving clozapine concomitantly with a benzodiazepine. An increased incidence of dizziness and sedation and greater increases in liver enzyme test results also have been reported with this drug combination.

The manufacturers of clozapine recommend caution when the drug is initiated in patients receiving benzodiazepine therapy. However, some clinicians advise that, pending further accumulation of data, greater precaution should be exercised. These clinicians recommend that since initial titration of clozapine may cause respiratory arrest requiring resuscitation, which may be potentiated by recent benzodiazepine therapy, these latter drugs should be discontinued for at least 1 week prior to initiating clozapine therapy. In addition, these clinicians recommend that clozapine therapy be initiated in a setting where facilities for resuscitation are immediately available for the first few hours after administration of the first dose. Other clinicians, however, state that institutional initiation of clozapine therapy may not be necessary or practical, although they recommend slow and cautious initiation of the drug at low dosages.

Other CNS Depressants Clozapine may be additive with, or may potentiate the action of, other CNS depressants such as opiates or other analgesics, barbiturates or other sedative/hypnotics, general anesthetics, or alcohol. When clozapine is used concomitantly with other CNS-depressant drugs, caution should be exercised to avoid excessive sedation.

■ **Other CNS-active Agents** Although a causal relationship has not been established, at least one death has been reported with concomitant clozapine and haloperidol therapy. A 31-year-old woman with schizophrenia developed respiratory arrest, became comatose, and died 4 days after receiving 10 mg of haloperidol orally and a single 100-mg dose of clozapine IM. The patient had been maintained on oral clozapine 200 mg daily for 2 years and also had received smaller doses of haloperidol concomitantly with clozapine therapy without unusual adverse effect.

Neuroleptic malignant syndrome has been reported rarely with clozapine therapy alone and during concomitant therapy with clozapine and carbamazepine, lithium, or other CNS-active agents. (See Extrapyramidal Reactions under Cautions: Nervous System Effects.)

Concomitant use of clozapine and lithium may also increase the risk of seizures.

Orthostatic hypotension, sometimes accompanied by profound collapse and respiratory and/or cardiac arrest, has been reported rarely with clozapine therapy alone and during concomitant therapy with other psychotropic agents. Although the clinical importance of this interaction has not been fully established, the manufacturers of clozapine state that the drug should be initiated with caution in patients receiving other psychotropic agents.

■ **Drugs Undergoing Hepatic Metabolism or Affecting Hepatic Microsomal Enzymes** Clozapine is a substrate for many cytochrome P-450 (CYP) isoenzymes, in particular 1A2, 2D6, and 3A4. The risk of metabolic interactions caused by an effect on an individual isoform is therefore minimized. However, concomitant use of clozapine with drugs that inhibit the CYP enzyme system (e.g., caffeine, cimetidine, erythromycin, quinidine, certain antidepressants, phenothiazines, type IC antiarrhythmics [e.g., propafenone, flecainide, encainide]) may result in increased plasma concentrations of clozapine. Conversely, concomitant use of clozapine with drugs that induce the CYP enzyme system (e.g., carbamazepine, nicotine, phenytoin, rifampin) may result in decreased plasma concentrations of clozapine. Caution should be observed if clozapine is used concomitantly with these drugs. Dosage adjustments of clozapine and/or other drugs may be necessary in patients receiving concomitant therapy with drugs that inhibit or induce the CYP enzyme system.

Phenytoin Substantial reductions in plasma clozapine concentrations and exacerbation of psychosis have been reported in patients receiving concomitant therapy with clozapine and phenytoin, and an increase in clozapine dosage may be required to reestablish antipsychotic efficacy in patients receiving such combined therapy. In 2 patients stabilized for 1–2 weeks on a given dosage of clozapine, addition of phenytoin for prevention of clozapine-induced seizures resulted in a 65–85% decrease in steady-state plasma clozapine concentrations. Control of psychotic manifestations was regained in both patients by gradually increasing clozapine dosage. Although the mechanism of this potential interaction has not been established, it has been suggested that phenytoin may increase clozapine metabolism via stimulation of the hepatic cytochrome P-450 (microsomal) enzyme system and/or displacement of clozapine from protein binding sites, or that phenytoin may decrease absorption of clozapine from the GI tract. Pending further study, clozapine-treated patients in whom phenytoin therapy is initiated should be monitored carefully for reemergence of psychotic manifestations and clozapine dosage adjusted accordingly.

Carbamazepine Concomitant use of clozapine and carbamazepine has been shown to decrease clozapine concentrations by about 40–50%. In addition, neuroleptic malignant syndrome has been reported rarely with clozapine therapy alone and during concomitant therapy with carbamazepine. (See Extrapyramidal Reactions under Cautions: Nervous System Effects.) Therefore, the manufacturers of clozapine state that concomitant use of these agents generally is not recommended. However, if clozapine and carbamazepine are used concomitantly, it should be considered that discontinuance of carbamazepine may result in increased plasma concentrations of clozapine.

Selective Serotonin-reuptake Inhibitors Concomitant use of clozapine with certain selective serotonin-reuptake inhibitors (SSRIs), including citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline, can increase plasma concentrations of clozapine and enhance clozapine's pharmacologic effects secondary to suspected inhibition of clozapine metabolism by SSRIs. Modest (less than twofold) elevations in plasma clozapine concentrations have been reported in patients receiving clozapine concomitantly with certain SSRIs (i.e., fluoxetine, paroxetine, sertraline), although substantial (threefold) increases in trough plasma clozapine concentrations have occurred in patients receiving concomitant therapy with clozapine and fluvoxamine. The manufacturers of clozapine state that caution should be exercised and patients should be closely monitored when clozapine is used in patients receiving SSRIs, and a reduction in clozapine dosage should be considered.

■ **Drugs with Anticholinergic Activity** Clozapine has potent anticholinergic effects and may potentiate the actions of other drugs possessing such activity (e.g., antimuscarinics).

■ **Hypotensive Agents** Clozapine may be additive with or potentiate the actions of hypotensive agents. In addition, the administration of epinephrine should be avoided in the treatment of clozapine-induced hypotension because of a possible reversal of epinephrine's vasopressor effects and subsequent further lowering of blood pressure.

■ **Smoking** Some evidence indicates that cigarette smoking may substantially reduce plasma clozapine concentrations. Limited data indicate that average plasma clozapine concentrations following a given dose in smokers average 60–82% of those in nonsmokers. Changes in liver enzyme activity and/or the GI tract induced by nicotine or other substances present in cigarette smoke may explain these reduced concentrations. These effects should be considered when adjusting clozapine dosage in patients who smoke cigarettes.

Acute Toxicity

■ **Pathogenesis** Acute toxicity studies in animals revealed that the LD_{50}s for clozapine administered orally, IV, or intraperitoneally are approximately 145–325, 58–61, and 90 mg/kg, respectively.

Although the acute lethal dose of clozapine in humans remains to be established, fatal overdoses with the drug generally have been associated with doses exceeding 2.5 g. However, there also have been reports of patients surviving overdoses that substantially exceeded 4 g of the drug.

■ **Manifestations** In general, overdosage of clozapine may be expected to produce effects that are extensions of pharmacologic and adverse effects. The most commonly reported signs and symptoms of clozapine overdosage have been altered states of consciousness and CNS depression (e.g., drowsiness, delirium, coma), tachycardia, cardiac arrhythmias, hypotension, respiratory depression or failure, aspiration, pneumonia, and hypersalivation. Seizures have occurred with overdosage in some patients. (See Seizures under Cautions: Nervous System Effects.)

A 24-year-old woman who ingested 2 g in excess of her prescribed daily dosage (i.e., total ingestion approximately 3 g within a 24-hour period) had a tonic-clonic (grand mal) seizure; her plasma clozapine concentration 1 hour after the seizure (1313 ng/mL) was 500 ng/mL higher than usual, but she recovered uneventfully. In a 50-year-old woman who ingested 1 g of clozapine, the only manifestations were confusion and hallucinations lasting about 48 hours. A 26-year-old man who ingested approximately 3 g of clozapine became drowsy, agitated, and disoriented; he also had visual hallucinations, dysarthria, tachycardia, and hypersalivation. The patient was treated with gastric lavage and also received diazepam, digitalis, and anti-infectives, but continued to exhibit manifestations of severe central anticholinergic toxicity. Administration of physostigmine salicylate 2 mg by slow IV injection resulted in improvement in the patient's mental status within minutes; however, symptoms recurred after approximately 1 hour. Symptoms finally remitted 18–24 hours later with no further treatment.

■ **Treatment** Treatment of clozapine overdosage generally requires symptomatic and supportive care, including monitoring of cardiac and vital signs. There is no specific antidote for the management of clozapine overdosage.

The manufacturers recommend establishing and maintaining an airway and ensuring adequate ventilation and oxygenation. Activated charcoal, which may be used with sorbitol, may be as or more effective than emesis or gastric lavage and should be considered in the treatment of clozapine overdosage. Electrolyte and acid-base balance should be monitored and adjusted accordingly. Peritoneal dialysis or hemodialysis is of limited value in the treatment of clozapine overdosage because the drug is almost totally bound to serum protein. Forced diuresis, hemoperfusion, and exchange transfusion also are unlikely to be of benefit. While physostigmine salicylate may be useful as adjunctive treatment if severe anticholinergic toxicity is present, the drug should *not* be used routinely because of its potential adverse effects.

Epinephrine should *not* be used for treating clozapine-induced hypotension, since clozapine can reverse epinephrine's vasopressor effects and cause a further lowering of blood pressure. Because of potential additive anticholinergic effects, quinidine or procainamide should be avoided when treating clozapine-induced arrhythmias. Surveillance of the patient should be continued for several days following overdosage because of the risk of delayed effects. In managing clozapine overdosage, the clinician should consider the possibility of multiple drug involvement.

Chronic Toxicity

Physical and/or psychological dependence have not been reported in patients receiving clozapine.

Chronic toxicity studies in mice, rats, dogs, and monkeys have revealed no specific organ toxicity. After 1 year of treatment with clozapine, a brown discoloration caused by increased lipopigment was observed in various organs in rats; this change normally appears with increasing age. Discoloration was noted in the thyroid, brain, liver, kidney, heart, spleen, and skeletal muscle of rats, but such increased pigmentation was not associated with deleterious changes. The liver did show slight, dose-dependent changes, including centrolobular vacuolation, hepatocyte swelling, and increased weight.

Pharmacology

Clozapine is a dibenzodiazepine-derivative antipsychotic agent. While clozapine shares some of the pharmacologic actions of other antipsychotic agents, the drug has been described as an atypical or second-generation antipsychotic agent since many of its CNS effects differ from those of typical agents (e.g., butyrophenones, phenothiazines). In fact, these apparent differences in actions on neostriatal dopaminergic receptors have led some investigators to question the importance of the dopaminergic system in mediating the therapeutic effects of neuroleptic drugs. The exact mechanism of antipsychotic action of clozapine has not been fully elucidated but appears to be more complex than that of conventional (typical) antipsychotic agents and may involve serotonergic, adrenergic, and cholinergic neurotransmitter systems in addition to more selective, regionally specific effects on the mesolimbic dopaminergic system. Because of differences in the neurologic effects of clozapine, the drug is not considered a classic neuroleptic agent.

■ **Nervous System Effects** Although the precise mechanism of action of antipsychotic drugs has not been fully elucidated, current data suggest that the therapeutic effects of these agents involve antagonism of dopaminergic systems in the CNS. In animals, classic neuroleptic agents increase muscle tone or induce postural abnormalities (catalepsy), antagonize stereotyped behaviors induced by the dopamine agonists apomorphine and amphetamine, accelerate dopamine turnover in various areas of the brain, increase serum prolactin concentrations, and produce dopamine receptor hypersensitivity on repeated administration. These effects, many of which have been attributed to blockade of dopamine receptors in the neostriatum, form the basis for the hypothesis that idiopathic psychoses result from overactivity of dopamine in neostriatal and mesolimbic systems.

Unlike typical antipsychotic agents, clozapine exerts relatively weak antidopaminergic action within the neostriatum and has a low propensity to produce extrapyramidal effects or stimulate prolactin secretion. While some studies have demonstrated that relatively high doses of clozapine suppress the conditioned avoidance response in animals, which is a characteristic of typical antipsychotic agents, this response is not completely blocked by clozapine, and tolerance to this effect develops rapidly with repeated dosing, suggesting that it is not specifically related to clozapine's antipsychotic action. Further research is needed to elucidate fully clozapine's antipsychotic action in terms of the drug's serotonergic, adrenergic, muscarinic, and peptidergic effects and their influences on functional alterations in dopamine receptor systems.

Antidopaminergic Effects The therapeutic effects of antipsychotic drugs are thought to be mediated by dopaminergic blockade in the mesolimbic and mesocortical areas of the CNS, while antidopaminergic effects in the neostriatum appear to be associated with extrapyramidal effects. Several (at least 5) different types or subtypes of dopamine receptors have been identified in animals and humans. The relative densities of these receptors and their distribution and function vary for different neuroanatomical regions, and clozapine's unique effects may be secondary to regionally specific receptor interactions and/or other effects on dopaminergic neurons. Results obtained from receptor binding, behavioral, metabolic, and electrophysiologic studies of clozapine as well as the apparently low incidence of extrapyramidal effects associated with clozapine therapy suggest that the drug is more active in the mesolimbic than the neostriatal dopaminergic system. Results of some studies suggest that clozapine is more effective in increasing dopamine turnover and release in the nucleus accumbens or olfactory tubercle than in the neostriatum with acute administration and that it reduces dopamine release in the accumbens but not in the neostriatum during prolonged administration, which suggests preferential effects on dopaminergic function in the limbic system. However, conflicting data (i.e., no preferential limbic effects) also have been reported with both acute and repeated administration of the drug, which may reflect differences in analytical techniques, regional differences in drug distribution or receptor affinity, or other variables.

Some evidence suggests that the effects of clozapine on dopamine metabolism in the neostriatum are dose related; unlike typical antipsychotic drugs, clozapine appears to increase striatal dopamine turnover only at suprathera-peutic doses. Single high doses (80 mg/kg intraperitoneally) of clozapine in rats interfere with dopaminergic transmission by blocking postsynaptic dopamine receptors and causing a compensatory increase in dopaminergic neuronal firing, while lower doses retard dopamine release. Clozapine appears to increase striatal dopamine content when given either in single high doses or repeated low doses, and low doses of the drug reportedly decrease the degradation of dopamine to 3-methoxy-4-hydroxyphenylacetic acid (homovanillic acid, HVA) in the neostriatum. In a rodent model of tardive dyskinesia, single low doses (up to 1.2 mg/kg intraperitoneally) of clozapine suppressed ketamine-induced linguopharyngeal movements, which resemble symptoms of tardive dyskinesia (e.g., tongue protrusions, retrusions, and swallows), by 15–75% compared with baseline measures. At clozapine doses of 4.8 mg/kg or higher, clozapine caused total suppression of these movements, and duration of suppression became dose dependent. Since suppression of abnormal linguopharyngeal movements occurred at doses substantially lower than those reported to alter dopamine turnover, it has been suggested that doses of the drug lower than those required for antipsychotic activity may be useful for treating antipsychotic-induced tardive dyskinesia.

Current evidence suggests that the clinical potency and antipsychotic efficacy of both typical and atypical antipsychotic drugs generally are related to their affinity for and blockade of central dopamine D_2 receptors; however, antagonism at D_2 receptors does not appear to account fully for the antipsychotic effects of clozapine.

In in vitro studies, clozapine is a comparatively weak antagonist at D_2 receptors. Clozapine's affinity for the D_2 receptor on a weight basis reportedly is approximately one-third (33%) that of loxapine, one-tenth (10%) that of chlorpromazine, and one-fiftieth (2%) that of haloperidol. In oral dosages of 300 mg daily, clozapine produces a 40–65% occupancy of D_1 and D_2 receptors. During long-term clozapine therapy, the relative occupancy of D_1 receptors may become greater than that of D_2 receptors, or the long-term effects of the drug on D_2 receptors may be antagonized by its nondopaminergic properties. Although the in vitro affinity of clozapine for D_1 and D_2 receptors in brain tissue of animals appears to be similar, the drug's in vivo effects in many animals resemble those of D_1 receptor-specific antagonists. Compared with typical antipsychotic agents, clozapine shows greater affinity for and appears to produce greater blockade of neostriatal dopamine D_1 receptors; other data suggest that clozapine preferentially but not selectively antagonizes D_1 receptor-mediated functions. At clinically effective dosages, however, the drug produces comparable blockade of D_1 and D_2 receptors and less D_2 blockade than typical antipsychotic drugs. Long-term administration of clozapine leads to a 35–50% "up-regulation" of D_1 receptors, which is comparable to that observed with administration of selective D_1 antagonists; however, the number of D_2 receptors is not changed, possibly because the proportion of occupied receptors required to elicit a response is less for D_1 than for D_2 receptors. Limited evidence suggests that D_1 receptors may exist either coupled to adenylate cyclase or in uncoupled form. Clozapine appears to be a potent, competitive inhibitor of

dopamine-stimulated adenylate cyclase in vitro, and the adenylate cyclase-coupled state of the D_1 receptor binds clozapine with high affinity; in contrast, typical antipsychotic agents bind preferentially to the uncoupled D_1 receptor.

Although their role in eliciting the pharmacologic effects of antipsychotic agents remains to be fully elucidated, dopamine D_3, D_4, and D_5 receptors also have been identified; clozapine appears to have a much higher affinity for the D_4 receptor than for D_2 or D_3 receptors. Current information on D_3-receptor affinity for antipsychotic drugs suggests that most antipsychotics probably bind to both D_2 and D_3 receptors, although with higher affinity to D_2 receptors; however, the magnitude of the difference in D_3- versus D_2-receptor binding is much less with atypical antipsychotics such as clozapine, suggesting that effects on D_3 receptors may play a more important role in the pharmacologic actions of atypical versus typical antipsychotic drugs. The high affinity of the D_4 receptor for clozapine and its preferential distribution in cortical and limbic areas in animals may explain, in part, the relative lack of tardive dyskinesia and extrapyramidal effects during clozapine therapy. The cloning of a gene for a neuron-specific dopamine D_5 receptor, which binds antipsychotic drugs with similar affinity as the D_1 receptor but has a tenfold higher affinity for dopamine, also has been reported.

Clozapine's clinical potency appears to be twice that of chlorpromazine on a weight basis, although the drug demonstrates considerably weaker D_2-receptor binding affinity than chlorpromazine and appears to be much less potent in elevating dopamine metabolite concentrations in the brain. Clozapine produces a more potent blockade of central serotonergic, adrenergic, histamine H_1, and muscarinic receptors than typical antipsychotic agents; also, long-term administration of clozapine enhances striatal D_1-receptor function in animals and results in "down-regulation" of cortical, type 2 serotonergic (5-HT_2) receptors, suggesting that an interaction between these central neurotransmitter systems may be important for the drug's antipsychotic efficacy. Antagonism at cholinergic and α_1-adrenergic receptors in the mesolimbic system, compensating for dopaminergic blockade in the neostriatum, may explain the apparent selectivity and low incidence of extrapyramidal effects seen with clozapine. The amygdala also may be a site of action for clozapine, since repeated administration of the drug selectively induces supersensitivity to locally applied dopamine in the amygdala, and amygdaloid neurons are excited by clozapine but generally unresponsive to other antipsychotic agents (e.g., haloperidol).

Further studies are needed to elucidate the mechanism of clozapine's antipsychotic effects in various areas of the CNS.

Neurophysiologic Effects In vitro and in vivo electrophysiologic studies in animals demonstrate different sensitivities of various brain areas to clozapine-mediated postsynaptic receptor blockade. While clozapine increases firing rates of both nigrostriatal (A9 pathway) and mesolimbic (A10 pathway) dopaminergic neurons after acute administration, only mesolimbic dopaminergic neurons exhibit prolonged depolarization blockade following repeated exposure to the drug. Repeated administration of typical antipsychotic agents (e.g., haloperidol) concomitantly with an anticholinergic agent (trihexyphenidyl) or an α_1-adrenergic blocking drug (prazosin) mimicked these selective effects of clozapine on mesolimbic versus nigrostriatal dopaminergic neurons, suggesting that α_1-adrenergic blocking and/or anticholinergic effects may be responsible, in part, for the differential effects of clozapine in these midbrain areas. Some evidence suggests that the nucleus accumbens has greater sensitivity for clozapine than do other regions, which may explain why the drug appears to produce depolarization blockade of dopaminergic neurons only in the mesolimbic area. However, some studies have shown that neurons in the neostriatum also may be responsive to clozapine. Clozapine reportedly produces an increase in dopamine metabolites in the neostriatum comparable to or even greater than that in the nucleus accumbens. Demonstrable dopamine-receptor supersensitivity in both striatal and limbic forebrain regions also has been reported with prolonged clozapine administration. Therefore, it has been suggested that there may be a dissociation between the effects of clozapine on synthesis and metabolism of dopamine within nigrostriatal neurons and the drug's effects on neuronal firing rate and dopamine release.

Adrenergic Effects Clozapine has adrenergic-blocking activity, which may be partially responsible for the sedation, muscle relaxation, and cardiac effects observed in patients receiving the drug. (See Cautions: Cardiovascular Effects.) Although the drug appears to have relatively weak α-adrenergic blocking effects compared with typical antipsychotic drugs such as chlorpromazine, clozapine's in vitro affinity (relative to dopamine D_2-receptor affinity) for α_1- and α_2-adrenergic receptors is much higher than that of other antipsychotics, including chlorpromazine, haloperidol, loxapine, and thioridazine. Clozapine increases the number and sensitivity of α_1-adrenergic, but not dopamine D_2, receptors. The turnover rate of epinephrine and norepinephrine also may be increased by clozapine, but to a lesser extent than that of dopamine. Substantial increases in plasma norepinephrine concentrations, which decreased following discontinuance of the drug but remained above basal levels, have been noted in both schizophrenic and healthy individuals receiving clozapine; such increases may be the result of feedback mechanisms activated by adrenergic blockade.

Clozapine's central α_1-adrenergic blocking activity also may be responsible for the dose-related hypothermia observed in mice given the drug. Clozapine also induces ataxia and blocks amphetamine-induced hyperactivity in mice, although repeated administration of the drug results in almost complete tolerance to these effects. It has been suggested that clozapine's α_1-adrenergic blocking properties may, in part, mediate its differential effects on midbrain dopamine receptors and be responsible for its relative lack of extrapyramidal effects. However, the clinical importance of the drug's α_1-adrenergic effects has not been fully elucidated.

Anticholinergic Effects Clozapine possesses potent anticholinergic activity in vitro; the drug's affinity for muscarinic receptors substantially exceeds that of other antipsychotic agents (e.g., 39–50 times greater than that of chlorpromazine and 100 times that of loxapine) and may be similar to that of tricyclic antidepressants and antimuscarinic antiparkinsonian agents (e.g., benztropine, trihexyphenidyl). It has been suggested that clozapine's anticholinergic effects may be more potent centrally than peripherally and that adverse anticholinergic effects generally are not dose limiting; however, peripheral anticholinergic effects such as dry mouth are common and may be troublesome. Clozapine-induced delirium, which reportedly has occurred with rapid dosage escalation, has been reversed by physostigmine; this suggests that clozapine has central antimuscarinic activity. Some evidence also suggests that clozapine's anticholinergic properties may counteract the effects of dopamine receptor blockade in the neostriatum and thus prevent extrapyramidal reactions. Limited data suggest that the propensity of antipsychotic drugs to cause extrapyramidal effects varies inversely with anticholinergic potency and antimuscarinic activity; however, the relatively potent anticholinergic activity of clozapine does not appear to account adequately for its atypical actions.

Serotonergic Effects It has been suggested that schizophrenia may involve a dysregulation of serotonin- and dopamine-mediated neurotransmission, and clozapine may at least partially restore a normal balance of neurotransmitter function, possibly through serotonergic regulation of dopaminergic tone. Clozapine blocks central type 2 serotonergic (5-HT_2) receptors; the drug also antagonizes central and peripheral type 3 serotonergic (5-HT_3) receptors. Long-term and acute administration of clozapine has produced down-regulation of 5-HT_2 receptors in the frontal cortex and neostriatum of male rats; single or repeated daily injections of clozapine also reduced the number of cortical 5-HT_2 receptors but did not change receptor affinity. In contrast to effects caused by typical antipsychotic agents, an increase in brain tryptophan, serotonin, and 5-hydroxyindoleacetic acid (5-HIAA) concentrations generally has been reported with clozapine administration in animals. It has been suggested that these effects might contribute to the pronounced sedative effects of clozapine, although increases in blood serotonin concentrations occurring during clozapine treatment in humans have been inconsistent and variable. (See Effects on Sleep under Pharmacology: Nervous System Effects.) Clozapine's serotonergic effects also reportedly may contribute to the drug's efficacy against negative symptoms of schizophrenia and to the weight gain observed during clozapine therapy. (See Cautions: Endocrine and Metabolic Effects.)

Effects on Other Central Neurotransmitters Clozapine appears to have important activity on the metabolism of γ-aminobutyric acid (GABA), which has inhibitory effects on dopaminergic neurons. In contrast to the effects of typical antipsychotic drugs, clozapine apparently augments GABA turnover in both the neostriatum and nucleus accumbens. Increases in neostriatal GABA turnover and release may attenuate extrapyramidal reactions, while a similar action in the nucleus accumbens may be related to antipsychotic efficacy.

Clozapine appears to have central histamine H_1-receptor blocking activity; such activity reportedly may be associated with sedation, hypotension, and weight gain. The drug's affinity (relative to dopamine D_2-receptor affinity) for histamine H_1-receptors is approximately 30 times that of chlorpromazine and 4 times that of loxapine.

Behavioral Effects in Animals Studies of the effects of clozapine on animal behavior routinely used to detect antipsychotic activity support its classification as an atypical antipsychotic drug. Such studies suggest that the neostriatum is relatively unresponsive to clozapine. Since the drug does not induce catalepsy or inhibit apomorphine-induced stereotypy, which are thought to be mediated principally by the nigrostriatal dopamine system, clozapine's antipsychotic activity appears to result from the drug's activity in other areas. Clozapine also does not block amphetamine-induced hyperactivity or apomorphine-induced emesis in animals as the typical antipsychotic agents do. Long-term administration of clozapine causes supersensitization of behaviors mediated by mesolimbic dopaminergic pathways (e.g., dopamine-induced locomotion) but not those mediated via neostriatal systems (e.g., dopamine-induced stereotypy). Long-term administration of clozapine in male rats caused a marked supersensitivity (of the same magnitude and duration as that of haloperidol) in the mesolimbic but not the nigrostriatal system. It has been suggested that supersensitivity of mesolimbic dopamine receptors may be associated with the apparent rebound psychosis that has been reported following clozapine therapy. (See Cautions: Other Nervous System Effects.)

EEG Effects Clozapine may produce dose-related changes in the EEG, including increased discharge patterns similar to those associated with seizure disorders, and may lower the seizure threshold; seizures have occurred in patients receiving the drug, particularly with high dosages (greater than 600 mg daily), rapid dosage increases, and/or in the presence of high plasma concentrations. (See Seizures in Cautions: Nervous System Effects.) Some EEG changes associated with clozapine administration are atypical of those generally seen with other antipsychotic agents, resembling more closely those produced by antidepressants. Like other drugs with antipsychotic activity, clozapine increases beta-, delta-, and theta-band amplitudes and slows dominant alpha frequencies in clinical EEG studies. However, in patients with severe, treatment-resistant schizophrenia, increases in delta and theta band frequencies are more pronounced with clozapine than with haloperidol or chlorpromazine therapy, a

finding that appears to parallel the drugs' relative antiserotonergic, antihistaminic, and anticholinergic activities. Enhanced EEG synchronization, paroxysmal sharp-wave activity, and spike and wave complexes also may develop during clozapine therapy. Clozapine-induced EEG changes generally appear soon after initiation of the drug and return to baseline upon cessation of therapy. In one study, the EEG showed slight general changes or slight diffuse slowing in 75% of patients receiving clozapine; in another study, clozapine caused marked EEG changes, including a slowing of basal activity, in 5% of patients.

Effects on Sleep Clozapine causes a shift in the sleep-wake pattern toward dozing in animals, with marked reductions in both slow-wave and paradoxical sleep times. However, tolerance to the drug's sedative effect usually occurs, although slowly in some patients, during continuous administration of clozapine. In a controlled study of short-term (3-day) administration in healthy young men, clozapine in dosages of 25 mg nightly substantially increased total sleep time on the first night of administration, but the duration of sleep returned to baseline by the third night. Clozapine did not substantially affect the time spent in stage 1, 2, 3, or slow-wave sleep, nor did it affect latency to the rapid eye movement (REM) period or the percentage of time spent in REM sleep. However, the percentage of time spent in stage 4 sleep was reduced substantially on the second and third nights of drug administration, while a variety of REM indices were increased on the third night of the study.

In a few patients receiving clozapine dosages of 150–800 mg daily, REM sleep increased to 85–100% of total sleep time after several days of drug therapy, with the onset of REM sleep occurring almost immediately after patients fell asleep. Intensification of dream activity also has been reported during clozapine therapy. Some clinicians have suggested that a correlation may exist between increases in body temperature and REM sleep and clozapine-induced improvement in psychosis. Cataplexy has been reported in some patients receiving clozapine.

■ **Neuroendocrine Effects** In contrast to typical antipsychotic drugs, clozapine therapy in usual dosages generally produces little or no elevation of prolactin concentration in humans. Administration of clozapine to rats has produced a transient, dose-related increase in prolactin concentrations that is of much shorter duration than that caused by other antipsychotic agents. Prolactin normally is inhibited by dopamine released from tuberoinfundibular (TIDA) neurons into the pituitary portal circulation. In rats, clozapine acutely increases the activity of TIDA neurons, which inhibit the release of prolactin; activation of TIDA neurons may be mediated by an enhanced release of neurotensin. Clozapine's effect on prolactin appears to be transient, possibly because the drug appears to dissociate from dopamine receptors more rapidly than typical antipsychotic agents and is therefore eliminated from the brain more rapidly.

Clozapine has an effect on corticotropin (ACTH) and corticosterone, possibly through its effects on dopamine metabolism in the hypothalamus. Short-term administration of clozapine (cumulative dose: 200 mg) to a few patients with schizophrenia resulted in marked inhibition of apomorphine-induced somatotropin (growth hormone) response, suggesting that clozapine may block the dopamine receptors responsible for eliciting this response. In contrast to typical antipsychotic agents, clozapine decreases or has no effect on basal cortisol levels. Clozapine markedly increases corticosterone concentrations in a dose-dependent fashion; other antipsychotic agents appear to increase corticosterone concentrations only at doses producing substantial D_2-receptor blockade. Clozapine-induced stimulation of corticosterone secretion may result from stimulation, rather than blockade, of dopamine receptors, but the exact mechanism has not been fully elucidated.

■ **Other Effects** Clozapine produced a dose-dependent delay in initiation of copulation in male rats, which may be related to blockade of mesolimbic dopamine receptors; however, the drug had no effect on copulatory behavior once the behavior had started. Fertility in male and female rats reportedly is not adversely affected by clozapine. (See Cautions: Pregnancy, Fertility, and Lactation.)

In animals, even small oral doses of clozapine cause ptosis, relaxation, and a reduction in spontaneous activity, effects that are consistent with the drug's sedative activity. Inhibition of locomotor activity induced by clozapine diminishes with repeated administration. With increasing doses of the drug, reactions to acoustic and tactile stimuli decline, and disturbances in equilibrium have been reported. Clozapine also inhibits isolation-induced aggression in mice at doses lower than those affecting motor function, suggesting a specific antiaggressive effect.

Studies in animals suggest that clozapine has a weak and variable diuretic effect; the clinical importance of this effect has not been established. In both rats and dogs, low doses of clozapine tend to increase the elimination of water and electrolytes, while higher doses are associated with increases in potassium excretion and sodium retention.

Pharmacokinetics

■ **Absorption** Clozapine is rapidly and almost completely absorbed following oral administration. However, because of extensive hepatic first-pass metabolism, only about 27–50% of an orally administered dose reaches systemic circulation unchanged. Some, but not all, evidence suggests that clozapine may exhibit nonlinear, dose-dependent pharmacokinetics, with oral bioavailability being approximately 30% less following a single 75-mg dose than at steady state following multiple dosing. GI absorption appears to occur principally in the small intestine and is approximately 90–95% complete within 3.5 hours after an oral dose. Food does not appear to affect the rate or extent of GI absorption of the drug. The relative oral bioavailability of clozapine has been shown to be equivalent following administration of commercially available 25-mg and 100-mg conventional tablets, conventional tablets and capsules, and conventional and orally disintegrating tablets of the drug in several studies.

Following oral administration of a single 25- or 100-mg oral dose of clozapine as tablets in healthy adults, the drug is detectable in plasma within 25 minutes, and peak plasma clozapine concentrations occur at about 1.5 hours. Peak plasma concentrations may be delayed with higher single doses and with multiple dosing of the drug. In one multiple-dose study, peak plasma clozapine concentrations at steady state averaged 319 ng/mL (range: 102–771 ng/mL) and occurred on average at 2.5 hours (range: 1–6 hours) after a dose with 100 mg twice daily as conventional tablets in healthy adults; minimum plasma concentrations at steady state averaged 122 ng/mL (range: 41–343 ng/mL). Steady-state plasma concentrations ranging from 200–600 ng/mL generally are achieved with oral dosages of 300 mg daily, and steady-state peak plasma concentrations generally occur within 2–4 hours after a dose. Steady-state plasma concentrations of clozapine are achieved after 7–10 days of continuous dosing.

Following multiple-dose administration of clozapine orally disintegrating tablets at a dosage of 100 mg twice daily in adults, peak plasma clozapine concentrations at steady state averaged 413 ng/mL (range: 132–854 ng/mL) and occurred on average at 2.3 hours (range: 1–6 hours). Minimum plasma concentrations at steady state in this study averaged 168 ng/mL (range: 45–574 ng/mL).

Considerable interindividual variation in plasma clozapine concentrations has been observed in patients receiving the drug, and some patients may exhibit either extremely high or extremely low plasma concentrations with a given dosage. Such variability may be particularly likely at relatively high dosages (e.g., 400 mg daily) of the drug. In one study, a sixfold interindividual variation in steady-state plasma clozapine concentration was observed in patients receiving such dosages. In addition, considerable intraindividual variation, particularly from week to week, may occur in some patients. However, substantial intraindividual variations in pharmacokinetic parameters typically are not observed from day to day. Although the interindividual variability in plasma clozapine concentrations is consistent with that reported for other antipsychotic drugs and may be secondary to differences in absorption, distribution, metabolism, or clearance of the drug, further study is needed to clarify whether such variation results principally from variable pharmacokinetics or other variables.

There is some evidence that interindividual differences in pharmacokinetic parameters for clozapine may result, at least in part, from nonlinear, dose-dependent pharmacokinetics of the drug. However, a linear dose-concentration relationship also has been reported. Results of a study in patients with chronic schizophrenia revealed a correlation between oral clozapine dosages of 100–800 mg daily and steady-state plasma concentrations of the drug. In addition, linearly dose-proportional changes in area under the plasma concentration-time curve (AUC) and in peak and trough plasma concentrations have been observed with oral dosages of 37.5, 75, and 150 mg twice daily in other studies.

Smokers appear to achieve plasma clozapine concentrations that are approximately 60–80% of those achieved by nonsmokers following oral administration of the drug, possibly because of alterations in hepatic metabolism and/or GI absorption of the drug caused by nicotine or other substances (e.g., polycyclic aromatic hydrocarbons) present in cigarette smoke. (See Drug Interactions: Smoking.) There also is limited evidence that gender may affect plasma clozapine concentrations, with concentrations being somewhat reduced, perhaps by as much as 20–30%, in males compared with females. In addition, smoking has a greater effect on clozapine plasma concentrations in men than in women, although this difference could result simply from gender differences in smoking behavior. Plasma concentrations may be increased in geriatric individuals compared with relatively young (e.g., 18–35 years old) individuals, possibly secondary to age-related decreases in hepatic elimination of clozapine.

Pharmacologic effects of clozapine (e.g., sedation) reportedly are apparent within 15 minutes and become clinically important within 1–6 hours. The duration of action of clozapine reportedly ranges from 4–12 hours following a single oral dose. In one study in patients with schizophrenia, the sedative effect was apparent within hours of the first dose of the drug and was maximal within 7 days. (See Effects on Sleep under Pharmacology: Nervous System Effects.) However, antipsychotic activity generally is delayed for one to several weeks after initiation of clozapine therapy, and maximal activity may require several months of therapy with the drug.

Correlations between steady-state plasma concentrations of clozapine and therapeutic efficacy have not been established, and some evidence suggests that the degree of clinical improvement is independent of plasma concentrations ranging from 100–800 ng/mL. However, it also has been suggested that serum clozapine concentrations less than 600 ng/mL may be adequate for therapeutic effect in most patients. Results of one study of 29 patients treated with clozapine 400 mg daily for 4 weeks showed that patients were most likely to respond to therapy when their plasma clozapine concentrations were at least 350 ng/mL and/or when plasma concentrations of clozapine plus norclozapine (an active metabolite) totaled at least 450 ng/mL. Further study is needed to determine whether nonresponding patients with plasma clozapine concentrations less than 350 ng/mL will benefit from increasing their dosage in an attempt to achieve higher concentrations.

Although a relationship between clozapine plasma concentrations and the risk of seizures has been suggested (see Seizures under Cautions: Nervous

System Effects), most clinicians believe that a relationship between plasma concentrations of the drug and the risk of adverse effects has not been established.

■ **Distribution** Distribution of clozapine into human body tissues is rapid and extensive; distribution of metabolites of the drug also appears to be extensive. In mice and rats, clozapine distributes principally into the lung, spleen, liver, kidney, gallbladder, and brain, achieving concentrations in these tissues up to 50 times those in blood. At 8 hours after IV injection, clozapine was still detectable in these organs but not in blood. There is limited evidence in animals that clozapine and its metabolites may be preferentially retained in the lungs by an energy-dependent, carrier-mediated process and by cellular binding. Evidence in animals also suggests that competition between clozapine and other drugs (e.g., chlorpromazine, imipramine, certain tetracycline antibiotics) for pulmonary binding sites may potentially affect plasma and tissue concentrations of clozapine, but the clinical importance, if any, of such an effect has not been established.

The volume of distribution of clozapine has been reported to be approximately 4.65 L/kg. In one study, the volume of distribution at steady state averaged 1.6 L/kg (range: 0.4–3.6 L/kg) in schizophrenic patients. Because the volume of distribution of clozapine is smaller than that of other antipsychotic agents, it has been suggested that clozapine is less sequestered in tissues than the other drugs. Clozapine is approximately 97% bound to serum proteins.

Results of receptor-binding studies in monkeys indicate that clozapine rapidly crosses the blood-brain barrier following IV injection. The highest brain uptake of the drug was in the striatum in these animals; lesser concentrations were achieved in the thalamus and mesencephalon, although they exceeded those in the cerebellum. The pharmacokinetic characteristics of the drug in the CNS paralleled those in plasma in these monkeys, with an elimination half-life from CNS of about 5 hours. Evidence from other animal studies indicates that CNS concentrations of the drug exceed those in blood. Distribution of the drug into the CNS in humans has not been characterized.

Clozapine reportedly is present in low concentrations in the placenta in animals; information on placental transfer of the drug in humans currently is unavailable. Results of animal studies indicate that clozapine distributes into milk. (See Cautions: Pregnancy, Fertility, and Lactation.)

■ **Elimination** The decline of plasma clozapine concentrations in humans is biphasic. The elimination half-life of clozapine following a single 75-mg oral dose reportedly averages 8 hours (range: 4–12 hours); that after a 100-mg oral dose appears to be similar. The elimination half-life of clozapine at steady state following administration of 100 mg twice daily reportedly averages 12 hours (range: 4–66 hours). The rapid elimination phase may represent redistribution and is followed by a slower apparent mean terminal elimination half-life of 10.3–38 hours. Although a study comparing single and multiple dosing of clozapine demonstrated an increase in elimination half-life with multiple dosing, other evidence suggests this finding is not attributable to concentration-dependent pharmacokinetics.

Clozapine is metabolized in the liver prior to excretion. Clozapine may undergo *N*-demethylation, *N*-oxidation, 3′-carbon oxidation, epoxidation of the chlorine-containing aromatic ring, substitution of chlorine by hydroxyl or thiomethyl groups, and sulfur oxidation. A glucuronide metabolite, tentatively identified as a quaternary ammonium *N*-glucuronide of clozapine, also has been identified. Metabolism of clozapine may occur by one or more of these routes.

The rate of formation and biologic activity of clozapine metabolites have not been fully elucidated. The desmethyl metabolite of clozapine (norclozapine) has limited activity while the hydroxylated and *N*-oxide derivatives are inactive. The *N*-oxide and desmethyl derivatives are found in urine and plasma of humans in a proportion of 2:1.

Approximately 32% of a single oral dose of clozapine is found in plasma as the parent compound after 3 hours, 20% in 8 hours, and 10% up to 48 hours following the dose. Only limited amounts (approximately 2–5%) of unchanged drug are detected in urine and feces. Approximately 50% of an administered dose is excreted in urine and 30% in feces; maximum fecal excretion has been estimated at 38%. Approximately 46% of an oral dose of clozapine is excreted in urine within 120 hours.

Total plasma and blood clearance of clozapine reportedly average 217 and 250 mL/minute, respectively, but show considerable interindividual variation.

Chemistry and Stability

■ **Chemistry** Clozapine is a dibenzodiazepine-derivative antipsychotic agent. The drug is a piperazine-substituted tricyclic antipsychotic agent that is structurally similar to loxapine but that differs pharmacologically from this and other currently available antipsychotic agents (e.g., phenothiazines, butyrophenones). Because of these pharmacologic differences, clozapine is considered an atypical or second-generation antipsychotic agent.

While the structure-activity relationships of phenothiazine antipsychotic agents have been well described, these relationships for heterocyclic antipsychotic agents, including clozapine, have not been as fully characterized. Generally, the unsubstituted benzene ring seems to be important for interactions at dopamine receptors, while the chloro-substituted benzene ring seems more important for action at muscarinic receptors. In addition, an open carbon side chain replacing the piperazine moiety of clozapine generally leads to loss of activity.

Clozapine differs structurally from most currently available antipsychotic agents by the presence of a seven- rather than a six-membered central ring and the spatial relationship between the piperazine moiety and the chloro-substituted benzene ring. The core tricyclic ring system of clozapine is nonplanar and allows the piperazine moiety limited freedom of rotation.

Clozapine differs structurally from loxapine by the presence of a diazepine rather than an oxazepine central ring in the tricyclic nucleus and by the presence of a chlorine atom at position 8 rather than 2 of the tricyclic nucleus. The presence of a chlorine atom at position 8 of the tricyclic nucleus of clozapine appears to be associated with its distinct pharmacologic profile and may be responsible for the drug's antimuscarinic activity.

Clozapine occurs as a yellow, crystalline powder and is very slightly soluble in water.

■ **Stability** Commercially available conventional clozapine tablets should be stored in tight containers at a temperature not exceeding 30°C. Clozapine orally disintegrating tablets should be stored in their original sealed blister at a controlled room temperature of 25°C, but may be exposed to temperatures ranging from 15–30°C. The orally disintegrating tablets should be protected from moisture.

Preparations

Clozapine is available only through distribution systems that ensure baseline and periodic testing of white blood cell counts and absolute neutrophil counts as a condition of provision of the patient's next supply of drug. The individual manufacturers should be contacted for additional information on current mechanisms for obtaining the drug.

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

Clozapine‡

Oral		
Tablets	25 mg*	**Clozapine Tablets**
		Clozaril* (scored), Novartis
	100 mg*	**Clozapine Tablets**
		Clozaril* (scored), Novartis
Tablets, orally disintegrating	25 mg	**FazaClo*** (scored), Alamo
	100 mg	**FazaClo*** (scored), Alamo

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

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

Olanzapine

■ Olanzapine is considered an atypical or second-generation antipsychotic agent.

Uses

Olanzapine is used for the symptomatic management of psychotic disorders (e.g., schizophrenia). In addition, olanzapine is used alone or in conjunction with lithium or divalproex sodium for the management of acute mixed or manic episodes associated with bipolar I disorder; the drug also is used for longer-term maintenance monotherapy in patients with this disorder. Olanzapine also is used for the management of acute agitation in patients with bipolar disorder or schizophrenia.

■ **Psychotic Disorders** Olanzapine is used for the symptomatic management of psychotic disorders (e.g., schizophrenia). Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to sustain symptom remission or control and to minimize the risk of relapse. Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia. Patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.

Schizophrenia Olanzapine is used orally for the management of schizophrenia. Schizophrenia is a major psychotic disorder that frequently has devastating effects on various aspects of the patient's life and carries a high risk of suicide and other life-threatening behaviors. Manifestations of schizophrenia involve multiple psychologic processes, including perception (e.g., hallucinations), ideation, reality testing (e.g., delusions), emotion (e.g., flatness, inappropriate affect), thought processes (e.g., loose associations), behavior (e.g., catatonia, disorganization), attention, concentration, motivation (e.g., avolition, impaired intention and planning), and judgment. The principal manifestations of this disorder usually are described in terms of positive and negative (deficit) symptoms, and more recently, disorganized symptoms. Positive symptoms include hallucinations, delusions, bizarre behavior, hostility, uncooperativeness, and paranoid ideation; while negative symptoms include restricted range and intensity of emotional expression (affective flattening), reduced thought and speech productivity (alogia), anhedonia, apathy, and