

DRUGDEX-EV 0723

MICROMEDEX

DRUGDEX® Evaluations  
Database updated September 2011**CLOZAPINE**

[Overview](#)  
[Dosing Information](#)  
[Pharmacokinetics](#)  
[Cautions](#)  
[Clinical Applications](#)  
[References](#)

**0.0 Overview****1) Class**

- a)** This drug is a member of the following class(es):

Antipsychotic  
Dibenzodiazepine

**2) Dosing Information****a) Adult**

- 1)** do not dispense without appropriate white blood cell count monitoring (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2010; Prod Info [CLOZARIL\(R\)](#) tablets, 2005).
- 2)** a 1-week supply of [clozapine](#) tablets may be supplied to the patient at the initiation of therapy for emergency use such as weather or holidays (Prod Info [CLOZARIL\(R\)](#) tablets, 2005; Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2010).
- 3)** discontinuation of treatment: gradual reduction in dose is recommended over a 1 to 2 week period; if a patient's medical condition requires abrupt discontinuation, the patient should be under careful observation for worsening disease or rebound cholinergic side effects (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2010; Prod Info [CLOZARIL\(R\)](#) tablets, 2005)
- 4)** interruption in treatment: for patients who have been off [clozapine](#) for 2 days or more, treatment should be reinitiated at 12.5 mg ORALLY 1 to 2 times a day; if that dose is well tolerated, it may be feasible to titrate patients back to a therapeutic dose more quickly than is recommended for initial treatment; any patient who has previously experienced respiratory or [cardiac arrest](#) with initial dosing, but was then able to be successfully titrated to a therapeutic dose, should be retitrated with extreme caution after even 24 hours off drug (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2010; Prod Info [CLOZARIL\(R\)](#) tablets, 2005)

**a) [Schizophrenia](#), Treatment-resistant**

- 1)** initial, 12.5 mg ORALLY 1 to 2 times a day, then continued with daily dosage increments of 25 to 50 mg/day, if well-tolerated, to achieve a target dose of 300 to 450

mg/day (in 2 to 3 divided doses) by the end of 2 weeks (Prod Info FAZACLO(R) orally disintegrating tablets, 2010; Prod Info CLOZARIL(R) tablets, 2005)

2) maintenance: dosage adjustments should be made no more than 1 to 2 times per week, in increments not to exceed 100 mg; MAX daily dosage is 900 mg/day (Prod Info FAZACLO(R) orally disintegrating tablets, 2010; Prod Info CLOZARIL(R) tablets, 2005)

**b) Schizophrenia** - Suicidal behavior, Recurrent

1) initial, 12.5 mg ORALLY 1 to 2 times a day, then continued with daily dosage increments of 25 to 50 mg/day, if well-tolerated, to achieve a target dose of 300 to 450 mg/day (in 2 to 3 divided doses) by the end of 2 weeks (Prod Info FAZACLO(R) orally disintegrating tablets, 2010)

2) maintenance: dosage adjustments should be made no more than 1 to 2 times per week, in increments not to exceed 100 mg; MAX daily dosage is 900 mg/day (Prod Info FAZACLO(R) orally disintegrating tablets, 2010)

**b) Pediatric**

1) safety and effectiveness in pediatric patients have not been established (Prod Info FAZACLO(R) orally disintegrating tablets, 2010; Prod Info CLOZARIL(R) tablets, 2005)

**3) Contraindications**

a) agranulocytosis or severe granulocytopenia, clozapine-induced, history; increased risk of subsequent episodes (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)

b) concomitant use with other drugs having a known potential to cause agranulocytosis or suppress bone marrow function (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)

c) hypersensitivity to clozapine or any other component of this drug (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)

d) myeloproliferative disorders, preexisting (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)

e) paralytic ileus, preexisting (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)

f) severe central nervous system depression or comatose states from any cause; preexisting (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)

g) uncontrolled epilepsy or other predisposing factors, preexisting; may increase risk of seizure (Prod Info CLOZARIL(R) Tablets, 2005)

**4) Serious Adverse Effects**

a) Agranulocytosis

b) Bowel obstruction

c) Cardiac arrest

d) Colitis, Necrotizing

e) Drug-induced eosinophilia

f) Fecal impaction

g) Gastrointestinal hypomotility

h) Hepatitis

i) Hyperglycemia

- j) Ischemic bowel disease
- k) Myocarditis
- l) Neuroleptic malignant syndrome
- m) Neutropenia
- n) Orthostatic hypotension
- o) Pancreatitis
- p) Paralytic ileus
- q) Perforation of intestine
- r) Pericardial effusion
- s) Pulmonary embolism
- t) Respiratory arrest
- u) Seizure
- v) Sudden cardiac death
- w) Syncope
- x) Tardive dyskinesia

## 5) Clinical Applications

### a) FDA Approved Indications

- 1) Schizophrenia, Treatment-resistant
- 2) Schizophrenia - Suicidal behavior, Recurrent

## 1.0 Dosing Information

[Drug Properties](#)

[Storage and Stability](#)

[Adult Dosage](#)

[Pediatric Dosage](#)

### 1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product Index)

B) Synonyms

[Clozapine](#)

C) Physicochemical Properties

#### 1) Molecular Weight

- a) 326.83 (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2010)

#### 2) Solubility

- a) Very slightly soluble in water (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2010).

### 1.2 Storage and Stability

A) Preparation

#### 1) Oral route

**a) Orally Disintegrating Tablets**

**1)** For administration of orally disintegrating tablets, peel back foil on blister pack to expose tablet; do NOT push the tablet through the foil backing. Gently remove the tablet from the blister unit and immediately place the entire tablet in the mouth. Tablets disintegrate rapidly in saliva and can be swallowed with or without liquid. Tablets may be chewed if desired (Prod Info FAZACLO(R) orally disintegrating tablets, 2010).

**b) Oral Tablets**

**1)** The oral tablets may be taken with or without regard to meals (Prod Info CLOZARIL(R) Tablets, 2005).

**B) Oral route****1) Tablet/Tablet, Disintegrating**

- a)** Store tablets below 30 degrees C (86 degrees F) (Prod Info CLOZARIL(R) oral tablets, 2010).
- b)** Store disintegrating tablets in original package at controlled room temperature of 25 degrees C (77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F). Protect from moisture (Prod Info FAZACLO(R) orally disintegrating tablets, 2010).

**C) Extemporaneous Formulation - Oral route**

**1)** A 20-milligram per milliliter (mg/mL) suspension prepared from crushed tablets in a pediatric mixture base (containing syrup, carboxymethylcellulose, methylhydroxybenzoate and propylhydroxybenzoate) was found to be chemically stable for 18 days at room temperature. However, an expiration date of 7 days was recommended due to lack of microbial testing (Ramuth et al, 1996).

**1.3 Adult Dosage****1.3.1 Normal Dosage****1.3.1.A Oral route****1.3.1.A.1 Schizophrenia, Treatment-resistant**

**a)** The recommended initial dose of clozapine for treatment-resistant schizophrenia is 12.5 mg (one-half 25 mg tablet) once or twice daily. If tolerated, daily dosage increments of 25 to 50 mg may be added to achieve a target dose of 300 to 450 mg/day by the end of 2 weeks. Subsequent increases should be made no more than 1 to 2 times weekly in increments not exceeding 100 mg. For maintenance therapy, the lowest dose of clozapine to maintain remission should be used (Prod Info CLOZARIL(R) tablets, 2005; Prod Info FAZACLO(R) orally disintegrating tablets, 2010).

**b)** If therapy is interrupted for two days or more, clozapine should be reinitiated at a dose of 12.5 mg once or twice daily. If well-tolerated, titration to the therapeutic dose may proceed more rapidly than recommended for initial therapy. Patients previously experiencing respiratory or cardiac arrest with initial therapy should be retitrated with caution after even 24 hours off the drug (Prod Info FAZACLO(R) orally disintegrating tablets, 2010; Prod Info CLOZARIL(R) tablets, 2005).

In schizophrenia, initial doses of oral clozapine have been suggested (Taniguchi & Icaza, 1996):

day 1	12.5 mg twice daily
day 2	25 mg in the AM

day 3	25 mg twice daily
day 4	25 mg in the AM, 50 mg at bedtime
day 5	50 mg twice daily
day 6	50 mg in the AM, 75 mg at bedtime
day 7 and 8	50 mg in the AM, 100 mg at bedtime
days 9 and 10	100 mg twice daily
days 11 and 12	50 mg in the AM, 200 mg at bedtime
days 13 and 14	100 mg in the AM, 200 mg at bedtime

Target doses of 300 to 450 mg/day are usually achieved by the end of 2 weeks. Cautious titration and a divided dosage schedule are necessary to minimize the risks of hypotension, seizures, and sedation (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2010).

**c)** In a double-blind trial conducted at a state psychiatric hospital (n=50), daily doses of 300 to 600 mg were generally superior to 100 mg/day. The study sample was severely and chronically ill with refractory [schizophrenia](#) or [schizoaffective disorder](#) (mean age: 45 years, mean illness duration: 25 years, mean length of current hospitalization: 8.6 years). Subjects were slowly titrated to one of three target doses (100, 300 or 600 mg/day) and treated for 16 weeks. Nonresponders at the target dose were crossed over to a different target dose for an additional 16-week period, with a third 16-week trial at the remaining target dose for continuing nonresponders. Only 10% (n=2 on 300 mg/day, n=3 on 600 mg/day) of this sample met response criteria. At the 16-week timepoint, the 600 mg/day dose was statistically superior to the lower doses (p less than 0.05). After 48 weeks, both 300 mg/day and 600 mg/day were statistically equivalent, with 100 mg/day being inferior to both (p less than 0.0001). In an open-label extension, four additional subjects responded to higher doses (800 to 900 mg/day) (Simpson et al, 1999).

**d)** To minimize the overall risk of adverse effects with [clozapine](#), investigators recommend using the lowest possible effective dose with very gradual dose titration (Miller, 2000a; Naber, 1999a).

#### 1.3.1.A.2 [Schizophrenia](#) - Suicidal behavior, Recurrent

**a)** The recommended initial dose of [clozapine](#) for reducing the risk of recurrent suicidal behavior in patients with [schizophrenia](#) or [schizoaffective disorder](#) is 12.5 mg (one-half 25 mg tablet) once or twice daily. If tolerated, daily dosage increments of 25 to 50 mg may be added to achieve a target dose of 300 to 450 mg/day by the end of 2 weeks. Subsequent increases should be made no more than 1 to 2 times weekly in increments not exceeding 100 mg. For maintenance therapy, the lowest dose of [clozapine](#) to maintain remission should be used (Prod Info [CLOZARIL\(R\)](#) tablets, 2005; Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2010).

**b)** If therapy is interrupted for two days or more, [clozapine](#) should be reinitiated at a dose of 12.5 mg once or twice daily. If well-tolerated, titration to the therapeutic dose may proceed more rapidly than recommended for initial therapy. Patients previously experiencing respiratory or [cardiac arrest](#) with initial therapy should be retitrated with caution after even 24 hours off the drug (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2010; Prod Info [CLOZARIL\(R\)](#) tablets, 2005).

In [schizophrenia](#), initial doses of oral [clozapine](#) have been suggested (Taniguchi & Icaza, 1996):

day 1	12.5 mg twice daily
day 2	25 mg in the AM
day 3	25 mg twice daily
day 4	25 mg in the AM, 50 mg at bedtime
day 5	50 mg twice daily
day 6	50 mg in the AM, 75 mg at bedtime
day 7 and 8	50 mg in the AM, 100 mg at bedtime
days 9 and 10	100 mg twice daily
days 11 and 12	50 mg in the AM, 200 mg at bedtime
days 13 and 14	100 mg in the AM, 200 mg at bedtime

Target doses of 300 to 450 mg/day are usually achieved by the end of 2 weeks. Cautious titration and a divided dosage schedule are necessary to minimize the risks of hypotension, seizures, and sedation (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2010; Prod Info [CLOZARIL\(R\)](#) tablets, 2005).

c) In a double-blind trial conducted at a state psychiatric hospital (n=50), daily doses of 300 to 600 mg were generally superior to 100 mg/day. The study sample was severely and chronically ill with refractory [schizophrenia](#) or [schizoaffective disorder](#) (mean age: 45 years, mean illness duration: 25 years, mean length of current hospitalization: 8.6 years). Subjects were slowly titrated to one of three target doses (100, 300 or 600 mg/day) and treated for 16 weeks. Nonresponders at the target dose were crossed over to a different target dose for an additional 16-week period, with a third 16-week trial at the remaining target dose for continuing nonresponders. Only 10% (n=2 on 300 mg/day, n=3 on 600 mg/day) of this sample met response criteria. At the 16-week timepoint, the 600 mg/day dose was statistically superior to the lower doses (p less than 0.05). After 48 weeks, both 300 mg/day and 600 mg/day were statistically equivalent, with 100 mg/day being inferior to both (p less than 0.0001). In an open-label extension, four additional subjects responded to higher doses (800 to 900 mg/day) (Simpson et al, 1999).

d) To minimize the overall risk of adverse effects with [clozapine](#), investigators recommend using the lowest possible effective dose with very gradual dose titration (Miller, 2000a; Naber, 1999a).

e) One author reports that therapeutic doses of [clozapine](#) range from 50 to 800 mg daily. Most patients appear to respond to doses of 200 to 400 mg daily. In most patients 3 divided doses at intervals of 4 to 6 hours appear to be effective; however, because of the sedating effects of [clozapine](#), it may be advantageous to either give low doses in the morning and at midday with the bulk of the total daily dose in the evening, or to give the entire daily dose in the evening (Ayd, 1974c).

#### 1.3.1.A.3) Important Note

a) [Clozapine](#) should NOT be dispensed without appropriate white blood cell count monitoring (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2010; Prod Info [CLOZARIL\(R\)](#) tablets, 2005).

b) A 1-week supply of [clozapine](#) tablets may be supplied to the patient at the initiation of therapy for emergency use such as weather or holidays (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2010; Prod Info [CLOZARIL\(R\)](#) tablets, 2005).

#### 1.3.1.A.4) Maximum Dose

a) Many patients with [schizophrenia](#) will respond to [clozapine](#) doses between 300 and 600 milligrams/day, but if necessary, the dose can be increased to 600 to 900 milligrams/day. Due to an enhanced risk of adverse effects, the dose should not exceed 900 milligrams/day and patients should be periodically re-evaluated to assess whether continued therapy is appropriate or whether a reduction in dose is possible (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2010; Prod Info [CLOZARIL\(R\)](#) tablets, 2005).

#### 1.3.1.A.5) Discontinuation of Treatment

a) Gradually reduce the dose over a 1- to 2-week period. If abrupt discontinuation is required, carefully monitor the patient for recurrence of psychotic and cholinergic rebound symptoms such as diarrhea, nausea, vomiting, and headache (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2010; Prod Info [CLOZARIL\(R\)](#) tablets, 2005).

#### 1.3.1.A.6) Reinitiation of Treatment in Patients Previously Discontinued

a) When reinitiating treatment in patients who have previously discontinued therapy or when restarting patients who have had even a brief interval off [clozapine](#) (i.e., 2 days or more since the last dose), it is recommended that treatment be reinitiated with 12.5 mg ORALLY 1 to 2 times a

day. If that dose is well tolerated, it may be feasible to titrate patients back to a therapeutic dose more quickly than is recommended for initial treatment. However, any patient who has previously experienced respiratory or [cardiac arrest](#) with initial dosing, but was then able to be successfully titrated to a therapeutic dose, should be retitrated with extreme caution after even 24 hours off drug (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2010).(Prod Info [CLOZARIL\(R\)](#) tablets, 2005)

### 1.3.4 Dosage in Geriatric Patients

A) Clinical studies of [clozapine](#) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. However, elderly patients may have an increased risk for [agranulocytosis](#) and should be carefully monitored during therapy (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2010; Prod Info [CLOZARIL\(R\)](#) tablets, 2005).

B) Elderly patients may be particularly susceptible to the anticholinergic effects of [clozapine](#), such as urinary retention and constipation (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2010; Prod Info [CLOZARIL\(R\)](#) tablets, 2005).

C) Many elderly patients with [Parkinson's disease](#) cannot tolerate an initial [clozapine](#) dose of 25 milligrams because of side effects including sedation and orthostasis. An initial dose of 6.25 or 12.5 milligrams should be considered in elderly psychotic patients with [Parkinson's disease](#) (Wolk & Douglas, 1994).

## 1.4 Pediatric Dosage

### 1.4.1 Normal Dosage

#### 1.4.1.A Oral route

1) Safety and effectiveness for use in children has not been established (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2010; Prod Info [CLOZARIL\(R\)](#) tablets, 2005).

### 1.4.5 Dosage in Other Disease States

#### A) Infectious/Inflammatory/Hypersensitivity Processes

1) If an infectious, hypersensitivity, or inflammatory process is suspected, [clozapine](#) plasma levels should be closely monitored and the [clozapine](#) dose may need to be reduced by up to 50% (de Leon & Diaz, 2003; Haack et al, 2003).

## 2.0 Pharmacokinetics

### [Onset and Duration](#)

### [Drug Concentration Levels](#)

### [ADME](#)

### 2.1 Onset and Duration

#### A) Onset

##### 1) Initial Response

a) [Schizophrenia](#), Oral: 3 months (Wilson, 1996).



1) In a small number of patients, clinical improvement may be delayed up to 12 months (Wilson, 1996).

## 2.2 Drug Concentration Levels

### A) Time to Peak Concentration

1) ORAL: 2.3 to 3 hours (range, 1 to 6 hours) (Prod Info [Fazaclo\(TM\)](#), 2003; Guitton et al, 1998; Prod Info [Clozaril\(R\)](#), 2002p; Cheng et al, 1988).

B) [Schizophrenia](#), 350 to 420 micrograms/Liter (not clearly defined) (Olesen, 1998); (Freeman & Oyewumi, 1997).

1) Plasma levels show a significant degree of variation (Kurz et al, 1998). Levels are higher in women and increase with age in all patients (Lane et al, 1999).

2) [Clozapine](#) and noreclozapine levels should only be quantified in plasma since serum levels underestimate blood levels (Kaladjian et al, 1999). Plasma and saliva levels of [clozapine](#) do not correlate ( $r=0.56$ ) (Dumortier et al, 1998).

## 2.3 ADME

### 2.3.1 Absorption

#### A) Effects of Food

1) No effect (Prod Info [Clozaril\(R\)](#), 2002p; Prod Info [Fazaclo\(TM\)](#), 2003).

B) [Clozapine](#) tablets and solution are equally bioavailable (Prod Info [Clozaril\(R\)](#), 2002p).

C) [Clozapine](#) orally disintegrating tablets ([Fazaclo \(TM\)](#)) are bioequivalent to [clozapine](#) tablets ([Clozaril \(R\)](#)) (Prod Info [Fazaclo\(TM\)](#), 2003).

### 2.3.2 Distribution

#### A) Distribution Sites

##### 1) Protein Binding

a) 97% (Prod Info [Clozaril\(R\)](#), 2000; Prod Info [Fazaclo\(TM\)](#), 2003).

##### 2) OTHER DISTRIBUTION SITES

a) Red blood cells

#### B) Distribution Kinetics

##### 1) Volume of Distribution

a) 6 L/kg (Guitton et al, 1998).

### 2.3.3 Metabolism

#### A) Metabolism Sites and Kinetics

1) Extrahepatic presystemic routes (Cheng et al, 1988), extensive (Prod Info [Clozaril\(R\)](#), 2002p; Ayd, 1974b; Stock et al, 1977).



- a) Metabolites are eliminated in the urine, principally in unconjugated form (Prod Info [Clozaril\(R\)](#), 2002p; Ayd, 1974b; Stock et al, 1977).
- b) The average hepatic extraction ratio is 0.2 (Cheng et al, 1988).
- c) The cytochrome P-450 enzyme system is involved in the metabolism of the parent compound to the major metabolites desmethylclozapine (both CYP1A2 and CYP3A4) and [clozapine](#) N-oxide (CYP3A4) (Eiermann et al, 1997; Jerling et al, 1997).

## B) Metabolites

### 1) N-desmethylclozapine, active (Guitton et al, 1998; Gerson et al, 1994a).

- a) N-desmethylclozapine, the major metabolite of [clozapine](#), is a potent 5-HT(1C) receptor antagonist and has affinity for the D(2) and 5-HT(2) receptors. It is further metabolized to an unstable compound that is toxic to hemopoietic precursors of both myeloid and erythroid lineages (Guitton et al, 1998; Gerson et al, 1994a).

### 2) Hydroxylated and n-oxide derivatives, inactive (Guitton et al, 1998; Prod Info [Clozaril\(R\)](#), 2002p).

## 2.3.4 Excretion

### A) Kidney

#### 1) Renal Excretion (%)

- a) 50% (Prod Info [Clozaril\(R\)](#), 2002p; Prod Info [Fazaclo\(TM\)](#), 2003).

- 1) Excreted in urine as the demethylated, hydroxylated, and n-oxide derivatives, only trace amounts of unchanged drug are detected in urine (Prod Info [Clozaril\(R\)](#), 2002p; Prod Info [Fazaclo\(TM\)](#), 2003).

#### 2) Feces, 30% (Prod Info [Clozaril\(R\)](#), 2002p; Prod Info [Fazaclo\(TM\)](#), 2003).

- a) Approximately 30% of a dose is excreted in the feces as the demethylated, hydroxylated, and n-oxide derivatives; only trace amounts of unchanged drug are detected in the feces (Prod Info [Clozaril\(R\)](#), 2002p; Prod Info [Fazaclo\(TM\)](#), 2003).

### B) Total Body Clearance

#### 1) 38 to 41 L/hr (Olesen, 1998; Guitton et al, 1998)

### C) Other

#### 1) OTHER EXCRETION

- a) Blood clearance, 250 mL/min (Cheng et al, 1988).

## 2.3.5 Elimination Half-life

### A) Parent Compound

- 1) ELIMINATION HALF-LIFE, 8 hours (range 4 to 12 hours), with single dose (Prod Info [Clozaril\(R\)](#), 2002p; Guitton et al, 1998; Prod Info [Fazaclo\(TM\)](#), 2003).

a) Elimination half-life is 12 hours (range, 4 to 66 hours) with multiple dosing (Prod Info [Fazaclo](#)(TM), 2003).

#### **B) Metabolites**

- 1) N-desmethylozapine, 13.2 hours (Guitton et al, 1998)
- 2) N-oxide metabolite, 7 hours (Guitton et al, 1998)

### **3.0 Cautions**

[Contraindications](#)

[Precautions](#)

[Adverse Reactions](#)

[Teratogenicity/Effects in Pregnancy/Breastfeeding](#)

[Drug Interactions](#)

#### **3.0.A Black Box WARNING**

Oral (Tablet; Tablet, Disintegrating)

##### **Agranulocytosis**

Because of a significant risk of agranulocytosis, a potentially life-threatening adverse event, clozapine should be reserved for use in (1) the treatment of severely ill patients with schizophrenia who fail to show an acceptable response to adequate courses of standard antipsychotic drug treatment, or (2) for reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at risk of reexperiencing suicidal behavior.

Patients being treated with clozapine must have a baseline white blood cell (WBC) count and absolute neutrophil count (ANC) before initiation of treatment as well as regular WBC counts and ANCs during treatment and for at least 4 weeks after discontinuation of treatment.

Clozapine is available only through a distribution system that ensures monitoring of WBC counts and ANCs according to the schedule described below prior to delivery of the next supply of medication.

##### **Seizures**

Seizures have been associated with the use of clozapine. Dose appears to be an important predictor of seizure, with a greater likelihood at higher clozapine doses. Caution should be used when administering clozapine to patients having a history of seizures or other predisposing factors. Patients should be advised not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others.

##### **Myocarditis**

Analyses of postmarketing safety databases suggest that clozapine is associated with an increased risk of fatal myocarditis, especially during, but not limited to, the first month of therapy. In patients in whom myocarditis is suspected, clozapine treatment should be promptly discontinued.

##### **Other Adverse Cardiovascular and Respiratory Effects**

Orthostatic hypotension, with or without syncope, can occur with clozapine treatment. Rarely, collapse can be profound and be accompanied by respiratory and/or cardiac arrest. Orthostatic hypotension is more likely to occur during initial titration in association with rapid dose escalation. In patients who have had even a brief interval off clozapine (ie, 2 or more days since the last dose) treatment should be started with 12.5 mg once or twice daily.

Since collapse, respiratory arrest and cardiac arrest during initial treatment has occurred in patients who were being administered benzodiazepines or other psychotropic drugs, caution is advised when clozapine is initiated in patients taking a benzodiazepine or any other psychotropic drug.

### Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analysis of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to 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 (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Clozapine is not approved for the treatment of patients with dementia-related psychosis (Prod Info FAZACLO(R) orally disintegrating tablets, 2008; Prod Info CLOZARIL(R) oral tablets, 2008; Novartis Pharmaceuticals Corporation, 2008).

### 3.1 Contraindications

- A) [agranulocytosis](#) or severe [granulocytopenia](#), clozapine-induced, history; increased risk of subsequent episodes (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)
- B) concomitant use with other drugs having a known potential to cause [agranulocytosis](#) or suppress bone marrow function (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)
- C) hypersensitivity to [clozapine](#) or any other component of this drug (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)
- D) [myeloproliferative disorders](#), preexisting (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)
- E) [paralytic ileus](#), preexisting (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)
- F) severe central nervous system depression or comatose states from any cause; preexisting (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)
- G) uncontrolled [epilepsy](#) or other predisposing factors, preexisting; may increase risk of seizure (Prod Info CLOZARIL(R) Tablets, 2005)

### 3.2 Precautions

- A) [agranulocytosis](#) may occur; monitoring recommended (Prod Info CLOZARIL(R) oral tablets, 2008; Prod Info FAZACLO(R) orally disintegrating tablets, 2008)

- B)** cardiovascular and/or [pulmonary disease](#); possible increased risk for adverse cardiovascular and/or respiratory events (Prod Info [CLOZARIL\(R\)](#) oral tablets, 2008; Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2008)
- C)** concurrent use of benzodiazepines or other psychotropic medications (Prod Info [CLOZARIL\(R\)](#) oral tablets, 2008; Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2008)
- D)** elderly patients with dementia-related [psychosis](#) (unapproved use); increased risk of death; most deaths were attributed to cardiovascular events (eg, [heart failure](#) or sudden death) or infections (eg, [pneumonia](#) (Prod Info [CLOZARIL\(R\)](#) oral tablets, 2008; Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2008)
- E)** [myocarditis](#), including fatalities, has been reported; consider discontinuing therapy; rechallenge not recommended (Prod Info [CLOZARIL\(R\)](#) oral tablets, 2008; Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2008)
- F)** orthostatic hypotension, with or without syncope may occur (Prod Info [CLOZARIL\(R\)](#) Tablets, 2005)
- G)** seizures, history or predisposing factors ; dose-related risk of seizures associated with [clozapine](#) therapy (Prod Info [CLOZARIL\(R\)](#) oral tablets, 2008; Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2008)
- H)** [cardiomyopathy](#) may occur (Prod Info [CLOZARIL\(R\)](#) oral tablets, 2008; Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2008)
- I)** concurrent general [anesthesia administration](#) (Prod Info [CLOZARIL\(R\)](#) oral tablets, 2008; Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2008)
- J)** [deep vein thrombosis](#) or respiratory symptomatology may occur; consider presence of [pulmonary embolism](#) (Prod Info [CLOZARIL\(R\)](#) oral tablets, 2008; Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2008)
- K)** [diabetes mellitus](#) or at risk of [diabetes mellitus](#); increased risk for severe [hyperglycemia](#) (Prod Info [CLOZARIL\(R\)](#) oral tablets, 2008; Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2008)
- L)** [eosinophilia](#) has been rarely reported; therapy interruption may be necessary (Prod Info [CLOZARIL\(R\)](#) oral tablets, 2008; Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2008)
- M)** fever, possibly benign, may occur; evaluate to rule out sign of infection, sign of [agranulocytosis](#), or [neuroleptic malignant syndrome](#) (Prod Info [CLOZARIL\(R\)](#) oral tablets, 2008; Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2008)
- N)** [glaucoma](#), narrow angle; condition may be exacerbated due to anticholinergic properties (Prod Info [CLOZARIL\(R\)](#) oral tablets, 2008; Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2008)
- O)** [hepatic disease](#); increased risk of [hepatitis](#) (Prod Info [CLOZARIL\(R\)](#) oral tablets, 2008; Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2008)
- P)** [hyperglycemia](#) (some extreme cases associated with [ketoacidosis](#) or [hyperosmolar coma](#) or death) has been reported (Prod Info [CLOZARIL\(R\)](#) oral tablets, 2008; Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2008)
- Q)** increased duration of treatment and/or higher cumulative doses; increased risk of [tardive dyskinesia](#) (Prod Info [CLOZARIL\(R\)](#) oral tablets, 2008; Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2008)
- R)** intestinal peristalsis impairment, ranging from constipation to [intestinal obstruction](#), fecal impaction and [paralytic ileus](#), including fatal cases, have been reported during postmarketing use (Prod Info [CLOZARIL\(R\)](#) oral tablets, 2008; Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2008)
- S)** Jewish background; associated with more cases of [agranulocytosis](#) than general US population (Prod Info [CLOZARIL\(R\)](#) oral tablets, 2008; Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2008)
- T)** [leukopenia](#), moderate, initial episode; increased risk for subsequent episodes of [agranulocytosis](#) (Prod Info [CLOZARIL\(R\)](#) oral tablets, 2008; Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2008)
- U)** [neuroleptic malignant syndrome](#), potentially fatal, has been reported in association with antipsychotic therapy; immediately discontinue drug has occurred (Prod Info [CLOZARIL\(R\)](#) oral tablets, 2008; Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2008)
- V)** phenylketonurics; [Fazaclo\(R\)](#) 12.5-mg, 25-mg, and 100-mg orally disintegrating tablets contain 0.87 mg, 1.74 mg, and 6.96 mg [phenylalanine](#) per tablet, respectively (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2008)
- W)** prostatic enlargement; condition may be exacerbated due to anticholinergic properties (Prod Info [CLOZARIL\(R\)](#) oral tablets, 2008; Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2008)

X) suicide risk (Prod Info [CLOZARIL\(R\)](#) oral tablets, 2008; Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2008)

Y) [tardive dyskinesia](#), potentially irreversible, may occur (Prod Info [CLOZARIL\(R\)](#) oral tablets, 2008; Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2008)

### 3.3 Adverse Reactions

#### 3.3.1 Cardiovascular Effects

##### 3.3.1.A Cardiac complication

1) In clinical trials, several patient cases have experienced ischemic changes, [myocardial infarction](#), and sudden death with [clozapine](#) therapy. Additionally, postmarketing evaluation revealed cases of [myocarditis](#), [pericarditis](#) and/or [pericardial effusions](#); causality was complicated because of serious preexisting cardiac disease (Prod Info [Clozaril\(R\)](#), 2002).

##### 3.3.1.B Cardiac dysrhythmia

1) Adverse effects temporally associated with [clozapine](#) and occurring at a frequency less than 1% include bradycardia. Other effects reported from postmarketing experience and a case report include [atrial fibrillation](#) and [ventricular fibrillation](#); a causal relationship with [clozapine](#) could not be determined (Prod Info [Clozaril\(R\)](#), 2002; Low et al, 1998).

2) A 69-year-old male with [chronic paranoid schizophrenia](#) developed [atrial fibrillation](#) and possible [congestive heart failure](#) after having his [clozapine](#) titrated to 325 mg/day over 3 weeks. This was confirmed upon rechallenge (Low et al, 1998).

##### 3.3.1.C Cardiomyopathy

1) In the US, the reported rate of [cardiomyopathy](#) in clozapine-treated patients is 8.9 per 100,000 person-years compared to a rate of 9.7 per 100,000 person-years in the general US population (1999 National Hospital Discharge Survey data). Eighty percent of the patients with [cardiomyopathy](#) treated with [clozapine](#) were less than 50 years of age. The duration of [clozapine](#) treatment prior to the diagnosis of [cardiomyopathy](#) was greater than 6 months in 65% of the patients. [Dilated cardiomyopathy](#) was the most frequently reported type. Signs and symptoms suggestive of [cardiomyopathy](#) include: exertional dyspnea, fatigue, orthopnea, paroxysmal nocturnal dyspnea and peripheral edema. If [cardiomyopathy](#) is confirmed, [clozapine](#) should be discontinued unless the benefit to the patient clearly outweighs the risk (Prod Info [Clozaril\(R\)](#), 2002).

2) Forty-one cases of [cardiomyopathy](#), including 10 deaths, were reported to the Food and Drug Administration in [clozapine](#) recipients over a 10-year period. In patients with [cardiomyopathy](#) who survived, the median [clozaril](#) dose (450 mg vs 500 mg) and the duration of therapy (8 months vs 10 months) were similar to those who died (La Grenade et al, 2001).

3) Voluntary postmarketing reports to the Adverse Drug Reactions Advisory Committee of Australia over 6 years included 15 cases of [myocarditis](#) and 8 cases of [cardiomyopathy](#) among 8000 registered [clozapine](#) recipients (0.29%). Objective evidence confirmed the diagnosis in all 23 cases (87% male, mean age 36 years, [clozapine](#) dose range 100 to 725 mg/day). The median onset of [myocarditis](#) was 15 days, with subsequent early death in 5 cases in which autopsy revealed florid myocardial inflammatory infiltrates (eosinophilic in 3, lymphocytic in 1, mixed in 1). Recovery was documented in 5 patients, while the outcome of the remaining 5 was unknown. Five of 8 [cardiomyopathy](#) cases manifested during months 2 to 6 of therapy, while the remaining 3 cases occurred much later (30 to 36 months after initiation). One case was fatal after 2 years; 2 patients were stable to improved; the final outcome was unknown in 5 cases. The investigators discovered no confounding factors to account for these cardiac complications (Kilian et al, 1999).

4) A case of [cardiomyopathy](#), possibly related to [clozapine](#), occurred in a 26-year-old woman with no prior cardiac history. Following a total of 5 months of therapy with [clozapine](#) 700 mg/day, the patient developed malaise, dyspnea, and edema. [Echocardiography](#) demonstrated [cardiomyopathy](#) with a low ventricular ejection fraction. The patient improved following discontinuation of [clozapine](#) and institution of [digoxin](#) therapy. Because baseline [echocardiography](#) studies were not performed, it is difficult to determine a causal relationship, or if therapy with [clozapine](#) aggravated a previously undiagnosed cardiac problem (Leo et al, 1996).

#### 3.3.1.D Edema

1) Edema and periorbital edema temporally associated with [clozapine](#) has been reported and occurs at a frequency 1% or less (Prod Info [Clozaril\(R\)](#), 2002). In a case report, a 24-year-old woman treated with [clozapine](#) 400 mg daily for 6 weeks, developed pedal edema and peri-orbital puffiness. After the dosage was reduced to 200 mg over 10 days the edema gradually disappeared (Durst et al, 2000).

#### 3.3.1.E Hypertension

1) [Hypertension](#) and chest pain/angina have been reported in 1% to 4% of patients(Prod Info [Clozaril\(R\)](#), 2002).

2) Four obese patients developed a pseudopheochromocytoma syndrome while being treated with [clozapine](#) for serious refractory psychiatric disturbances. All patients manifested [hypertension](#) and profuse sweating. Urinary catecholamine concentrations were elevated in all 4 patients. [Pheochromocytoma](#) was excluded. In 2 cases, catecholamine concentrations normalized and clinical features improved or resolved with withdrawal of the drug. [Clozapine](#) dose was reduced in one patient, and treatment was continued unchanged in one patient because of spontaneous lowering of his blood pressure. The author suggested that concurrent sulpiride may have contributed to clinical symptoms in 2 patients (Krentz, 2001).

3) A 34-year-old male with [paranoid schizophrenia](#) developed moderate [hypertension](#), [tachycardia](#), pallor, and irritability after the initiation of [clozapine](#) (confirmed upon rechallenge). [Propranolol](#) 180 mg/day in divided doses was used successfully to control his blood pressure while [clozapine](#) was increased to 350 mg/day (George & Winther, 1996). In a similar case, a 19-year-old man developed [tachycardia](#) and [hypertension](#) and was successfully treated with [atenolol](#) (Ennis & Parker, 1997).

4) A 27-year-old man with [catatonic schizophrenia](#) treated with [clozapine](#) 300 mg developed [hypertension](#). [Blood pressure increased](#) to 146/106 (previously 110/70 to 120/80). [Amlodipine](#) 5 mg daily controlled the [high blood pressure](#). Upon further testing, it was noted that urinary adrenaline and noradrenaline were also elevated mimicking a pheochromocytoma-type reaction. [Clozapine](#) was eventually withdrawn over 10 weeks (Li et al, 1997).

#### 3.3.1.F Hypotension

1) Hypotension and syncope were reported with an incidence greater than 5% of patients, usually after the first dose or during dosage escalation. Rarely, the collapse can be profound and may be accompanied by respiratory arrest and/or [cardiac arrest](#) (Prod Info [Clozaril\(R\)](#), 2002).

2) A 51-year-old male maintained on [clozapine](#) 600 mg/day suffered from refractory hypotension following [coronary artery bypass graft surgery](#). The initial postoperative systolic blood pressure reading was 50 mL of mercury (mmHg), necessitating vasoconstrictor ([methoxamine](#) and [metaraminol](#)) and inotropic ([dopamine](#)) support. Even with the addition of [epinephrine](#), systolic pressure was only 60 mmHg. A 3-day [norepinephrine](#) infusion was required to maintain blood pressure. The alpha-1 blockade and resultant [vasodilatation induced](#) by [clozapine](#) was the likely etiology (Donnelly & MacLeod, 1999).

#### 3.3.1.G Myocarditis



## 1) Summary

- a) There have been postmarketing reports of [myocarditis](#) with [clozapine](#) use in the United States, Canada, United Kingdom, and Australia. Most cases of [myocarditis](#) were reported within the first month of [clozapine](#) therapy and some cases were fatal. Monitor for signs and symptoms of [myocarditis](#) (eg, unexplained fatigue, dyspnea, tachypnea, fever, chest pain, palpitations, other signs or symptoms of [heart failure](#), ST-T wave abnormalities, or [arrhythmias](#)), especially during the first month of therapy, and discontinue [clozapine](#) if [myocarditis](#) occurs (Prod Info [CLOZARIL](#)(R) oral tablets, 2008).
- 2) A total of 82 reports of [myocarditis](#) associated with [clozapine](#) use have been received from the United States, Canada, United Kingdom, and Australia. The incidence of [myocarditis](#) was 5, 16.3, 43.2, and 96.6 cases per 100,000 patient years, respectively. This is 17 to 322 times higher than the rate of [myocarditis](#) in the general population. In 51 (62%) of these cases, [myocarditis](#) occurred during the first month of treatment. There were 31 (38%) fatalities in this group with 25 of the 31 patients showing evidence of [myocarditis](#) at autopsy (Prod Info [CLOZARIL](#)(R) oral tablets, 2008).
- 3) Twenty-eight cases of [myocarditis](#), including 18 deaths, were reported to the Food and Drug Administration in [clozapine](#) recipients over a 10-year period. Patients who developed [myocarditis](#) and survived were generally treated for a shorter time (median 2 weeks vs 4 weeks) and took a lower daily [clozapine](#) doses (median 225 mg vs 450 mg) than those who died (La Grenade et al, 2001).
- 4) Voluntary postmarketing reports to the Adverse Drug Reactions Advisory Committee of Australia over 6 years included 15 cases of [myocarditis](#) and 8 cases of [cardiomyopathy](#) among 8000 registered [clozapine](#) recipients (0.29%). Objective evidence confirmed the diagnosis in all 23 cases (87% male, mean age 36 years, [clozapine](#) dose range 100 to 725 mg/day). The median onset of [myocarditis](#) was 15 days, with subsequent early death in 5 cases in which autopsy revealed florid myocardial inflammatory infiltrates (eosinophilic in 3, lymphocytic in 1, mixed in 1). Recovery was documented in 5 patients, while the outcome of the remaining 5 was unknown. Five of 8 [cardiomyopathy](#) cases manifested during months 2 to 6 of therapy, while the remaining 3 cases occurred much later (30 to 36 months after initiation). One case was fatal after 2 years; 2 patients were stable to improved; the final outcome was unknown in 5 cases. The investigators discovered no confounding factors to account for these cardiac complications (Kilian et al, 1999).
- 5) [Myocarditis](#) was described in 2 patients who were receiving [clozapine](#) for [paranoid schizophrenia](#). The first patient was a hospitalized 30-year-old male who complained of not feeling well and developed a fever and night sweats 12 days after starting [clozapine](#) therapy (titrated from 12.5 mg at bedtime up to 250 mg at bedtime). Although he had a normal [electrocardiogram](#) (ECG) with no QT-interval prolongation prior to [clozapine](#) therapy, the patient had an abnormal ECG ([sinus tachycardia](#) at 113 beats/minute (bpm); QTc of 463 msec; mild global hypokinesia) after 14 days of therapy; additionally, an [echocardiogram](#) revealed an ejection fraction (EF) of 40% to 45%. [Clozapine](#) was discontinued on day 14 and all other psychotropic medications were held on day 15 when the patient continued to experience declining cardiac function ([sinus tachycardia](#) at 123 bpm, QTc elevation of 466 msec, [right ventricular hypertrophy](#), and an EF of 34% on radionuclide [ventriculogram](#)). Additionally, troponin-T (0.23 nanograms/mL), B-type natriuretic peptide (BNP) (491 picograms (pg)/mL), and [creatinine kinase](#) (CK) (322 to 690 units/L) levels were elevated. Eosinophils were normal throughout admission, and bacterial and viral infections were ruled out. The patient was started on [carvedilol](#) 3.125 mg twice daily and [lisinopril](#) 2.5 mg daily on day 15; however, [lisinopril](#) was discontinued 2 days later due to mild hypotension. Laboratory values normalized by hospital discharge and the final ECG demonstrated normal sinus rhythm. The second patient was a 27-year-old male who was admitted to the hospital with complaints of chest pain, a productive cough, low-grade fevers, [dysphagia](#), dehydration, and night sweats 13 days after starting [clozapine](#) therapy (titrated from 50 mg at bedtime up to 300 mg at bedtime) for hallucinations and increased paranoia. He was also receiving [haloperidol](#) 20 mg/day, [divalproex](#) sodium 1500 mg/day, [venlafaxine](#) extended-release 150 mg/day, and [atomoxetine](#) 25 mg in the morning. The patient reported that the symptoms had started the week prior. On admission, an ECG showed [tachycardia](#) (118 bpm) and a QTc of 423 msec. All psychotropic medications



were discontinued. During the hospitalization, troponin-T (0.12 to 0.82 nanograms/mL), BNP (947 to 1609 pg/mL), CK (285 to 542 Units/L), and CK-MB (7.2 to 29.8 nanograms/mL) levels were elevated, eosinophil counts were normal, and viral titers were negative. On the second day of hospitalization (day 14 after starting [clozapine](#)), the patient had an elevated WBC count (11,100 to 12,200) and [ceftriaxone](#) and [azithromycin](#) were started for suspected [pneumonia](#). Also, the patient had difficulty breathing and received [furosemide](#) 60 mg IV for [pulmonary edema](#). An ECG revealed continued [sinus tachycardia](#) (136 bpm) and a prolonged QTc (430 msec); a [cardiac catheterization](#) performed the next day showed an EF of 25% and [left ventricular systolic dysfunction](#). The patient was discharged on [lisinopril](#) 2.5 mg daily and [carvedilol](#) 3.125 mg twice daily in addition to psychotropic medications (which did not include [clozapine](#)) (Grgas et al, 2010).

### 3.3.1.H Orthostatic hypotension

1) Orthostatic hypotension with or without syncope can occur during [clozapine](#) therapy; usually occurring during initial titration in association with rapid dose escalation. In rare cases (approximately 1 case per 3000 patients), collapse can be profound and may be seen with respiratory arrest and/or [cardiac arrest](#). Collapse and respiratory arrest have occurred with initial doses as low as 12.5 mg. If patients have been off [clozapine](#) therapy for 2 days or more, reinstitute with 12.5 mg once or twice daily. Some patients experiencing collapse, respiratory arrest, or [cardiac arrest](#) also received benzodiazepines or other psychotropic drugs. Elderly patients, particularly those with compromised cardiac functioning, may be more susceptible to these effects (Prod Info [Clozaril](#)(R), 2002; Kane, 1996a).

2) In clinical trials (n=842), greater than 5% of patients experienced syncope (Prod Info [Clozaril](#)(R), 2002).

### 3.3.1.I Pericardial effusion

1) [Pancreatitis](#) followed by [pericardial effusion](#) occurred in a 17-year-old, male, patient who was receiving [clozapine](#) for the treatment of [paranoid schizophrenia](#). Following 23 days of treatment during which time the [clozapine](#) dose was titrated from 25 mg/day to 175 mg/day, the patient experienced mild epigastric pain and had elevated levels of pancreas [amylase](#) and lipase. A diagnosis of [pancreatitis](#) was made and the [clozapine](#) was discontinued. One day later, the [clozapine](#) was resumed at 100 mg/day and the epigastric pain disappeared within 3 days. [Amylase](#) and lipase levels returned to normal after 19 days. Four days after decreasing the dose, the patient experienced inspiratory chest pain, increasing pain in both shoulders, and had a heart rate of 120 beats/min. A [CT scan](#) of the chest revealed a [pericardial effusion](#). The [clozapine](#) was again discontinued and the patient recovered following [cardiocentesis](#) that removed 250 mL of slightly hemorrhagic fluid (Wehmeier et al, 2003).

### 3.3.1.J Phlebitis

1) Adverse effects temporally associated with [clozapine](#) and occurring at a frequency less than 1% include [phlebitis](#), [thrombophlebitis](#), cyanosis, and [epistaxis](#) (Prod Info [Clozaril](#)(R), 2002).

### 3.3.1.K Sudden cardiac death

1) In a large, retrospective, cohort study that included a primary cohort of 93,300 users of antipsychotic drugs and 186,600 non-users of antipsychotic drugs, there was an increased risk of sudden cardiac death in adult participants 30 to 74 years of age (mean age of 45.7 years) who were using [clozapine](#) compared to those who were not using antipsychotic drugs (incidence-rate ratio, 3.67; 95% confidence interval (CI), 1.94 to 6.94; p less than 0.001). In participants being treated with atypical antidepressants ([clozapine](#), [olanzapine](#), [quetiapine](#), [risperidone](#)), the incidence-rate ratio for sudden cardiac death increased from 1.59 (95% CI, 1.03 to 2.46) for those using low doses to 2.86 (95% CI, 2.25 to 3.65) for those using high doses (p=0.01) (Ray et al, 2009).

### 3.3.1.L Tachyarrhythmia

1) Incidence: 25%

2) **Tachycardia** has been observed in approximately 25% of patients receiving **clozapine** and may be sustained. The sustained **tachycardia** is present in all positions monitored; the average increase in pulse is 10 to 15 beats per minute. Adverse effects temporally associated with **clozapine** and occurring at a frequency less than 1% include palpitations (Prod Info **Clozaril**(R), 2002; Wolf & Otten, 1991).

3) A 44-year-old man with **chronic schizophrenia** developed **ventricular tachycardia** after 2 weeks of **clozapine** therapy. He presented with a fever (38.5 degrees Celsius), pallor, and lethargy. Macular rashes appeared on his forearms and feet. **Electrocardiogram** showed ST elevation in leads V2 and V3. He was treated with **lidocaine** and **amiodarone** via a central line. **Atrial fibrillation** also developed lasting for 24 hours (Varma & Achan, 1999).

### 3.3.1.M Ventricular premature beats

1) Incidence: less than 1% (Prod Info **CLOZARIL**(R) oral tablets, 2008)

2) In clinical trials, **premature ventricular contractions** were reported in less than 1% of patients who received **clozapine** (Prod Info **CLOZARIL**(R) oral tablets, 2008).

## 3.3.2 Dermatologic Effects

### 3.3.2.A Cellulitis

1) Summary

a) A 37-year-old male developed right **arm cellulitis** and progressively increasing eosinophil count after 5 days of **clozapine** therapy and a left-sided **pleural effusion** after 12 days. **Clozapine** was discontinued and he improved with antibiotics. A later trial of **clozapine** 25 milligrams daily resulted in recurrence of symptoms (Chatterjee & Safferman, 1997).

### 3.3.2.B Dermatological finding

1) Summary

a) Adverse effects temporally associated with **clozapine** and occurring at a frequency less than 1% include **PRURITUS**, **PALLOR**, **ECZEMA**, **ERYTHEMA**, **BRUISE**, **DERMATITIS**, **PETECHIAE**, and **URTICARIA**. Voluntary postmarketing reports included **STEVENS-JOHNSON SYNDROME**, **ERYTHEMA MULTIFORME**, **PHOTOSENSITIVITY**, and **VASCULITIS**. However, a causal relationship could not be determined (Prod Info **Clozaril**(R), 2002).

2) Rash has occurred with some frequency in patients during **clozapine** therapy. Adverse effects temporally associated with **clozapine** and occurring at a lower frequency include **pruritus**, **pallor**, **eczema**, **erythema**, **sweating**, **bruising**, **dermatitis**, **petechiae**, and **urticaria**. Reports of other rare adverse effects include **Stevens-Johnson syndrome**, **erythema multiforme**, **photosensitivity**, and **vasculitis**.

### 3.3.2.C Rash

1) Summary

a) In clinical trials, rash occurred in 2% of patients (n=842) during **clozapine** therapy (Prod Info **Clozaril**(R), 2002).

2) Incidence: 2%

### 3) LITERATURE REPORTS

a) A well-circumscribed, erythematous, papular [pruritic rash](#) spread over the torso and extremities of a 37-year-old female approximately 9 days after [clozapine](#) initiation and titration to 150 milligrams/day. An initial [skin biopsy](#) revealed possible [furunculosis](#), but a later biopsy was consistent with a [drug hypersensitivity](#) reaction. The rash was preceded by fever to 39.9 degrees Celsius, headache, neck stiffness and chest pain, evolving into [bilateral pleural effusions](#). All signs and symptoms began to subside shortly after [clozapine's](#) discontinuation (Stanislav & Gonzalez-Blanco, 1999).

#### 3.3.2.D Sweating symptom

##### 1) Summary

a) A 31-year-old male developed increased sweating with [clozapine](#) therapy. [Biperiden](#), titrated to 6 milligrams per day, resulted in prompt cessation of generalized sweating (Richardson et al, 2001).

2) Incidence: 6%

### 3.3.3 Endocrine/Metabolic Effects

#### 3.3.3.A Acid-base balance - finding

1) Refractory [lactic acidosis](#) and [diabetic ketoacidosis](#) have been reported with [clozapine](#) use.

#### 3.3.3.B Body temperature finding

1) Adverse effects temporally associated with [clozapine](#) and occurring at a frequency of less than 1% include chills, hot flashes, and [hypothermia](#) (Prod Info [Clozaril](#)(R), 2002).

#### 3.3.3.C Diabetes mellitus

##### 1) Summary

a) [Hyperglycemia](#), [glucose intolerance](#), and new-onset [diabetes](#) have been reported with [clozapine](#) therapy. [Clozapine](#) therapy may modify glucose-insulin homeostasis by increasing [insulin](#) secretion, either by a direct effect on the pancreatic beta cells or via induction of peripheral [insulin](#) resistance, and impairing growth hormone secretion (Rigalleau et al, 2000; Melkersson et al, 1999; Popli et al (1997). One study found patients receiving [clozapine](#) tended to have [diabetes type 2](#) or [impaired glucose tolerance](#) more often than a control group of patients receiving depot neuroleptics (Hagg et al, 1998). The manufacturer reports that severe [hyperglycemia](#), sometimes leading to [ketoacidosis](#), [hyperosmolar coma](#), or death, has been reported in patients with no prior history of [hyperglycemia](#), but that a causal relationship could not be definitively established (Prod Info [Clozaril](#)(R), 2004). A case-control study investigated the possible association between [clozapine](#) use and development of [diabetes mellitus](#); it found no significant relationship (Wang et al, 2002).

##### 2) Literature Reports

a) A case-control study found no significant association between [clozapine](#) use and development of [diabetes mellitus](#). Using data from the New Jersey (NJ) Medicaid program (covering the period January 1, 1990 to June 30, 1995), NJ Medicare, and NJ Pharmaceutical Assistance to the Aged and Disabled program, 7227 cases of newly treated [diabetes](#) were compared to 6780 controls. Both groups represented patients having psychiatric diagnoses recorded in the previous 6 months. In the group with newly diagnosed [diabetes](#), 1.3% were using [clozapine](#). In the control

group (ie, patients with psychiatric diagnoses but not newly diagnosed with [diabetes](#)), 1.7% were using [clozapine](#) ( $p=0.073$ ). The adjusted odds ratio (OR) of developing [diabetes](#) with [clozapine](#) use was 0.98. There was no increased risk associated with higher [clozapine](#) doses or longer duration of [clozapine](#) therapy. By comparison, persons in the control group using non-clozapine antipsychotic medication had a modest but significantly increased risk of developing [diabetes](#) (OR 1.13). The antipsychotic agents particularly associated with an increased risk for [diabetes](#) were [chlorpromazine](#) (adjusted OR 1.31) and [perphenazine](#) (adjusted OR 1.34). The data also showed that there was an increased risk of developing [diabetes](#) among those using [prochlorperazine](#) (adjusted OR 1.21) and an oral corticosteroid (Wang et al, 2002).

**b)** A Chinese male [schizophrenia](#) patient developed [hyperglycemia](#), [hyperlipemia](#), and periodic paralysis while taking [clozapine](#). Symptoms resolved when [clozapine](#) was withdrawn and recurred when [clozapine](#) treatment was reestablished. Symptoms appeared at [clozapine](#) doses as low as 37.5 milligrams (mg) per day. Other drugs were not as effective as [clozapine](#) for treating his mental state. His mental state was finally stabilized with a combination of [clozapine](#) 25 mg/day and [haldol](#) 20 mg/day, without elevations of blood glucose or lipids (Wu et al, 2000).

**c)** Three cases of new-onset [diabetes](#) were reported in Caucasian men who were on [clozapine](#) for 3 to 6 months. They had a distinct presentation including weight loss, [ketosis](#) (one [ketoacidosis](#)), severe [hyperglycemia](#) requiring [insulin](#) therapy, and relative [insulin](#) deficiency. In all cases, [insulin](#) was discontinued one month after the [clozapine](#) was stopped (Rigalleau et al, 2000).

**d)** [Clozapine](#) therapy may modify glucose-insulin homeostasis by increasing [insulin](#) secretion, either by a direct effect on the pancreatic beta cells or via induction of peripheral [insulin](#) resistance, and impairing growth hormone secretion. In a study of 28 patients (median age: 42) on classical antipsychotics and 13 patients (median age: 35) on [clozapine](#) for [schizophrenia](#) and related [psychotic disorders](#), body mass index (BMI), fasting serum glucose, fasting serum [insulin](#), and insulin-like growth factor binding protein-1 (IGFBP-1) did not differ statistically between groups. Age-correlated insulin-like growth factor-1 (IGF-1) was significantly lower in [clozapine](#) recipients, which investigators speculated may be due to decreased growth hormone secretion. A higher percentage of [clozapine](#) users (46% versus 21%,  $p=NS$ ) had above normal [insulin](#) levels, but only one subject had abnormal glucose levels. BMI was elevated in 54% and 46% of the classical and [clozapine](#) groups, respectively. Findings unique to [clozapine](#) users were lack of correlations between IGFBP-1 and [insulin](#) and between IGFBP-1 and BMI; a negative correlation between IGF-1 and IGFBP-1; and a positive correlation between serum drug concentration and [insulin](#). These data, and their relationship to the risk of developing or exacerbating [diabetes mellitus](#), require further confirmation (Melkersson et al, 1999).

**e)** Patients receiving [clozapine](#) tended to have [diabetes type 2](#) or [impaired glucose tolerance](#) more often than a control group of patients receiving depot neuroleptics (Hagg et al, 1998). Patients at a psychiatric clinic receiving either [clozapine](#) or depot neuroleptics were recruited for a [diabetes](#) screening. None of the patients had a previous diagnosis or evidence of [diabetes mellitus](#). After screening, 13 out of 60 patients (22%) treated with [clozapine](#) were diagnosed with [type 2 diabetes](#) or [impaired glucose tolerance](#) while only 6 out of 63 (10%) in the depot neuroleptic group received these diagnoses. The difference did not reach statistical significance ( $p=0.06$ ).

**f)** Severe [hyperglycemia](#) (blood glucose 585 milligrams/deciliter) was reported in a 37-year-old Jewish male after 11 weeks of [clozapine](#) therapy. This was accompanied with refractory [lactic acidosis](#), [agranulocytosis](#), fever, [candidiasis](#) and fatal [myocardial failure](#) (Koren et al, 1997).

**g)** Four adults developed increasing [glucose intolerance](#) following the initiation of [clozapine](#) therapy (Popli et al, 1997). Two of the patients developed severe [diabetic ketoacidosis](#). The other 2 patients developed an exacerbation of their preexisting, well-controlled, [diabetes mellitus](#) within 2 weeks of initiation of [clozapine](#) therapy. The authors, in their limited experience (treated 147

patients over 10 years), noted a 2.7% incidence of clinically significant changes in glucose tolerance during [clozapine](#) therapy.

**h)** Two cases of patients developing [diabetes mellitus](#) and 2 cases of exacerbation of preexisting, but well controlled [diabetes mellitus](#), in patients starting [clozapine](#) therapy were reported (Popli et al, 1997).

See Drug Consult reference: ATYPICAL ANTIPSYCHOTIC AGENTS - EFFECT ON GLUCOSE AND RISK OF [DIABETES](#)

### 3.3.3.D [Diabetic ketoacidosis](#)

#### 1) Summary

**a)** Four case reports have noted the development of [ketoacidosis](#) with therapeutic use of [clozapine](#) therapy (Avram et al, 2001; Colli et al, 1999; Ai et al, 1998; Pierides, 1997).

#### 2) Literature Reports

**a)** A 33-year-old male, without past or family history of [diabetes mellitus](#), developed [diabetic ketoacidosis](#) after taking [clozapine](#) 50 milligrams twice a day for 8 months (Avram et al, 2001).

**b)** A 31-year-old Caucasian man developed [ketoacidosis](#) 3 months after beginning [clozapine](#) 200 milligrams daily (Colli et al, 1999). His blood sugars rapidly normalized after the discontinuation of [clozapine](#). A repeat trial of [clozapine](#) resulted in increased blood sugars within 72 hours.

**c)** A 30-year-old Afro-Caribbean man treated with [clozapine](#) 150 milligrams twice daily for 5 months developed [ketoacidosis](#) (Ai et al, 1998). Initially he was treated with [insulin](#) until [clozapine](#) was discontinued. He was then switched to an oral hypoglycemic agent. Eight months after discontinuing the [clozapine](#), the patient still required an oral agent.

**d)** [Hyperglycemia](#), hyperkalemia and [ketoacidosis](#) (pH 7.09) developed after 1 week of initiating and titrating [clozapine](#) from 25 milligrams/day (mg/day) to 300 mg/day in a 50-year-old male with chronic refractory [schizophrenia](#). Presenting symptoms included lethargy, thirst, chest pain, and dyspnea. The patient improved with [clozapine](#) withdrawal and [insulin](#) therapy (Pierides, 1997).

### 3.3.3.E Disorder of fluid AND/OR electrolyte

**1)** In voluntary postmarketing reports adverse effects of [hyperuricemia](#) and [hyponatremia](#) occurred during [clozapine](#) therapy. A causal relationship could not be determined (Prod Info [Clozaril\(R\)](#), 2002).

### 3.3.3.F [Excessive salivation](#)

**1)** Incidence: 31% (Prod Info [Clozaril\(R\)](#), 2002)

**2)** In clinical trials, increased salivation was reported in 31% of patients (n=842). Salivation may be profuse particularly during sleep but may be diminished with a dosage reduction (Prod Info [Clozaril\(R\)](#), 2002).

### 3.3.3.G [Hyperlipidemia](#)

#### 1) Summary

**a)** There have been case reports of significant [hyperlipidemia](#) associated with [clozapine](#) use (Ball et al, 2005; Wu et al, 2000), in one case precipitating acute [pancreatitis](#) (Ahmed et al, 2009).

#### 2) Literature Reports

**a)** In a case report, a 47 year old male treated for 2 years with [clozapine](#) for treatment-resistant [schizophrenia](#) developed [xanthomas](#) associated with significant [dyslipidemia](#) which developed into acute [pancreatitis](#). Following discontinuation of [clozapine](#) therapy, his metabolic parameters normalized. When rechallenged with [clozapine](#), significant [dyslipidemia](#) reoccurred within 10



weeks. The patient had no personal or family history of abnormal lipids or elevated blood glucose prior to [clozapine](#) initiation. He was maintained on [clozapine](#) 450 mg daily with an average plasma level of 490 nanograms/mL and presented with [xanthomas](#), fasting cholesterol 772.2 mg/dL, fasting [triglyceride](#) 4886.1 mg/dL, and a normal fasting glucose. [Clozapine](#) therapy was continued with the addition of statin therapy for the next 11 years. The patient was admitted with acute [pancreatitis](#), cholesterol 1404 mg/dL, [triglyceride](#) 14,418 mg/dL, and fasting glucose of 147.6 mg/dL. Discontinuation of [clozapine](#) resulted in normalization of metabolic parameters within 3 weeks. When psychotic symptoms deteriorated, [clozapine](#) was reintroduced and titrated up to 400 mg daily. Within 10 weeks, the cholesterol level increased to 417.3 mg/dL, [triglyceride](#) 3008.2 mg/dL, and fasting glucose 167.4 mg/dL. [Clozapine](#) discontinuation normalized levels within 10 days (Ahmed et al, 2009).

b) New-onset [hyperlipidemia](#) was reported in the case of a 42-year-old schizophrenic patient treated with [clozapine](#). At a dose of 300 mg/day, corresponding total cholesterol (TC) was increased at 256 mg/dL and [triglycerides](#) (TG) at 285 mg/dL. At [clozapine](#) doses of 500 mg/day, TG increased to greater than 400 mg/day. Lipid-lowering drug therapy did not adequately improve the lipid profile. The highest levels measured were TC 477 mg/dL and TG 4758 mg/dL. With sporadic [clozapine](#) compliance, TC measured 213 mg/dL, TG 298 mg/dL and low density lipoprotein cholesterol (LDL-C) 146 mg/dL. [Clozapine](#) was discontinued, and [aripiprazole](#) initiated and titrated to 45 mg/day. After 3 weeks, TC measured 107 mg/dL, TG 49 mg/dL and LDL-C 47 mg/dL (Ball et al, 2005).

c) A Chinese male [schizophrenia](#) patient developed [hyperglycemia](#), [hyperlipidemia](#), and periodic paralysis while taking [clozapine](#). Symptoms resolved when [clozapine](#) was withdrawn and recurred when [clozapine](#) treatment was reestablished. Symptoms appeared at [clozapine](#) doses as low as 37.5 milligrams (mg) per day. Other drugs were not as effective as [clozapine](#) for treating his mental state. His mental state was finally stabilized with a combination of [clozapine](#) 25 mg/day and [haloperidol](#) 20 mg/day, without elevations of blood glucose or lipids (Wu et al, 2000).

### 3.3.3.H [Hyperprolactinemia](#)

#### 1) Summary

a) With [clozapine](#) therapy, resolution of chronic [hyperprolactinemia](#) was observed in 2 female patients (Dickson et al, 2000). [Clozapine](#) does not cause sustained increases in serum prolactin levels as the traditional neuroleptics do. One author theorized that due to both the resolution of impaired sexual functioning secondary to [hyperprolactinemia](#) and improved social interactions secondary to [clozapine](#) treatment, higher birth rates may occur with [clozapine](#) therapy (Dickson & Edwards, 1997).

#### 2) Literature Reports

a) [Clozapine](#) does not cause sustained increases in serum prolactin levels as the traditional neuroleptics do. One author theorized that due to both the resolution of impaired sexual functioning secondary to [hyperprolactinemia](#) and improved social interactions secondary to [clozapine](#) treatment, higher birth rates may occur with [clozapine](#) therapy. At the Calgary General Day Hospital clinic, 235 patients were treated primarily for [schizophrenia](#) with 12% taking [clozapine](#). In this small group taking [clozapine](#), 4 babies were born (to 3 patients), while the other 88% of the patients not taking [clozapine](#) produced only 5 children (to 4 patients). Further studies are needed to elicit the effects of [clozapine](#) on fertility (Dickson & Edwards, 1997).

### 3.3.3.I [Lactic acidosis](#)

1) Refractory [lactic acidosis](#) (blood pH 6.97, bicarbonate 8 mEq/liter, and lactate 92.3 milligrams/deciliter), with [hyperglycemia](#) and [heart failure](#), [agranulocytosis](#) and [candidiasis](#), has been reported following several weeks of [clozapine](#) therapy (Koren et al, 1997).

### 3.3.3.J Metabolic syndrome

See Drug Consult reference: ANTIPSYCHOTIC AGENTS - [METABOLIC SYNDROME](#)

### 3.3.3.K Selenium deficiency

#### 1) Summary

- a) [Clozapine](#) was associated with decreased plasma and red-cell selenium concentrations in one study. [Selenium deficiency](#) has been associated with [cardiomyopathy](#) and with [myocarditis](#) and these same adverse effects are also known to occur with [clozapine](#) treatment (Vaddadi et al, 2003).
- 2) Plasma and red-cell selenium concentrations were significantly (p less than 0.01) lower in schizophrenic patients treated with [clozapine](#) (n=54) compared to patients with mood disorders (n=36), schizophrenic patients not treated with [clozapine](#) (n=41) and a healthy control group (n=56). The plasma and red-cell selenium concentrations (micromoles/liter) were 1.28 +/- 0.33, 1.47 +/- 0.57; 1.39 +/- 0.29, 1.70 +/- 0.40; 1.47 +/- 0.41, 1.70 +/- 0.48; and 1.49 +/- 0.30, 1.80 +/- 0.58 for the four groups respectively. [Selenium deficiency](#) has been associated with [cardiomyopathy](#) and with [myocarditis](#) and these same adverse effects are also known to occur with [clozapine](#) treatment. Although it could not be determined by this study whether [clozapine](#) causes [selenium deficiency](#) or if treatment-resistant schizophrenic patients (who are often treated with [clozapine](#)) are selenium deficient prior to treatment, the authors suggested that it may prove beneficial to provide selenium supplementation to schizophrenic patients receiving [clozapine](#) (Vaddadi et al, 2003).

### 3.3.3.L Sweating

- 1) Incidence: 4% to 6% (Prod Info [Clozaril](#)(R), 2002)
- 2) In clinical trials (n=842) with therapeutic use of [clozapine](#) increased sweating was reported in 4% to 6% of patients (Prod Info [Clozaril](#)(R), 2002).

### 3.3.3.M Weight gain

#### 1) Summary

- a) In clinical trials (n=842) weight gain was reported in 4% to 6% of patients with therapeutic use of [clozapine](#). One percent of patients experienced an appetite increase (Prod Info [Clozaril](#)(R), 2000). In other studies the report of weight gain and increased appetite was as high as 50% to 75% (Briffa & Meehan, 1998; Cohen et al, 1990; Norris & Israelstam, 1975). Two proposed mechanisms of clozapine-induced weight gain include increased [insulin](#) secretion, either by a direct effect on the pancreatic beta cells or via induction of peripheral [insulin](#) resistance, and impaired growth hormone secretion (Melkersson et al, 1999).
- 2) Incidence: 4%
- 3) Literature Reports

- a) The weight plateau achieved with [clozapine](#) apparently depends on genotype. Male monozygotic twins developed [paranoid type schizophrenia](#) at ages 17.4 years and 17.6 years. The first one was treated with [risperidone](#) and gained 17 kilograms (kg) over 11 months. The other was treated with classic antipsychotics for 2 months and gained 2 kg. Because of insufficient clinical response, both were switched to [clozapine](#) (500 mg/day and 450 mg/day). Both gained weight. Both twins developed binge eating episodes (2 to 3 per week) after starting [clozapine](#). At the time



of this report, weight gains since the initiation of antipsychotic treatment had totaled 38 and 40 kg (Theisen et al, 2001).

**b)** Two proposed mechanisms of clozapine-induced weight gain include increased [insulin](#) secretion, either by a direct effect on the pancreatic beta cells or via induction of peripheral [insulin](#) resistance, and impaired growth hormone secretion. In a study of 28 patients (median age: 42) on classical antipsychotics and 13 patients (median age: 35) on [clozapine](#) for [schizophrenia](#) and related [psychotic disorders](#), body mass index (BMI), fasting serum glucose, fasting serum [insulin](#), and insulin-like growth factor binding protein-1 (IGFBP-1) did not differ statistically between groups. Age-correlated insulin-like growth factor-1 (IGF-1) was significantly lower in [clozapine](#) recipients, which investigators speculated may be due to decreased growth hormone secretion. A higher percentage of [clozapine](#) users (46% versus 21%,  $p=NS$ ) had above-normal [insulin](#) levels, but only one subject had abnormal glucose levels. BMI was elevated in 54% and 46% of the classical and [clozapine](#) groups, respectively. Findings unique to [clozapine](#) users were lack of correlations between IGFBP-1 and [insulin](#) and between IGFBP-1 and BMI; a negative correlation between IGF-1 and IGFBP-1; and a positive correlation between serum drug concentration and [insulin](#). These data require further confirmation (Melkersson et al, 1999).

**c)** In four case reports (males with [schizophrenia](#) or other [psychotic disorders](#), aged 32 to 42), [clozapine](#) therapy (500 to 900 milligrams (mg)/day) was associated with increased serum [triglyceride](#) levels, which declined after [clozapine](#) discontinuation. Individual changes in [triglyceride](#) levels after substitution of [risperidone](#) for [clozapine](#) included: 229 to 104 mg/deciliter (dL); 140 to 60 mg/dL; 309 to 164 mg/dL; and 194 to 150 mg/dL. Total cholesterol levels showed similar reductions in two cases, but remained stable in two cases; all values were below 200 mg/dL. Two individuals stopped [risperidone](#) and restarted [clozapine](#), with accompanying increases in [triglyceride](#) levels of 164 to 270 mg/dL and 150 to 262 mg/dL, respectively (Ghaeli & Dufresne, 1999).

**d)** Significant weight gain occurred in patients prescribed [clozapine](#) (Briffa & Meehan, 1998). In a group of 48 patients, a mean absolute weight gain of 3.6 kilograms (kg) occurred over the first 3 months of therapy. An average of 4.95 kg was gained by 36 patients while 12 patients lost an average of 0.4 kg. Weight increase was most notable in men. After 1 year, 36 patients were available for follow-up and they gained an average of 3.35 kg. An average of 7.48 kg was gained by 25 patients while 11 patients lost an average of 4.7 kg.

**e)** Nine of 13 patients receiving [clozapine](#) (10 for the treatment of behavior disorder and 3 for [schizophrenia](#)) had an enormous and persistent increase in appetite resulting in day-long compulsive eating. Four patients gained between 10 and 20 kg within a 2-month period. After discontinuation of [clozapine](#) in 2 patients, their weight gain was rapidly lost (Norris & Israelstam, 1975).

**f)** Significant weight gain occurs during both short- and long-term treatment with [clozapine](#). A group of 82 patients were studied for a period of 90 months; the cumulative incidence of patients becoming 20% or more overweight was 54%. Monitoring and dietary counseling are necessary to minimize this long-term health risk (Umbricht et al, 1994). Six of 7 patients gained between 6 and 69 pounds with [clozapine](#) therapy (Cohen et al, 1990).

### 3.3.3.N Weight loss

**1)** Significant weight loss is reported in 3 patients after starting [clozapine](#). A 34-year-old female noted gradual decrease in body mass from 67 kg to 34 kg (BMI 29.6 kg/m(2) to 15.4 kg/m(2)) over 3 years of [clozapine](#) therapy. No changes in diet or menstrual patterns occurred during this time; physical exam and laboratory evaluation remained normal, extensive medical evaluation revealed no other apparent cause for weight loss. Approximately 5 years after starting [clozapine](#) she developed generalized seizures and was treated with sodium [valproate](#). At time of report, the patient continued [clozapine](#) 800 mg/day and

sodium [valproate](#) 1300 mg/day. The second patient, a 41-year-old male, experienced 18 kg weight loss over 18 weeks of therapy with [clozapine](#) (from 98 kg to 80 kg; BMI 26.9 kg/m(2) to 21.4 kg/m(2)). He was treated for [hypertension](#) prior to [clozapine](#), and diagnosed with [diabetes mellitus](#) one month after starting [clozapine](#). Despite reporting poor appetite, the patient continued [clozapine](#) 400 mg/day. The third patient is a 33-year-old female whose weight decreased by 14.4 kg in 21 weeks after starting [clozapine](#); BMI decreased from 25.9 kg/m(2) to 20.3 kg/m(2). No physical exam or laboratory abnormalities were noted; the patient continued [clozapine](#) 450 mg/day (Hanwella et al, 2010).

### 3.3.4 Gastrointestinal Effects

#### 3.3.4.A Abdominal discomfort

- 1) Incidence: 4% (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2007)
- 2) Abdominal discomfort/heartburn occurred in 4% of patients treated with [clozapine](#) in clinical trials (n=842) (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2007).

#### 3.3.4.B Bowel obstruction

- 1) In postmarketing reports, [intestinal obstruction/paralytic ileus](#) has occurred in patients receiving [clozapine](#) with some cases resulting in death. Treat constipation with adequate hydration and ancillary medications (eg, bulk laxatives) and consider consulting with a gastroenterologist for serious cases (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2007).
- 2) [Intestinal obstruction](#) necessitating hospitalization occurred in a 51-year-old male and a 35-year-old female with resistant [schizophrenia](#) receiving [clozapine](#) 275 milligrams (mg)/day for 2 months and 500 mg/day for 4 months, respectively. No other predisposing factors were identified. The patients recovered with conservative management and continued on [clozapine](#) therapy with adjunctive dietary measures and stool softeners (Tang & Ungvari, 1999).

#### 3.3.4.C Colitis, Necrotizing

- 1) A 36-year-old male developed fatal necrotizing [colitis](#) 4 months after beginning [clozapine](#) (Shammi & Remington, 1997).

#### 3.3.4.D Constipation

- 1) Incidence: 14% (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2007)
- 2) Constipation occurred in 14% of patients treated with [clozapine](#) in clinical trials (n=842). Elderly patients may be particularly susceptible to the anticholinergic effects of [clozapine](#), such as constipation. Intestinal peristalsis leading to fecal impaction, [paralytic ileus](#), and [intestinal obstruction](#) has also been reported with some cases resulting in death. Treat constipation with adequate hydration and ancillary medications (eg, bulk laxatives) and consider consulting with a gastroenterologist for serious cases (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2007).
- 3) Constipation occurs when the daily dose exceeds 150 milligrams. These adverse effects may disappear with continued administration of the same dose. However, if not, they are managed easily by dose reduction or temporary discontinuation of [clozapine](#) (Ayd, 1974a).

#### 3.3.4.E Diarrhea

- 1) Incidence: 2% (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2007)
- 2) Diarrhea occurred in 2% of patients treated with [clozapine](#) in clinical trials (n=842) (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2007).

3) Diarrhea, associated with decreasing lymphocyte counts, was reported in 3 patients between 13 days and 9 months following initiation of clozapine therapy. Rechallenge in 2 cases did not cause further diarrhea. The mechanism for this is unclear (Harvey et al, 1992).

#### 3.3.4.F Excessive salivation

1) Incidence: 31% (Prod Info FAZACLO(R) orally disintegrating tablets, 2007)

2) Salivation occurred in 31% of patients treated with clozapine in clinical trials (n=842). Salivation may be profuse, particularly during sleep, but may be diminished with a dosage reduction (Prod Info FAZACLO(R) orally disintegrating tablets, 2007).

3) Ipratropium nasal spray given sublingually provided relief of sialorrhea in 8 patients receiving daily clozapine. A retrospective analysis of patients receiving daily clozapine (150 to 600 milligrams (mg)) for schizophrenia or bipolar disorder who complained about excessive drooling was conducted. Nine patients received an intranasal formulation of ipratropium (0.03% or 0.06%) to be used sublingually (2 sprays) up to 3 times daily, if needed, for excessive drooling. After several weeks of use, full response was reported by 2 patients, partial response (symptoms controlled for 2 to 8 hours) by 5 patients, and no response by 1 patient. One patient rated the spray not effective and discontinued drug after a few days. Sublingual ipratropium nasal spray may be useful for situations in which drooling would be socially undesirable (Freudenreich et al, 2004).

4) An overview of clozapine-induced hypersalivation explores possible mechanisms involved as well as management options. Potential contributing factors are clozapine's muscarinic M4 receptor stimulation, alpha-2 antagonism and/or interference with the normal swallowing reflex. Published data have not documented any increase in daytime salivary flow rate with clozapine; however, nighttime flow rates have not been studied. Management strategies include clozapine dosage reduction if clinically feasible, sleeping with a towel over the pillow to absorb excess saliva, chewing gum to stimulate swallowing, and as a last resort, an anticholinergic agent or alpha-2 agonist. Because supportive studies are lacking, treatment decisions must be individualized (Davydov & Botts, 2000).

5) In a 50-year-old schizophrenic woman, hypersalivation and sedation developed after several days on clozapine. By day 10, she developed aspiration pneumonia. This prompted the authors to warn that aspiration precautions may be necessary with hypersalivation due to clozapine (Hinkes et al, 1996).

6) Hypersalivation was reported in 16 of 19 patients receiving clozapine therapy. Doses ranged from 75 to 800 milligrams (mg)/day (Lapierre et al, 1980). Nocturnal hypersalivation occurred at a dosage range of 225 to 800 mg/day (Kirkegaard et al, 1982).

#### 3.3.4.G Fecal impaction

1) In postmarketing reports, fecal impaction has occurred in patients receiving clozapine with some cases resulting in death. Treat constipation with adequate hydration and ancillary medications (eg, bulk laxatives) and consider consulting with a gastroenterologist for serious cases (Prod Info FAZACLO(R) orally disintegrating tablets, 2007).

2) A 20-year-old otherwise healthy male receiving clozapine for schizophrenia had fecal impaction and experienced fatal bowel ischemia and infarction following complaints of constipation. During a 1-year period, the patient was titrated up to a clozapine dose of 900 milligrams (mg)/day; additionally, amisulpiride 400 mg twice daily had been added for persistent negative symptoms with good results after one month. He presented to his physician with severe abdominal pain following a 2-day history of constipation and was prescribed medication and returned home. The patient collapsed and died a few hours later before reaching a hospital; subsequently, a postmortem examination discovered the patient had impacted feces leading to bowel-wall ischemia and infarction (Townsend & Curtis, 2006).

#### 3.3.4.H Gastrointestinal hypomotility

1) A review of pharmacovigilance data from the Australian Adverse Drug Reactions Advisory Committee (ADRAC) and New Zealand's Intensive Medicines Monitoring Program (IMMP) identified 74 cases of serious clozapine-induced [gastrointestinal hypomotility](#) (CIGH). A total of 102 cases of suspected life-threatening CIGH were compiled using data from ADRAC and IMMP. Cases of CIGH were further identified as serious in the database if they were recorded as: 1) serious or life-threatening constipation or constipation resulting in hospitalization, surgery, or a fatal outcome; 2) fecal impaction; 3) ileus; 4) [bowel obstruction](#), [ischemia](#), necrosis, or perforation; or 5) [megacolon](#). Only cases identified by pharmacovigilance staff as having possible or probable association with [clozapine](#) were included from the ADRAC data while 2 authors identified and excluded cases with confounding pathology from the IMMP data. Additionally, multiple reports of the same or similar adverse events for 1 patient were treated as single cases to avoid [duplication](#). There were 57 and 17 cases, respectively, from ADRAC and IMMP data that met the criteria for being cases of serious CIGH. Of these cases, the mortality rate was 27.5% and incidence was higher in males (66.7%) than in females (30.4%). Of the patients who developed serious CIGH, 20% developed it within the first month of treatment, 36.3% within the first 4 months, and 50% within the first year of treatment. The risk seemed to be greater at higher doses of [clozapine](#) (535 milligrams/day in fatal cases) (Palmer et al, 2008).

### 3.3.4.I Heartburn

- 1) Incidence: 4% (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2007)
- 2) Abdominal discomfort/heartburn occurred in 4% of patients treated with [clozapine](#) in clinical trials (n=842) (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2007).

### 3.3.4.J Ischemic bowel disease

1) A 20-year-old otherwise healthy male receiving [clozapine](#) for [schizophrenia](#) experienced fatal [bowel ischemia](#) following complaints of constipation. During a 1-year period, the patient was titrated up to a [clozapine](#) dose of 900 milligrams (mg)/day; additionally, amisulpiride 400 mg twice daily had been added for persistent negative symptoms with good results after one month. He presented to his physician with severe abdominal pain following a 2-day history of constipation and was prescribed medication and returned home. The patient collapsed and died a few hours later before reaching a hospital; subsequently, a postmortem examination discovered the patient had impacted feces leading to bowel-wall ischemia and infarction (Townsend & Curtis, 2006).

### 3.3.4.K Nausea

- 1) Incidence: 5% (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2007)
- 2) Nausea occurred in 5% of patients treated with [clozapine](#) in clinical trials (n=842) (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2007).
- 3) Nausea occurs when the daily dose exceeds 150 milligrams. These adverse effects may disappear with continued administration of the same dose; however, if not, they are managed easily by dose reduction or temporary discontinuation of [clozapine](#) (Ayd, 1974a).

### 3.3.4.L Nausea and vomiting

- 1) Incidence: 3% (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2007)
- 2) Nausea/vomiting occurred in 3% of patients treated with [clozapine](#) in clinical trials (n=842) (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2007).
- 3) Nausea occurs when the daily dose exceeds 150 milligrams. These adverse effects may disappear with continued administration of the same dose; however, if not, they are managed easily by dose reduction or temporary discontinuation of [clozapine](#) (Ayd, 1974a).

### 3.3.4.M Pancreatitis

- 1) In postmarketing reports, [pancreatitis](#) has occurred in patients receiving [clozapine](#) (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2007).
- 2) [Pancreatitis](#) followed by [pericardial effusion](#) occurred in a 17-year-old male patient who was receiving [clozapine](#) for the treatment of [paranoid schizophrenia](#). Following 23 days of treatment, during which time the [clozapine](#) dose was titrated from 25 milligrams (mg) per day to 175 mg/day, the patient experienced mild epigastric pain and had elevated levels of pancreas [amylase](#) and lipase. A diagnosis of [pancreatitis](#) was made and the [clozapine](#) was discontinued. One day later, the [clozapine](#) was resumed at 100 mg/day and the epigastric pain disappeared within 3 days. [Amylase](#) and lipase levels returned to normal after 19 days. Four days after decreasing the dose, the patient experienced inspiratory chest pain, increasing pain in both shoulders, and had a heart rate of 120 beats per minute. A [CT scan](#) of the chest revealed a [pericardial effusion](#). The [clozapine](#) was again discontinued and the patient recovered following [cardiocentesis](#) that removed 250 milliliters of slightly hemorrhagic fluid (Wehmeier et al, 2003).
- 3) In one study of reported cases (n=192) of antipsychotic-induced [pancreatitis](#), 40% of the cases were associated with the use of [clozapine](#) at a mean daily dose of 306.7 milligrams. In most patients, time to onset of [pancreatitis](#) was within 6 months after initiation of treatment (Koller et al, 2003c).

### 3.3.4.N Paralytic ileus

- 1) Patients with [paralytic ileus](#) should not receive [clozapine](#). In postmarketing reports, [intestinal obstruction/paralytic ileus](#) has occurred in patients receiving [clozapine](#) with some cases resulting in death. Treat constipation with adequate hydration and ancillary medications (eg, bulk laxatives) and consider consulting with a gastroenterologist for serious cases (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2007).
- 2) [Intestinal obstruction](#) necessitating hospitalization occurred in a 51-year-old male and a 35-year-old female with resistant [schizophrenia](#) receiving [clozapine](#) 275 milligrams (mg)/day for 2 months and 500 mg/day for 4 months, respectively. No other predisposing factors were identified. The patients recovered with conservative management and continued on [clozapine](#) therapy with adjunctive dietary measures and stool softeners (Tang & Ungvari, 1999).

### 3.3.4.O Parotitis

- 1) A 49-year-old woman receiving [clozapine](#) 300 milligrams (mg) daily developed [parotitis](#). She was first noted to have swelling on the right side of her face and pain in her right parotid gland. She received a 7-day course of [penicillin](#) and [benztropine](#) 2 mg. Her symptoms improved after 1 week (Southall & Fernando, 1999).

### 3.3.4.P Perforation of intestine

- 1) [Colon perforation](#) with [peritonitis](#) and sepsis occurred in a 49-year-old patient receiving [clozapine](#) 200 milligrams twice daily for 6 weeks. [Clozapine](#) was discontinued and after emergency [hemicolectomy](#) and [colostomy](#), the patient was successfully treated with [risperidone](#) (Freudenreich & Goff, 2000).

### 3.3.4.Q Summary

- 1) Common gastrointestinal effects associated with [clozapine](#) therapy include constipation (14%) and nausea (5%). Elderly patients may be particularly susceptible to the anticholinergic effects of [clozapine](#), such as constipation. Intestinal peristalsis leading to fecal impaction, [paralytic ileus](#), and [intestinal obstruction](#) has also been reported with some cases resulting in death. Treat constipation with adequate



hydration and ancillary medications (eg, bulk laxatives) and consider consulting with a gastroenterologist for serious cases (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2007).

#### 3.3.4.R Swelling of salivary gland

- 1) In postmarketing reports, salivary gland swelling has occurred in patients receiving [clozapine](#) (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2007).
- 2) A 49-year-old woman receiving [clozapine](#) 300 milligrams (mg) daily developed [parotitis](#). She was first noted to have swelling on the right side of her face and pain in her right parotid gland. She received a 7-day course of [penicillin](#) and [benztropine](#) 2 mg. Her symptoms improved after 1 week (Southall & Fernando, 1999).
- 3) Salivary gland swelling has been reported with [clozapine](#). One case describes transient swelling of the left submandibular salivary gland in a patient on stable [clozapine](#) treatment for 13 months (Troia et al, 1996). Another case describes painless, bilateral swelling in the parotid region associated with [hypersalivation](#) after only 14 days of therapy (Patkar & Alexander, 1996).

#### 3.3.4.S Vomiting

- 1) Incidence: 3% (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2007)
- 2) Vomiting occurred in 3% of patients treated with [clozapine](#) in clinical trials (n=842) (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2007).

#### 3.3.4.T Xerostomia

- 1) Incidence: 6% (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2007)
- 2) Dry mouth occurred in 6% of patients treated with [clozapine](#) in clinical trials (n=842) (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2007).

### 3.3.5 Hematologic Effects

#### 3.3.5.A Agranulocytosis

##### 1) Summary

- a) In pre-marketing evaluation, the cumulative incidence of [agranulocytosis](#) at 1 year was 1.3% (15 of 1743 patients). [Agranulocytosis](#) was defined as a neutrophil count of less than 500 cells/mm<sup>2</sup>. In the United States, there have been 585 cases (n=150,409) of [agranulocytosis](#) as of August 21, 1997; 19 of which were fatal. Few deaths have been reported since 1977 due to increased knowledge of clozapine-induced [agranulocytosis](#) and the importance of white blood cell monitoring (Prod Info [Clozaril\(R\)](#), 2002). One reference reports that the incidence of [agranulocytosis](#) following [clozapine](#) treatment is 10 to 20 times higher than that of phenothiazines (Oren et al, 1993).
- b) Asymptomatic [agranulocytosis](#) developing in a patient several months after start of treatment with [clozapine](#) for treatment-resistant [schizophrenia](#) was initially attributed to [clozapine](#) treatment but later was found to be a result of a large B-cell [lymphoma](#). Replacement of [clozapine](#) with [chlorpromazine](#) and [quetiapine](#) resulted in deterioration of the patient's mental state, resulting in hospitalization. During hospitalization, the [lymphoma](#) was discovered and was treated with chemotherapy. [Clozapine](#) was later reintroduced for better antipsychotic control and was continued with good effect, despite significant [neutropenia](#) secondary to the chemotherapy (Hundertmark & Campbell, 2001).
- c) In data evaluating 11,555 patients, the majority of [agranulocytosis](#) occurred within the first three months of drug therapy; older patients and women appeared to be at an increased risk. Recent studies suggest people of Jewish and Asian origin may also be at higher risk (Meged et al, 1999;

Munro et al, 1999). The hazard can be reduced by weekly monitoring of the white blood cell count (Alvir et al, 1993). Some cases of clozapine-induced [agranulocytosis](#) have been successfully treated with [filgrastim](#) or [sargramostim](#) (Gullion & Yeh, 1994).

2) Incidence: 1.3%

### 3) LITERATURE REPORTS

a) Two 18-year-old, female monozygotic twins developed [schizophrenia](#) within 2 weeks of one another and both developed [agranulocytosis](#) after 9 weeks of treatment with [clozapine](#). Twin A responded poorly to initial treatment with [haloperidol](#) (prominent extrapyramidal symptoms) and was switched to sulpiride 400 mg/day and [clozapine](#) 6 mg/day. Her condition worsened and she was given 4 electroconvulsive (ECT) treatments. She was discharged, fully remitted, at 6 weeks after the start of [clozapine](#) treatment, with a maintenance dose of [clozapine](#) 150 mg/day. At discharge her leucocyte count was 13,700/mL. At 10 weeks after start of [clozapine](#) treatment, her [leukocyte](#) count was 1400/mL. [Clozapine](#) was discontinued. Her [leukocyte](#) level normalized within 3 weeks, but psychotic symptoms recurred. Complete remission was obtained with [risperidone](#) 5 mg/day. Because of her sister's experience with [haloperidol](#), twin B was treated immediately with [clozapine](#), up to a dose of 300 mg/day. Because of insufficient response, she was given 8 ECT treatments. After 8 weeks of treatment, she was discharged, fully remitted. Her [leukocyte](#) count at discharge was 6100/mL. By 9 weeks after start of [clozapine](#) treatment, her [leukocyte](#) count was 1800/mL. [Clozapine](#) was discontinued, resulting in a recurrence of psychotic symptoms. [Leukocytopenia](#) persisted for 11 weeks. After control of her psychotic symptoms, her [leukocyte](#) level normalized. Her psychotic symptoms disappeared only after addition of [oxazepam](#) 15 mg/day to her regimen of [risperidone](#) 4 mg/day. This case report suggests that genetic factors play a role in the timing of onset of [schizophrenia](#) and also on the timing of [agranulocytosis](#) in response to [clozapine](#) treatment (Horacek et al, 2001).

b) In a study of 50 Jewish [clozapine](#) recipients, a 20-year-old female of Ashkenazi origin with the human [leukocyte](#) antigens (HLA) B38 and DR4 developed [agranulocytosis](#) with sepsis 12 weeks after initiation of [clozapine](#) (last dose: 300 mg/day). She recovered with antibiotic treatment and colony stimulating factor support. Two other females, a 20-year-old of Ashkenazi origin with HLA-B38 and a 33-year-old of non-Ashkenazi origin without suspected HLA haplotypes, experienced [neutropenia](#). Overall, 38% of the study sample were of Ashkenazi origin, yet they represented two-thirds of those with resultant [neutropenia/agranulocytosis](#). An additional 7 individuals manifested abnormalities in white blood cell count such as reduction that did not meet criteria for [neutropenia](#) (n=4); [eosinophilia](#) (n=2); and [leukocytosis](#) (n=1). Five of 7 (71%) in this group were of Ashkenazi origin. Because of the small numbers involved, none of the comparisons reached statistical significance. The authors note that the HLA susceptibility antigens are B38 and DR4 in Jews, and B7 and DR2 in non-Jews. Investigation is continuing as to whether a rare allele of these HLA haplotypes is responsible for [agranulocytosis](#) in the presence of [clozapine](#) and whether other non-major histocompatibility complex genes might be involved (Meged et al, 1999).

c) The cumulative incidence of clozapine-induced [agranulocytosis](#) was 0.73%, based on the [Clozaril](#) Patient Monitoring System (1990 to 1997, n=12,760) in the United Kingdom and Ireland. The peak onset was during weeks 6 to 18 of therapy. Only 2 of 93 cases were fatal. In this registry, the average and mean maximum [clozapine](#) doses were 388 and 462 milligrams/day, respectively. Cox proportional hazards regression analysis revealed a 53% increased risk with each 10-year increase in age at [clozapine](#) initiation (p=0.0001) and a 2.4 times higher risk among Asians compared to Caucasians (p=0.03). The authors categorized "Asian" and "Oriental" races separately without explanation. Maximum dose was inversely associated with risk (Munro et al, 1999).

d) Toxicity, inborn errors of metabolism, and/or immunological reactions may be involved in clozapine-induced [agranulocytosis](#) (Claas, 1989; Hasegawa et al, 1994). Other authors have



suggested that genetic factors marked by major histocompatibility complex haplotypes may be associated with the susceptibility to [agranulocytosis](#) (Lieberman et al, 1990; Joseph et al, 1992). There is a 20% incidence in a Jewish group of patients strongly correlating with the presence of the haplotype HLA-B38, DR4, or DQW3. In addition, clozapine-induced [agranulocytosis](#) was reported in two non-Jewish patients, both of whom expressed HLA-B38 but did not express DR4 or DQW3 (Joseph et al, 1992).

e) A 37-year-old, Ashkenazic Jewish man developed fatal [agranulocytosis](#) and fever 11 weeks after starting [clozapine](#) therapy. At 10 weeks, the patient's white blood cell count fell to 3900 cells/cubic millimeter (mm<sup>3</sup>) with a neutrophil count of 1400 cells/mm<sup>3</sup> and [lymphocyte](#) count of 2000 cells/mm<sup>3</sup>. The [clozapine](#) was discontinued. Four days later the patient was admitted with fever and severe [agranulocytosis](#) (neutrophil count 120 cells/mm<sup>3</sup>, [lymphocyte](#) count 810 cell/mm<sup>3</sup>). [Filgrastim](#), [piperacillin](#) and [gentamicin](#) were initiated. However, 6 hours later the patient collapsed and was found to have severe [hyperglycemia](#) (blood glucose 1000 milligrams/dl) and [lactic acidosis](#) (pH 7.13; bicarbonate 10 mEq/liter, and lactate 79.3 mg/dL). Despite intensive treatment the patient developed intractable hypotension, [anuria](#) and [cardiac arrest](#). He died 36 hours after admission (Koren et al, 1997).

f) Clozapine-induced [agranulocytosis](#) was prolonged in 3 patients with the initiation of [olanzapine](#) therapy. The granulocyte recovery time was 21 days, as compared to an average 3 days in a group of patients not receiving [olanzapine](#). The authors recommend avoiding [olanzapine](#) in this setting until hematologic indices have returned to normal (Flynn et al, 1997).

g) Five cases of clozapine-induced [agranulocytosis](#) were reported as being successfully treated with rG-CSF ([filgrastim](#)) (Gullion & Yeh, 1994). The patients were treated with at least 300 mcg/day of [filgrastim](#) administered subcutaneously with the onset of [agranulocytosis](#), increasing by 300 mcg/day for the first 3 days to a total of 900 mcg/day until resolution of [agranulocytosis](#). Time from onset until resolution was a mean of 8.2 days, as compared to a historical control group of 15.7 days. One patient was successfully treated with [sargramostim](#) 3 mcg/kg/day for 4 days (Oren et al, 1993).

h) [Clozapine](#) has been associated with a significant risk for [granulocytopenia](#) during clinical trials at therapeutic dosages and onset of symptoms occur between the 6th and 18th week of therapy (Bablenis et al, 1989; Povlsen et al, 1985).

### 3.3.5.B Blood coagulation disorder

1) An increased aPPT of 34.2 sec (control 27 sec) was reported as a result of a positive [lupus](#) anticoagulant in a 39 year-old male after therapy with [clozapine](#) (225 mg/day), [Klonopin](#), [Cogentin](#), and [Lipid](#). Normal laboratory tests included PT (14 sec), CBC, TT (21 sec), and a negative ANA titer (Kanjolia et al, 1997).

### 3.3.5.C Disorder of hematopoietic structure

#### 1) Summary

a) Adverse effects that were temporally associated with [clozapine](#) and occurred in less than 1% of patients include [anemia](#) and [leukocytosis](#). Other adverse effects voluntarily reported by the manufacturer include elevated [hemoglobin](#), elevated hematocrit, increased [erythrocyte sedimentation](#) rate, [thrombocytopenia](#), and sepsis; a causal relationship could not be determined (Prod Info [Clozaril](#)(R), 2002).

#### 2) LITERATURE REPORTS

a) [Aplastic anemia](#) developed in a 53-year-old man with [Parkinson's disease](#) following the administration of [clozapine](#). The patient developed [aplastic anemia](#) after taking [clozapine](#) 50 mg/day for the treatment of dopamine-induced [psychosis](#) with hallucinations. The man developed

a fever one week after beginning therapy. Blood tests exposed a severe form of [drug-induced aplastic anemia](#). [Clozapine](#) was discontinued and the patient received treatment including [blood transfusions](#), hematopoietic growth factors and antibiotics. The [aplastic anemia](#) resolved within 14 days and the patient's hallucinations and delusions were successfully treated with [quetiapine](#) (Ziegenbein et al, 2003).

**b)** N-desmethyleclozapine, the major metabolite of [clozapine](#), is toxic. N-desmethyleclozapine is further metabolized to an unstable compound that is toxic to hemopoietic precursors of both myeloid and erythroid lineages (Gerson et al, 1994).

### 3.3.5.D Drug-induced [eosinophilia](#)

#### 1) Summary

**a)** In clinical studies, 1% of patients developed [eosinophilia](#); rarely were cases substantial. If a differential count indicates a total eosinophil count above 4000 cell/mm(3), interrupt therapy until the count falls below 3000 cells/mm(3) (Prod Info [Clozaril](#)(R), 2002). The onset of [eosinophilia](#) usually occurs after 3 to 5 weeks of treatment (Meged et al, 1999; Chatterton, 1997; Pirmohamed & Park, 1997a).

**2)** Incidence: 1% (Prod Info [Clozaril](#)(R), 2002)

#### 3) LITERATURE REPORTS

**a)** A In a study of 50 Jewish [clozapine](#) recipients, two males aged 34 and 46 years developed [eosinophilia](#) 4 and 6 weeks after [clozapine](#) initiation, respectively. Their most recent [clozapine](#) doses were 150 and 300 mg/day, respectively. Their eosinophil counts peaked at 1365 and 984 cells/mm(3), respectively (Meged et al, 1999).

**b)** In a study comparing the incidences of [eosinophilia](#) and [neutropenia](#) for patients on [clozapine](#) (n=41) versus [haldol](#) (n=29), no significant differences were found. During a 6 month period, patients were monitored weekly for [blood dyscrasias](#). [Eosinophilia](#) was defined as an absolute eosinophil level in excess of 500 cells/mm(3) and [neutropenia](#) was defined as an absolute neutrophil count below 2000 cells/mm(3). In the [clozapine](#) group, [eosinophilia](#) and [neutropenia](#) occurred in 32% and 7% of the patients, while the occurrence in the [haloperidol](#) group was 31% and 7%, respectively. Most patients developed [eosinophilia](#) in the first 6 weeks. No significant differences were found between men and women, ethnic groups, or age groups. Also, [eosinophilia](#) did not predict [neutropenia](#) (Ames et al, 1996). In a retrospective review, the rate of [eosinophilia](#) reported at an Australian hospital was 13% (Chatterton, 1997).

**c)** A 30-year-old woman receiving [clozapine](#) 200 mg/day developed [eosinophilia](#) with a peak of 1320/mL on treatment day 26 (Lucht & Rietschel, 1998). [Clozapine](#) was discontinued and the eosinophil count decreased to 220/mL on day 45. Also of note is that [neutropenia](#) developed with a low of 1800/mL on day 32 and IgE increased to 254 IU/dL (reference value less than 120 international units/dL).

**d)** A 37-year-old man developed [eosinophilia](#) (700 cells/mm(3)) 2 weeks after beginning [clozapine](#) therapy. The eosinophil count remained stable for 7 weeks until he developed severe [agranulocytosis](#), necessitating [clozapine](#) discontinuation. After 3 weeks the granulocyte count returned to normal. It has been theorized that [eosinophilia](#) predicts later [agranulocytosis](#) (Amital et al, 1997).

**e)** [Eosinophilia](#) developed in a 38-year-old schizophrenic patient following 5 weeks of [clozapine](#) therapy (eosinophil count of 1500 cells/mm(3)). Within 4 days of [clozapine](#) discontinuation, [leukocyte and differential counts](#) returned to normal and [clozapine](#) was restarted with no further abnormalities (Tihonen & Paanila, 1992). Another case of [eosinophilia](#) has been reported when

treated therapeutically with [clozapine](#); anecdotal knowledge of several more cases exists (Stricker & Tielens, 1991).

### 3.3.5.E Neutropenia

#### 1) Summary

**a)** In clinical studies, [neutropenia](#) occurred in 2.7 to 22% of patients, with peak onset during weeks 6 to 18 of therapy. Cox proportional hazards regression analysis revealed a 17% decreased risk with each 10-year increase in age at [clozapine](#) initiation and a 77% greater risk in African-Caribbean subjects compared to Caucasians. The racial difference may be partially explained by significantly lower baseline white blood cell counts (an independent predictor of [neutropenia](#)) among African-Caribbeans. Maximum dose was inversely associated with risk (Prod Info [Clozaril](#)(R), 2002; Munro et al, 1999; Atkin et al, 1996; Hummer et al, 1997a).

**2)** Incidence: 3%

#### 3) LITERATURE REPORTS

**a)** Although recommended by the manufacturer, the emergence of [neutropenia](#) in clozapine-treated patients has not required discontinuation of [clozapine](#) therapy in several cases. In a retrospective chart review, researchers assessed outcome over 600 days in patients (n=5) who continued [clozapine](#) therapy despite the development of [neutropenia](#) in the "red alert zone" (ie, white blood cell count below 3000 cells/mm(3)) or absolute neutrophil count (ANC) below 1500 cells/mm(3)). All five patients were maintained on [clozapine](#) after initial onset and recovery of [neutropenia](#) with no recurrence of [neutropenia](#) during the observation period. In three patients, the neutrophil counts remained at or just above the "amber zone" (ie, ANC 1500 to 2000 cells/mm(3)) throughout long-term follow-up while no hematological abnormalities were observed in the other two patients. Favorable response to [clozapine](#) treatment was observed in four of the five patients as assessed by Clinical Global Impression-Severity scores. The authors suggest the need for methods to differentiate between benign [neutropenia](#) and [neutropenia](#) progressing to [agranulocytosis](#) (Ahn et al, 2004).

**b)** Transient [neutropenia](#) developed in a 44-year-old Caucasian man after taking [clozapine](#) (200 to 400 mg/day) for the treatment of [paranoid schizophrenia](#). Twenty-seven weeks after initiation of [clozapine](#) therapy, the patient's morning neutrophil count had declined to 1300 cells/mm(3), while the total white blood cell (WBC) count was within a normal range (4100 cells/mm(3)). However, the blood sample taken the same afternoon at 2 pm. showed that the neutrophil count had returned to normal (2200 cells/mm(3)) and the total WBC count had risen to 5500 cells/mm(3). Blood tests were continued twice a week and whenever the morning neutrophil counts fell between 1200 and 1900 cells/mm(3) (WBC counts: 4100 to 4700 cells/mm(3)), they were between 2200 and 2700 cells/mm(3) in the afternoon (WBC counts: 5400 to 5800 cells/mm(3)). Because the neutrophil counts were normal in the afternoon, the risk of the patient developing [agranulocytosis](#) was considered to be low and [clozapine](#) was continued at a dose of 200 mg/day. Decreased neutrophil counts were no longer observed after 30 weeks of [clozapine](#) therapy (Esposito et al, 2003).

**c)** After 20 months of [clozapine](#) treatment, the white blood cell (WBC) count declined over a four-month period and resulted in [neutropenia](#) in a 36-year-old chronic, paranoid schizophrenic man. During the prior 20 months of [clozapine](#) therapy (400 mg/day), the patient's WBC count was stable and ranged between 6000 and 10000 cells/mm(3)). On the 21st and 22nd months of treatment, his WBC count decreased to an average of 4500 with an absolute neutrophil count (ANC) of 2300. By the fourth week of the 25th month of treatment, his WBC count continued its steady decline and was 2400 with an ANC of 1100. At that time the patient developed a high fever and the diagnosis of [neutropenia](#) was made and [clozapine](#) was discontinued (Taman et al, 2001).

d) The cumulative incidence of clozapine-induced **neutropenia** was 2.7%, based on the Clozaril Patient Monitoring System (1990 to 1997, n=12,760) in the United Kingdom and Ireland. The peak onset was during weeks 6 to 18 of therapy. In this registry, the average and mean maximum **clozapine** doses were 388 and 462 mg/day, respectively. Cox proportional hazards regression analysis revealed a 17% decreased risk with each 10-year increase in age at **clozapine** initiation (p=0.0003) and a 77% greater risk in African-Caribbean subjects compared to Caucasians (p=0.003). The age association is opposite that observed for **agranulocytosis** risk. The racial difference may be partially explained by significantly lower baseline white blood cell counts (an independent predictor of **neutropenia**) among African-Caribbeans. Maximum dose was inversely associated with risk (Munro et al, 1999).

e) **Neutropenia** has been reported in up to 22% of patients therapeutically treated with **clozapine** (Hummer et al, 1997a).

f) A 17-year-old boy with severe **schizophrenic disorder** was able to continue **clozapine** treatment (50 mg) despite decreased **leukocytes** (2480 cells/mm(3)), decreased neutrophil granulocytes (800 cells/mm(3)) and an acute febrile respiratory infection. He received G-CSF 300 mg with an increase in **leukocytes** and neutrophils 6 hours later (2680/mm(3) and 1250/mm(3), respectively), and normal body temperature the next morning. Over the next 2 days he received 2 more G-CSF injections. He continued **clozapine** for an additional 38 weeks until he experienced another decrease in granulocytes and **clozapine** was discontinued. One year later, the patient again required **clozapine** and after 20 weeks of therapy required G-CSF. After 2 doses of G-CSF 300 mcg, he was again maintained on **clozapine** for an additional 8 months (Sperner-Unterweger et al, 1998).

g) A 29-year-old male with **schizophrenia** was able to reinstitute **clozapine** therapy despite previous **neutropenia** after receiving pretreatment with **lithium**. **Clozapine** was previously discontinued after a decrease in granulocytes to 1400 cells/mm(3). After failing other antipsychotics, **lithium** was initiated and increased to 0.8 to 1.1 mmol/L. **Clozapine** was introduced 2 weeks later at 12.5 mg and increased to 200 mg/day. Over the next 9 months white blood cell counts remained stable. The rationale for **lithium** use was to increase granulopoiesis by enhancement of the production of granulocyte-macrophage colony-stimulating factor (Silverstone, 1998).

### 3.3.5.F Thrombosis of cerebral veins

1) A 30-year-old female developed **cerebral venous thrombosis** following treatment with **clozapine**. The patient had a 15 year history of **chronic paranoid schizophrenia** which had been treated with other antipsychotic medications without improvement. The patient presented to the emergency room following 5 days of irritability, vomiting, increased fatigue, and poor hygiene. Physical exam revealed weakness of her left upper and lower limbs. She had normal cognitive functions, intact sensorium, and showed no signs intracranial pressure or worsening psychotic symptoms. For 3 years the patient was taking **clozapine** 400 mg/day. She had 1 episode of seizure which was successfully treated with **valproate** sodium 400 mg/day for the last 2 years. Testing revealed **thrombosis** of the superior and inferior sagittal sinus, right transverse sinus, and right jugular bulb. All applicable risk factors for **thrombosis** were ruled out. **Anticoagulation** therapy was initiated with **heparin** 5000 international units four times daily, then substituted with nicoumalone 2 mg/day. **Clozapine** was gradually discontinued and **aripiprazole** was initiated. She recovered from the **cerebral venous thrombosis** over the following 2 weeks with no psychotic symptoms. Her medications upon discharge included **aripiprazole** 45 mg/day, nicoumalone 2 mg/day, and trihexyphenidyl 2 mg/day. Five months following discharge, the patient had no recurrence of any thromboembolic event (Srinivasaraju et al, 2010).

### 3.3.5.G Venous thrombosis

1) Between April 1989 and March 2000, 6 cases of [pulmonary embolism](#) and 6 cases of venous [thrombosis](#) were reported during [clozapine](#) therapy. The adverse reaction was fatal in 5 cases. The affected patients were 3 women and 9 men. [Venous thromboembolism](#) (VTE) complications developed within the first 3 months of [clozapine](#) therapy in 8 of the patients. The mean [clozapine](#) dose was 277 mg/day (Hagg & Soderstrom, 2000). After reviewing the available literature on case reports of VTE from the Swedish Adverse Reactions Advisory Committee, the authors suggest that VTE may not be [clozapine](#) associated after all and that other risk factors, such as reduced motor activity, should be taken into account. The authors concluded that an increased risk of VTE seems to be a general property of the antipsychotic drugs (Thomassen et al, 2000).

### 3.3.6 Hepatic Effects

#### 3.3.6.A Hepatotoxicity

##### 1) Summary

a) In clinical trials of [clozapine](#), LIVER FUNCTION ABNORMALITIES occurred; in patients with clinically relevant elevations or with [jaundice](#), [clozapine](#) should be discontinued. [CHOLESTASIS](#), [HEPATITIS](#), and [JAUNDICE](#) were voluntarily reported in postmarketing experience (Prod Info [Clozaril](#)(R), 2002). A 39-year-old male also developed fatal acute [fulminant LIVER FAILURE](#) with [encephalopathy](#) and [coagulopathy](#) after 8 weeks of [clozapine](#) therapy (Macfarlane et al, 1997).

#### 3.3.6.B Increased liver enzymes

##### 1) Summary

a) [Clozapine](#), in therapeutic dosages, has been associated with a rise in liver enzymes in 37. 3% to 61% of patients (Hummer et al, 1997a; Gaertner et al, 2001). A case report also notes this adverse effect (Panagiotis, 1999).

##### 2) LITERATURE REPORTS

a) In a prospective study, the incidence of [alanine aminotransferase](#) (ALT) elevation to more than twice the upper normal limit was statistically greater with [clozapine](#) (37%, n=167) than with [haloperidol](#) (17%, n=71). Among those receiving [clozapine](#), the rates of elevations in [aspartate aminotransferase](#) (AST) and gamma-glutamyl transpeptidase (GGT) to more than twice the upper normal limit were 12% and 15%, respectively. No such increases in [bilirubin](#) or [alkaline phosphatase](#) occurred in clozapine-treated patients. These effects were transient in the majority of patients (disappearing by week 13) with no clinical manifestations reported (Hummer et al, 1997a).  
b) A 30-year-old man developed abnormal liver enzymes and a grand mal seizure while receiving [clozapine](#) 400 milligrams (Panagiotis, 1999). Liver enzymes and [electroencephalogram](#) (EEG) were normal before therapy. After 4 weeks, he presented with a grand mal seizure and [clozapine](#) was reduced to 300 milligrams. Liver enzymes were evaluated 5 days after the seizure. The [aspartate aminotransferase](#) and [gamma-glutamyl transferase](#) were 3 times the upper limits of normal and the [alanine aminotransferase](#) was 5 times the upper limits of normal. [Clozapine](#) was discontinued.

#### 3.3.6.C Liver finding

1) Liver function abnormalities have occurred with [clozapine](#) therapy that include elevated liver enzymes, [liver failure](#), [jaundice](#), [hepatitis](#) and [cholestasis](#).

### 3.3.7 Immunologic Effects



### 3.3.7.A Drug-induced lupus erythematosus, Systemic

#### 1) Summary

- a) Two cases of lupus-like reactions have been reported with [clozapine](#) therapy (Kanjolia et al, 1997; Wickert et al, 1994).

#### 2) LITERATURE REPORTS

- a) A positive [lupus](#) anticoagulant, with resultant increased aPTT, was reported in an adult male taking [clozapine](#) (225 milligrams/day), [Klonopin](#), [Cogentin](#) and [Lopid](#). The etiologic relationship of [clozapine](#) to the [lupus](#) anticoagulant is probable (Kanjolia et al, 1997).
- b) A case of systemic [lupus](#) erythematosus-like reaction was reported in a 39-year-old man taking 300 milligrams per day of [clozapine](#) for [paranoid schizophrenia](#). The patient rapidly improved over 5 days following discontinuation of the [clozapine](#). The symptom complex included: fever, fatigue, cough, chest pain, arthralgia, elevated activated partial thromboplastin time, and other hematological abnormalities (Wickert et al, 1994).

### 3.3.7.B Immune hypersensitivity reaction

#### 1) Summary

- a) [Hypersensitivity reactions](#) have been noted in a few case reports during [clozapine](#) therapy. Monitor plasma levels if a [hypersensitivity reaction](#) is suspected (Haack et al, 2003; Stanislav & Gonzalez-Blanco, 1999; Jaunkalns et al, 1992; Stoppe et al, 1992).

#### 2) LITERATURE REPORTS

- a) A [hypersensitivity reaction](#) to [clozapine](#) manifested as fever, [bilateral pleural effusions](#) and rapidly spreading papular rash in a 37-year-old woman 9 days after initiation and titration to 150 milligrams/day. Other etiologies were ruled out. Signs and symptoms began to resolve within a week of discontinuing [clozapine](#) (Stanislav & Gonzalez-Blanco, 1999).
- b) A 33-year-old woman with [chronic paranoid schizophrenia](#) refractory to numerous neuroleptics started [clozapine](#) at 25 milligrams daily increments. On day 15, fever myalgia, arthralgia, and urticarial plaques on elbows and knees developed. [Clozapine](#) was stopped and symptoms abated. All tests including rechallenge with [clozapine](#) indicated that the extremely high titers of antimyeloperoxidase antibodies may have contributed to the pathogenesis of the syndrome. The relationship between idiosyncratic drug reactions, especially [agranulocytosis](#), and myeloperoxidase system was described (Jaunkalns et al, 1992).
- c) A 69-year-old woman suffering from [chronic paranoid schizophrenia](#) received [clozapine](#) for three weeks with no complications. For unknown reasons [clozapine](#) was discontinued. Two years later and 1 day after the first dose of [clozapine](#), this patient developed an alarming, life-threatening allergic asthmatic reaction requiring intensive care treatment. When [clozapine](#) was restarted, the patient had a similar asthma-like attack. This reaction could be a [delayed hypersensitivity](#) or pseudoallergic reaction to the drug. This reaction is not due to its weak binding to D, and D2 [dopamine](#) receptors, or the blockage of 52 serotonergic, alpha, adrenergic, muscarinic, and H1 [histamine](#) receptors (Stoppe et al, 1992).

### 3.3.7.C Immune system finding

- 1) Malaise and [hypersensitivity reactions](#) occurred with [clozapine](#) therapy.

### 3.3.7.D Systemic lupus erythematosus

See Drug Consult reference: [DRUG-INDUCED SYSTEMIC LUPUS ERYTHEMATOSUS](#)

### 3.3.8 Musculoskeletal Effects

#### 3.3.8.A Musculoskeletal finding

##### 1) Summary

a) In clinical trials (n=842), during [clozapine](#) therapy adverse effects temporally associated with [clozapine](#) and occurring at a frequency less than 1% included TWITCHING. A voluntary postmarketing report noted [MYASTHENIC SYNDROME](#) however a causal relationship could not be determined (Prod Info [Clozaril](#)(R), 2002).

2) Muscle weakness, muscle spasms, muscle pain, back pain, neck pain, and leg pain occurred in patients with [clozapine](#) therapy. Adverse effects temporally associated with [clozapine](#) and occurring at a lower frequency include twitching and joint pain. Other less common effects include [rhabdomyolysis](#), lupus-like findings, CPK elevations, and [myasthenic syndrome](#).

#### 3.3.8.B Pain

##### 1) Summary

a) In clinical trials, MUSCLE WEAKNESS, MUSCLE SPASMS, MUSCLE PAIN, BACK PAIN, NECK PAIN, and LEG PAIN occurred in 1% of patients (n=842) during [clozapine](#) therapy. JOINT PAIN was temporally associated with [clozapine](#) and occurring at a frequency less than 1% (Prod Info [Clozaril](#)(R), 2002).

#### 3.3.8.C Polyserositis

##### 1) Summary

a) [Polyserositis](#) developed in a 74-year-old man after receiving [clozapine](#) (initial, 25 milligrams (mg) daily, then increased by 12.5 mg increments at weekly intervals) for the treatment of [schizoaffective disorder](#). Initial symptoms, including dry cough, chills, and fever, developed twenty days after the initiation of therapy. He was treated for an assumed chest infection; however, respiratory symptoms worsened and the patient developed a [PERICARDIAL EFFUSION](#) and [BILATERAL PLEURAL EFFUSION](#). [Clozapine](#) was withdrawn and systematic symptoms resolved within a week (Lim et al, 2003).

#### 3.3.8.D Rhabdomyolysis

1) A case report describes a 29-year-old with [schizoaffective disorder](#) who developed [rhabdomyolysis](#) following coadministration of [clozapine](#) and [lithium](#). The patient was originally diagnosed with [bipolar disorder](#) at age 16 and with [schizophrenia](#) at age 26. Multiple medications were administered but without adequate response. [Clozapine](#) 125 mg/day to 200 mg/day was prescribed. At age 29, the patient was hospitalized and diagnosed with [schizoaffective disorder](#) due to recurring florid psychotic and manic symptoms. [Clozapine](#) was titrated up to a dose of 450 mg/day over a period of 5 weeks with [valproic acid](#) 2000 mg/day added within a month. The patients psychotic symptoms improved, however his mood did not. Between days 43 and 68, electroconvulsive (ECT) therapy was initiated with some improvement. However, within a week of ECT conclusion, his manic symptoms returned. On day 72, [clozapine](#) was increased to 500 mg/day and [lithium](#) was added on day 78 and titrated up to 1200 mg/day within a week. Following [clozapine](#) dosage increase, muscle aches were noted and laboratory tests revealed increased CK levels (6776 international units/L). A diagnosis of [rhabdomyolysis](#) was made once infection and [neuroleptic](#)



[malignant syndrome](#) was ruled out. On day 90, [clozapine](#) was reduced to a dose of 400 mg/day. By day 109, he physical symptoms and CK levels had returned to normal and he was discharged with no further issues [2](#) (Tseng & Hwang, 2009).

[3](#)) A 42-year-old man receiving [clozapine](#) and being treated for polydipsia developed [rhabdomyolysis](#) during the correction of the [hyponatremia](#). After correction of his [hyponatremia](#), his [creatinine kinase](#) (CK) level was 8184 units/L and then 6186 units/L; however at 68 hours after admission, his CK peaked at 62,730 units/L. He had no muscle aches. To prevent [acute renal insufficiency](#), high-volume alkaline diuresis was initiated. The CK concentration fell and returned to normal after 14 days. The authors feel that the [rhabdomyolysis](#) may have been enhanced by the use of [clozapine](#) (Wicki et al, 1998).

### 3.3.8.E Serum [creatinine](#) raised

#### 1) Summary

[a](#)) [Clozapine](#) may be associated with increases in [creatinine kinase](#) (CK), without features of [neuroleptic malignant syndrome](#), and mild [MYOPATHY](#). In 37 consecutive clozapine-treated outpatients, weekly CK levels were evaluated. Extreme CK elevations (greater than 20,000 International Units/Liter(IU/L)) without myoglobinuria occurred in 3 patients, and moderate CK elevation (between 725 and 20,000 IU/L) in 10 patients. Six patients in the moderately elevated CK group also had MUSCLE WEAKNESS. Five patients had mild myopathic dysfunction by [electromyography](#). The CK elevations were not dependent upon [clozapine](#) dose (Scelsa et al, 1996).

## 3.3.9 Neurologic Effects

### 3.3.9.A Dizziness

#### 1) Summary

[a](#)) In clinical trials (n=842), dizziness and VERTIGO occurred in 19% of patients during therapeutic use of [clozapine](#) (Prod Info [Clozaril](#)(R), 2002).

[2](#)) Incidence: 19%

### 3.3.9.B [Dystonia](#)

#### 1) Summary

[a](#)) During the first few days after initiating treatment with an antipsychotic medication, symptoms of [dystonia](#) may occur in susceptible individuals. Symptoms may include spasm of neck muscles, which may progress to tightening of the throat, swallowing difficulty, breathing difficulty, and/or protrusion of the tongue. These symptoms can occur at low doses but most often occur (and occur with a greater severity) with high potency and at higher doses of first generation antipsychotic medications. Males and younger age groups appear to be at greater risk for developing acute [dystonia](#) (Prod Info [CLOZARIL](#)(R) oral tablets, 2008).

[b](#)) Several case reports note dystonic reactions in patients during therapeutic use of [clozapine](#) (Mendhekar & Duggal, 2006)(Elliott et al, 2000)(Molho & Factor, 1999; Poersch et al, 1996; Kastrup et al, 1994). In the manufacturer's clinical trials (n=842), a few cases of [tardive dyskinesia](#) have also been reported in patients receiving [clozapine](#); however, a causal relationship could not be established(Prod Info [Clozaril](#)(R), 2002). Atypical antipsychotics such as [clozapine](#) are associated with a lower risk of extrapyramidal symptoms (EPS) than conventional antipsychotics because of higher (ie, more balanced) serotonin-to-dopamine blockade ratios. This may also partially explain the decreased incidence of [tardive dyskinesia](#) with atypical agents, as one proposed mechanism of

[tardive dyskinesia](#) involves "supersensitivity" to chronic, unopposed [dopamine](#) blockade (Glazer, 2000; Reynolds, 2000).

2) A case of [clozapine](#) induced [tardive dyskinesia](#) occurred in a 47-year-old woman with a history of [schizophrenia](#) and [hypothyroidism](#). Significant past medical history include extrapyramidal side effects from [haloperidol](#). The patient's concurrent medications included [levothyroxine](#) (100 mg/day) and [clozapine](#) (150 mg/day). She presented with dyskinetic movements of the tongue and horizontal grinding movements of the lower jaw 7 months after starting [clozapine](#). She was initially and unsuccessfully treated by discontinuing her [levothyroxine](#) for 8 weeks; her dyskinetic movements persisted and her thyroid stimulating hormone level increased. Diagnostic testing, which included [computed tomography](#) scan and [electroencephalogram](#), were unremarkable. She was restarted on [levothyroxine](#) and also given a sequential trial of [propranolol](#) (80 mg/day) and tetrabenazine (125 mg/day) with improvement only in her thyroid profile. She subsequently was diagnosed with [tardive dyskinesia](#) and an attempt to reduce her [clozapine](#) dose to 125 mg/day failed. The dose reduction worsened her psychotic symptoms requiring an even higher dose of [clozapine](#) (200 mg/day) to manage her [schizophrenia](#). Neither reduction nor increase of her [clozapine](#) dose improved the dyskinetic movements, which she continued to exhibit (Mendhekar & Duggal, 2006).

3) An acute dystonic reaction involving the tongue and neck developed in a 44-year-old male inpatient the day after a 50-milligram (mg) [clozapine](#) dosage increase to 450 mg/day. Despite a 20-year history of [schizophrenia](#), extrapyramidal symptoms and [tardive dyskinesia](#) had not been previously documented. However, a pseudoparkinsonian tremor and orofacial movements consistent with [tardive dyskinesia](#) were noted on admission. His outpatient medication regimen had included [clozapine](#) and [haloperidol](#). At the time of the dystonic reaction, the only concomitant medications were [vitamin E](#) and [aspirin](#). The [dystonia](#) abated following a dose of intramuscular [diphenhydramine](#) (Elliott et al, 2000).

4) Tardive [dystonia](#) characterized by left rotational torticollis with intermittent spasms was attributed to [clozapine](#) 825 milligrams/day in a 37-year-old male with a 21-year history of [schizophrenia](#). The [dystonia](#) first appeared 2 years after initiation of [clozapine](#) monotherapy and continued to worsen despite daily trihexyphenidyl. Other concomitant medications included [metformin](#) and [glyburide](#). The torticollis continued unabated 4 years later, as the patient was intolerant to increased dosages of trihexyphenidyl (Molho & Factor, 1999).

5) 58-year-old patient treated for [psychosis](#) with [clozapine](#) 600 milligrams and benperidol 30 milligrams daily experienced episodes of ASTERIXIS, [tachycardia](#) and sweating, exacerbated by [hypoglycemia](#) (blood sugar 65 to 75 milligrams/deciliter). The symptoms disappeared upon reduction in an oral hypoglycemic agent that the patient was taking concurrently (Poersch et al, 1996).

6) A case of acute [DYSTONIA](#) manifested as retrocollic torsion and dystonic cramps of the tongue and mouth was reported after six weeks of therapy with [clozapine](#) at a dose of 400 milligrams/day. The [dystonia](#) was successfully treated with [biperiden](#) and the [clozapine](#) tapered to 250 milligrams/day. [Biperiden](#) was then discontinued without further incidences of [dystonia](#) (Kastrup et al, 1994).

### 3.3.9.C EEG finding

#### 1) Summary

a) EEG changes have been noted in patients with [clozapine](#) use. There is some disagreement on whether these changes are dose-related occurrences or normal baselines within the patient population being treated with [clozapine](#) (Silvestri et al, 1998; Welch et al, 1994; Tihonen et al, 1991; Spatz et al, 1978).

#### 2) LITERATURE REPORTS

a) One author states that most patients receiving [clozapine](#) treatment have abnormal EEGs. However, they believed that abnormal EEGs should not contraindicate increase of the [clozapine](#)

dose beyond 600 milligrams/day if no signs of clinical adverse effects are observed (Tihonen et al, 1991). However, another author advocates lowering the [clozapine](#) dose by 25 to 50 milligrams per day and adjusting the dose weekly until the EEG returns to baseline (Welch et al, 1994).

**b)** In a group of 35 patients, 26 (74%) were found to have evidence of EEG abnormalities (slowing, [dysrhythmia](#), or paroxysmal discharges) during [clozapine](#) treatment (Welch et al, 1994). EEGs were measured as a means of detecting clinical toxicity and reducing the incidence of seizures.

**c)** Eight out of 12 psychiatric patients receiving [clozapine](#) were found to have interictal epileptiform abnormalities on EEG. Six of the 8 had seizures while receiving [clozapine](#). The abnormalities were focal or multifocal with a predominance of left temporal foci (Silvestri et al, 1998).

**d)** Changes in the EEG pattern similar to those caused by other neuroleptics has been seen in patients receiving [clozapine](#). Monthly EEGs were evaluated in 34 schizophrenic patients treated with [clozapine](#) 100 to 700 milligrams daily. After 2 to 6 months of treatment, the EEG in 6 patients showed [dysrhythmias](#) and other changes similar to those caused by other neuroleptics. In 2 months after discontinuation of [clozapine](#), the EEG had reverted to the pretreatment pattern (Gross & Langner, 1966). Similar results have been reported by other authors (Spatz et al, 1978).

### 3.3.9.D Headache

#### 1) Summary

**a)** In clinical trials (n=842) 7% of patients experienced headache with [clozapine](#) therapy (Prod Info [Clozaril\(R\)](#), 2002).

2) Incidence: 7%

### 3.3.9.E Movement disorder

#### 1) Summary

**a)** In clinical trials (n=842) 6% of patients experienced TREMOR. The following adverse effects were also reported in 1% to 4% of patients: HYPOKINESIA, [AKINESIA](#), RIGIDITY, [AKATHISIA](#), HYPERKINESIA, WEAKNESS, and ATAXIA. Adverse effects that were temporally associated with [clozapine](#) and occurred in less than 1% of patients include TICS, POOR COORDINATION, INVOLUNTARY MOVEMENTS, [DYSARTHRIA](#), HISTRIONIC MOVEMENTS, SHAKINESS, [PARKINSONISM](#), and NUMBNESS (Prod Info [Clozaril\(R\)](#), 2002). One case of asterixis has been reported (Poersch et al, 1996).

### 3.3.9.F Myoclonus

#### 1) Summary

**a)** Myoclonic jerking and EPILEPTIFORM MOVEMENTS have developed in patients taking therapeutic doses of [clozapine](#) (Prod Info [Clozaril\(R\)](#), 2002); (Antelo et al, 1994). A case report noted that 40-year-old man developed OROLARYNGEAL MYOCLONUS after 1 month of [clozapine](#) therapy. The myoclonus resolved with a reduction in [clozapine](#) dose (Knoll, 1997).

### 3.3.9.G Neuroleptic malignant syndrome

#### 1) Summary

**a)** The estimated overall incidence of [neuroleptic malignant syndrome](#) (NMS) is 1% in patients receiving neuroleptics. Although the incidence is thought to be less with [clozapine](#) than with other neuroleptics, there are reports in the literature describing this syndrome following therapy with [clozapine](#), some in conjunction with other neuroleptics or [lithium](#). The syndrome generally occurs

within the first two weeks of treatment and is associated with elevated creatine phosphokinase (CPK) and white blood cell count (WBC); symptoms usually persist 5 to 10 days after medications are discontinued. Without prompt treatment, patients may experience crippling effects of muscle destruction, renal impairment, encephalopathy, and even death (Prod Info Clozaril(R), 2002); (Kontaxkis et al, 2001)(Karagianis et al, 1999; Dalkilic & Grosch, 1997; Campellone et al, 1995; Viner & Escobar, 1994; Keshavan et al, 1994; DasGupta & Young, 1991); (Miller et al, 1991) (Anderson & Powers, 1991); (Muller et al, 1988).

**b)** Clozapine-induced neuroleptic malignant syndrome (NMS) developed in a 52-year-old man with a concomitant underlying brain injury. The patient was admitted to the hospital for exacerbation of psychotic and affective symptoms, including self-injurious behavior, after having been treated effectively for bipolar disorder for the previous ten years with clozapine at a daily dose of 400 milligrams (mg). Clozapine was increased to 500 mg daily on the first day of hospitalization. On day 4, altered mental status, moderate rigidity, urinary retention, and fever were observed; and laboratory findings revealed leucocytosis, elevated levels of creatine phosphokinase (CPK), alanine aminotransferase (ALT), and aspartate aminotransferase (AST). Clozapine was discontinued after magnetic resonance imaging showed a subacute bilateral frontal hematoma. The CPK peaked on day 5 at 18,000 international units/liter and then started to decrease, returning to normal on day 9 along with resolution of fever, rigidity, and altered mental status. The author attributes the development of NMS in this patient to concurrent clozapine administration and an underlying brain injury, which may have been caused by the patient's self-injurious behavior (Duggal, 2004).

## 2) LITERATURE REPORTS

**a)** Two patients presented with neuroleptic malignant syndrome associated with clozapine which was not similar to the presentation with classical neuroleptic agents. One man presented after 16 days of clozapine therapy with a temperature of 38.4 degrees Celsius (C) and increased heart rate. There was no rigidity noted. Five days later his white blood cell (WBC) count peaked at 15,000/mm(3) and his creatine kinase at 1501 units/liter(L). Marked neck rigidity was noted. Medications were discontinued and he recovered; however, intubation was required. In the other case, a woman treated with clozapine for 2 years developed diaphoresis, pallor and vomiting. Her temperature was 37.7 C. Two weeks later, she was found to be disoriented. Finally, 1 week later she was admitted and found to have a mild neck stiffness. Her temperature peaked at 38.3 C. Her WBC count was 10,600/mm(3). Her creatine kinase peaked at 189 units/L (normal 20 to 184). Clozapine was discontinued and she improved after 1 week (Karagianis et al, 1999).

**b)** In a review of clozapine and cases of presumed neuroleptic malignant syndrome, approximately 9 of the 19 cases were designated as having high probability of actually being neuroleptic malignant syndrome. Alternative diagnoses in low probability cases included benzodiazepine withdrawal, infection, drug-drug interaction, or serotonin syndrome (Hasan & Buckley, 1998).

**c)** The Australian Adverse Drug Reactions Advisory Committee has received 11 reports of Neuroleptic Malignant Syndrome associated with clozapine therapy (1 case questionable). The patients were all male (median age 40 years) and onset occurred primarily in the first two weeks after initiating treatment but ranged from 6 days to 9 months. Clozapine doses ranged from 75 to 600 milligrams (mg) daily (median 400 mg). Clinical symptomology included fever, confusion, disorientation, profuse sweating, tachycardia, and delirium. Laboratory tests revealed leukocytosis in 7 cases and elevated creatinine kinase levels in 10 cases (230 to 12,800 units/liter); all but 1 patient recovered (Anon, 1997a).

**d)** A patient with a history of neuroleptic malignant syndrome (NMS) following neuroleptic therapy also developed NMS after initiation of clozapine. After 4 days of clozapine treatment (12.5 milligrams daily), the patient experienced marked changes in mental status, weakness, and

dizziness; creatine phosphokinase (CPK) was significantly elevated. Following discontinuation of the drug, the patient completely recovered after several days (Illing & Ancill, 1996).

e) A 71-year-old man with [chronic paranoid schizophrenia](#) presented with fever, rigidity, and altered mental status. Medications were therapeutic doses of [clozapine](#) and 1500 milligrams of [valproic acid](#) used for prophylaxis for clozapine-induced seizures. His creatine phosphokinase level was 2536 units/liter, his urine contained myoglobin, and he had evidence of [acute renal insufficiency](#). Despite discontinuation of [clozapine](#), intravenous hydration, [bromocriptine](#), [diazepam](#), [dantrolene](#), etc, the patient developed pulmonary and [renal infection](#), multiorgan failure, [gastrointestinal hemorrhage](#) and subsequently died (Campellone et al, 1995).

### 3.3.9.H Neurological finding

#### 1) Summary

a) In clinical trials (n=842), the following adverse effects were reported in 1% to 4% of patients were CONFUSION, FATIGUE, LETHARGY, and SLURRED SPEECH. Adverse effects that were temporally associated with [clozapine](#) and occurred in less than 1% of patients include LOSS OF SPEECH, [AMENTIA](#), [STUTTERING](#), [DYSARTHRIA](#), [NYSTAGMUS](#), [AMNESIA](#)/MEMORY LOSS and PARESTHESIA. (Prod Info [Clozaril\(R\)](#), 2002).

2) Drowsiness and sedation are very common dose-dependent adverse effects with therapeutic use of [clozapine](#) and are likely to subside with continued therapy or dose reduction. Dizziness and vertigo also commonly occur. Tremor, headache and seizures occur with some frequency. The following adverse effects that were less frequently reported and include hypokinesia, [akinesia](#), agitation, rigidity, [akathisia](#), confusion, fatigue, hyperkinesia, weakness, lethargy, ataxia, [delirium](#), EEG changes, asterixis, paresthesia, slurred speech, and epileptiform movements/myoclonic jerks. Adverse effects that were temporally associated with [clozapine](#) therapy include loss of speech, tics, poor coordination, involuntary movements, [stuttering](#), [dysarthria](#), histrionic movements, shakiness, [parkinsonism](#) and numbness. Several cases of dystonic reactions have been reported but a causal relationship could not be established.

### 3.3.9.I Paralysis

1) A Chinese male [schizophrenia](#) patient developed [hyperglycemia](#), [hyperlipemia](#), and PERIODIC PARALYSIS while taking [clozapine](#). The episodes of paralysis often lasted 30 to 40 minutes and then spontaneously stopped. Symptoms resolved when [clozapine](#) was withdrawn and recurred when [clozapine](#) treatment was reestablished. Symptoms appeared at [clozapine](#) doses as low as 37.5 milligrams (mg) per day. Other drugs were not as effective as [clozapine](#) for treating his mental state. His mental state was finally stabilized with a combination of [clozapine](#) 25 mg/day and [haldol](#) 20 mg/day, without elevations of blood glucose or lipids (Wu et al, 2000).

### 3.3.9.J Seizure

#### 1) Summary

a) In the manufacturer's clinical trials (n=842) one or more seizures occurred in 5% (61 of 1743) of patients. During earlier clinical trials, the reported prevalence of seizures was also 5% of patients treated with 600 to 900 milligrams daily. Therapeutic use of [clozapine](#) has been reported to lower the seizure threshold, especially in epileptic patients and patients with organic [brain disease](#). Seizures appear to be dose-related. Patients with a history of seizures or predisposing factors should be closely monitored during [clozapine](#) therapy. These patients should not be engaged in any activities where the sudden loss of consciousness could cause serious risk to themselves or others. [STATUS EPILEPTICUS](#) was reported, however a causal relationship with [clozapine](#) could not



be determined. (Prod Info [Clozaril\(R\)](#), 2002; Supprian et al, 1999; Panagiotis, 1999; Devinsky & Pacia, 1994; Haller & Binder, 1990a).

2) Incidence: 5%

### 3) LITERATURE REPORTS

a) In one case, a 30-year-old man developed a grand mal seizure and liver toxicity after 3 weeks of [clozapine](#) therapy which had been increased to 400 milligrams per day (Panagiotis, 1999).

b) A 49-year-old female on maintenance [clozapine](#) therapy for refractory [schizophrenia](#) experienced a generalized [epileptic seizure](#) after a self-imposed dose increase to 750 milligrams (mg)/day. Myoclonic jerks continued for 2 hours, necessitating intravenous [phenytoin](#). Electroencephalographic abnormalities (initial diffuse slowing progressing to triphasic sharp waves) had previously coincided with dosage increases from 450 to 650 mg/day. Preceding the seizure was new-onset [stuttering](#) at 700 mg/day, with dose-related fluctuations in severity. After the seizure, the patient was stabilized on [valproate](#) 900 mg/day and [clozapine](#) 600 mg/day, with no further [stuttering](#) or seizures during 6 months of follow-up. The authors speculated that clozapine-induced [stuttering](#) might be an indicator of epileptic brain activity (Supprian et al, 1999).

c) Seizures occur in approximately 1% of patients treated with antipsychotic drugs, but the reported prevalence of seizures is higher with [clozapine](#) and appears to be dose-dependent: 1% with less than 300 milligrams/day, 3% with 300 to 599 milligrams/day, and 5% with 600 to 900 milligrams/day. Clinical management of the seizures including the use of anticonvulsants or the discontinuation of [clozapine](#) has been outlined (Haller & Binder, 1990a). Another author reported similar results (Devinsky et al, 1991).

d) Some data do not clearly confirm the dose-dependent effect (Devinsky & Pacia, 1994). A 28-year-old woman with [schizophrenia](#) experienced a grand mal seizure while receiving [clozapine](#) at a low dose of 200 milligrams (Ravasia & Dickson, 1998). This occurred after 6 months of [clozapine](#) that included a 5-month initial taper. Her [clozapine](#) level was, however, 3290 nmol/liter (suggested range: 153 to 1836 nmol/liter).

See Drug Consult reference: PREVENTION OF CLOZAPINE-INDUCED SEIZURES

### 3.3.9.K Somnolence

#### 1) Summary

a) In the manufacturer's clinical trials with [clozapine](#) therapy, drowsiness and SEDATION were reported in 39% of patients (n=842) and was reported likely to subside with continued therapy or dose reduction (Prod Info [Clozaril\(R\)](#), 2002). Earlier studies have also noted that drowsiness was a common dose-dependent adverse effect of [clozapine](#) (Bablenis et al, 1989; Haller & Binder, 1990a; Kirkegaard et al, 1982; Ayd, 1974a; Battagay et al, 1977).

2) Incidence: 39%

### 3.3.9.L Stuttering

#### 1) Summary

a) [Stuttering](#) was noted to occur with [clozapine](#) use.

#### 2) LITERATURE REPORTS

a) A 28-year-old, paranoid schizophrenic, man began [stuttering](#) when his [clozapine](#) dose reached 300 milligrams (mg) per day. An earlier EEG taken when he was receiving 150 mg/day showed bilateral frontotemporal slowing (left more than right), a photic convulsive response, and generalized nonparoxysmal sharp and slow waves. As he had a good response to [clozapine](#) his



dose was increased to 300 mg/day and he began to [stutter](#). At 425 mg/day he had a generalized tonic-clonic seizure. His [clozapine](#) dose was reduced to 200 mg/day and [valproate](#) 800 mg/day was added. There was no recurrence of [stuttering](#) when his [clozapine](#) dose was again increased to 300 mg/day. The authors speculate that [stuttering](#) accompanied by left-sided slowing or other EEG abnormalities may be a forerunner to seizures (Duggal et al, 2002).

### 3.3.10 Ophthalmic Effects

#### 3.3.10.A Eye / vision finding

##### 1) Summary

a) In clinical manufacturer trials, VISUAL DISTURBANCES occurred in 5% of patients (n=842) during [clozapine](#) therapy. MYDRIASIS, [EYELID DISORDER](#), and BLOODSHOT EYES occurred in less than 1% of patients; a causal relationship with [clozapine](#) could not be determined (Prod Info [Clozaril](#)(R), 2002). ACCOMMODATION DIFFICULTIES may also be noted (Reynolds, 2000). No pathological pigmentation in the refractive media or retina were observed in 11 patients treated with [clozapine](#) for 6 months to 2 years (Gross & Langner, 1970).

2) Visual disturbances have occurred in patients during [clozapine](#) therapy that include mydriasis, [eyelid disorder](#), accommodation difficulties and bloodshot eyes.

### 3.3.11 Otic Effects

#### 3.3.11.A Disorder of ear

##### 1) Summary

a) Ear disorder was temporally associated with [clozapine](#) therapy and occurred at a frequency less than 1% (Prod Info [Clozaril](#)(R), 2002).

#### 3.3.11.B Ear and auditory finding

1) Ear disorder was temporally associated with [clozapine](#) therapy.

### 3.3.12 Psychiatric Effects

#### 3.3.12.A [Delirium](#)

##### 1) Summary

a) [Delirium](#) may occur, secondary to antimuscarinic side-effects, following therapeutic dosages (Reynolds, 2000; Burke et al, 1998); (Wilkins-Ho & Hollarder, 1997). An incidence of 8% was reported in a case series of 391 treatments in 315 inpatients (Gaetner et al, 1989). Some authors recommended a low starting dose and gradual titration in retreatment with [clozapine](#) (Szymanski et al, 1991b)

##### 2) LITERATURE REPORTS

a) Two cases of NEUROLEPTIC-SENSITIVITY were reported with [clozapine](#) therapy in patients with [Lewy body dementia](#). Both received low doses of [clozapine](#) (6.25 or 12.5 milligrams) and experienced increased confusion, hallucinations, and behavioral symptoms. These symptoms persisted despite discontinuation of [clozapine](#). Both families noted that the patients never returned to their pre-clozapine level of mental function (Burke et al, 1998).

- b) A 48-year-old woman with a past history of alcohol dependency developed [delirium](#) after 3 days of [clozapine](#) therapy. [Clozapine](#) was discontinued and a slower upward titration resulted in no recurrence of her schizoaffective symptoms or her [delirium](#) (Wilkins-Ho & Hollander, 1997).
- c) A 22-year-old man with [chronic schizophrenia](#) experienced acute symptoms of an [ANTICHOLINERGIC SYNDROME](#) ([delirium](#), DECREASED GASTROINTESTINAL MOTILITY, [TACHYCARDIA](#), and urinary hesitancy), antiadrenergic symptoms (orthostatic hypotension), and drug-induced [HYPERBILIRUBINEMIA](#) and [HYPERAMYLASEMIA](#), after reintroduction of [clozapine](#) at a moderate and previously well-tolerated dosage. The authors recommended a low starting dose and gradual titration in retreatment with [clozapine](#) (Szymanski et al, 1991b).

### 3.3.12.B Obsessive-compulsive disorder

#### 1) Summary

- a) Adverse effects that have been reported during [clozapine](#) therapy are unmasked [obsessive compulsive disorder](#), PSYCHOTIC EXACERBATIONS and [CATAPLEXY](#) (Prod Info [Clozaril](#)(R), 2002; Biondi et al, 1999; de Haan et al, 1999; Suppes & Rush, 1996; Baker et al, 1992).

#### 2) LITERATURE REPORTS

- a) In a retrospective cohort study of recent-onset [schizophrenia](#) or other [psychotic disorders](#) (n=121, mean age 21 years, 79% male), significantly more [clozapine](#) recipients (7 of 34, 21%) reported emergent or worsened obsessions compared to recipients of other antipsychotics (1 of 76, 1.3%, p less than 0.01). Clozapine-associated obsessions were new-onset in 5 of 7 (71%) cases. Discontinuation of [clozapine](#) produced complete remission of obsessive symptoms in one case. Three were successfully managed with [clozapine](#) dosage reduction plus adjunctive selective serotonin reuptake inhibitor (SSRI) therapy. Obsessions were refractory to SSRI therapy in the remaining patients (de Haan et al, 1999).
- b) A 27-year-old man experienced obsessive-compulsive symptoms while receiving [clozapine](#) 150 milligrams/day for his [schizophrenia](#) (Biondi et al, 1999). Symptoms emerged after 5 weeks of [clozapine](#). He had no previous history of [obsessive-compulsive disorder](#). His score on the Yale-Brown Obsessive Compulsive Scale was 30. This decreased to 10 after [clomipramine](#) 110 milligrams/day was added.
- c) [Clozapine](#) has produced or unmasked obsessive compulsive symptoms in 6 patients. In a review of 49 patients treated with [clozapine](#) for at least 3 months, five patients experienced de novo obsessive compulsive symptoms or a worsening of previous obsessive compulsive symptoms with improvement of [psychosis](#) (Baker et al, 1992). A similar case has been reported (Suppes & Rush, 1996).

### 3.3.12.C Psychiatric sign or symptom

#### 1) Summary

- a) In clinical trials (n=842), the following adverse effects were reported in 1% to 4% of patients; DISTURBED SLEEP/NIGHTMARES, RESTLESSNESS, AGITATION, PANIC, INSOMNIA, DEPRESSION, and ANXIETY. Adverse effects that were temporally associated with [clozapine](#) and occurred in less than 1% of patients include [AMENTIA](#), DELUSIONS/HALLUCINATIONS, AMNESIA/MEMORY LOSS, PARANOIA, and IRRITABILITY. (Prod Info [Clozaril](#)(R), 2002; Bressan et al, 2000).

- 2) The following adverse effects that were less frequently reported include disturbed sleep/nightmares, depression, restlessness, insomnia, and anxiety disorders. Adverse effects that were temporally associated

with clozapine therapy include [amentia](#), delusions/hallucinations, amnesia/memory loss, paranoia and irritability. Other adverse effects that have been reported are unmasked [obsessive compulsive disorder](#), psychotic exacerbation and [cataplexy](#).

### 3) LITERATURE REPORTS

- a) A 34-year-old woman treated with clozapine 400 milligrams (mg) daily, developed daily PANIC and agoraphobic symptoms after 20 weeks that confined her to the house. Even with a reduction of clozapine to 250 mg daily, the patient only showed modest improvement. Clozapine was discontinued and changed to [olanzapine](#) without further recurrence of anxiety symptoms (Bressan et al, 2000).

### 3.3.13 Renal Effects

#### 3.3.13.A Interstitial nephritis

- 1) During postmarketing surveillance, [interstitial nephritis](#) has been reported in patients who received clozapine (Prod Info CLOZARIL(R) oral tablets, 2008).

- 2) A 57-year-old female developed [acute renal failure](#) (ARF) possibly resulting from [interstitial nephritis](#) following 5 doses of clozapine for treatment-resistant [schizophrenia](#). The patient had developed ARF with clozapine approximately 4 years prior; however, because she had also been on concomitant [lithium](#) therapy when the ARF occurred and because she was currently refractory to other antipsychotic treatment, the patient was rechallenged with clozapine (12.5 mg once daily at night for one day, then 12.5 mg twice daily). Three days prior to starting clozapine, the patient had normal hematology and [blood chemistry](#) results. Additionally, the patient continued to receive [olanzapine](#) 10 mg nightly, sodium [valproate](#) 1100 mg/day, and [haloperidol](#) 5 mg as needed. On the second day of treatment with clozapine, the patient reported not feeling well and she developed [tachycardia](#) (115 beats per minute) and a fever (37.5 degrees C). On day 3, RBC and trace amounts of protein were observed in a [urine dipstick test](#) and the patient was started on [trimethoprim](#) for a suspected [urinary tract infection](#). On day 4, an elevated C-reactive protein (CRP) level (197 mg/L), [lymphocyte](#) count ( $1.04 \times 10^9$ ), and neutrophil count ( $8.2 \times 10^9$ ) were detected; however, the [creatinine](#) level (87 mcml/L) and other [blood chemistry](#) results were normal. Clozapine and [trimethoprim](#) were discontinued on day 4 and a 5-day course of [amoxicillin](#) was started for a chest infection. The patient continued to experience [tachycardia](#) but her fever resolved over the next few days. On day 8, a laboratory analysis revealed a decreased CRP level (138 mg/L) but an elevated [creatinine](#) level (126 mcml/L) and the patient had an estimated GFR of 40 mL/min/1.73 m<sup>2</sup>. On day 9, the [creatinine](#) level was decreased (106 mcml/L) and renal function gradually returned to normal over the next few days (Hunter et al, 2009).

- 3) In one report, a 49-year-old man developed [acute renal failure](#) due to [interstitial nephritis](#) during treatment with clozapine. He received no other medication except [diazepam](#) as needed. On clozapine day 42, blood draw showed marked [renal impairment](#). He was dehydrated and pyrexial on day 45 with no abnormality on physical exam or [chest x-ray](#). Blood and urine cultures were negative, clozapine was stopped, and he was started on intravenous [cefotaxime](#). Despite hydration, [dopamine](#), and [furosemide](#) infusions his plasma urea and [creatinine](#) continued to rise. On day 47 he started [peritoneal dialysis](#). A [percutaneous renal biopsy](#) on day 50 showed a florid [interstitial nephritis](#). He was treated with intravenous [methylprednisolone](#) 1 gram on each of days 51 to 53 then switched to oral [prednisolone](#). He was switched to [hemodialysis](#) on day 52 and by day 61, his biochemistry improved and was taken off dialysis. Discontinuation of the drug often leads to resolution in those with mild to moderate [renal failure](#) but unless the offending agent is discontinued, the [renal failure](#) may be irreversible. Also included were details of 7 additional cases of [acute renal failure](#) associated with clozapine therapy reported to the Committee On Safety Of Medicines in the UK (Fraser and Jibani, 2000).

- 4) Investigators reported a case of [acute interstitial nephritis](#), diagnosed by [renal biopsy](#) in a 38-year-old female, which they attributed to a [hypersensitivity reaction](#) to clozapine. Eleven days after initiation of

clozapine 125 milligrams twice daily, the patient developed anuric renal failure necessitating hemodialysis and the discontinuation of all medications. Other possible etiologies were ruled out. The patient began improving after 1 week with renal function values normalizing by day 15 (Elias et al, 1999).

### 3.3.13.B Nocturnal enuresis

1) The incidence of nocturnal enuresis was 41% in a sample of 61 Chinese inpatients with chronic schizophrenia treated with clozapine for at least 3 months. Daytime urinary incontinence accompanied nocturnal enuresis in 11 of 25 cases (Lin et al, 1999).

2) Bladder urgency and/or enuresis occurred in a series of 10 patients during treatment with clozapine. Eight of the patients experienced these symptoms during medication initiation, and two of the patients had preexistent enuresis that worsened with clozapine therapy. Oxybutynin (5 to 15 milligrams/day) was effective in relieving the symptoms of enuresis and urgency in five patients; intranasal desmopressin was effective in another four. The authors also report a cumulative incidence of enuresis in two previous studies of 28% and suggest that all clozapine-treated patients be questioned about changes in bladder habits (Frankenburg et al, 1996).

3) Nocturnal enuresis has been reported to occur in at least 0.23% of patients treated with clozapine. Desmopressin acetate administered intranasally at a dose of one puff (10 micrograms) in each nostril at bedtime was reported as successfully treating this side effect in one case report (Steingard, 1994).

### 3.3.13.C Urgent desire to urinate

1) In clinical trials (n=842), urinary urgency/frequency occurred in 1% of patients during clozapine therapy (Prod Info CLOZARIL(R) oral tablets, 2008).

### 3.3.13.D Urinary incontinence

1) Incidence: 1% (Prod Info CLOZARIL(R) oral tablets, 2008)

2) In clinical trials (n=842), urinary incontinence occurred in 1% of patients during clozapine therapy (Prod Info CLOZARIL(R) oral tablets, 2008).

3) In a retrospective review of 61 Chinese inpatients with chronic schizophrenia treated with clozapine for at least 3 months, the incidence of urinary incontinence was 44%. Investigators compared age, gender, clozapine dose and duration, length of hospitalization, duration of illness and age at onset of illness and found no significant difference between those who did and did not experience urinary incontinence. The same characteristics were also statistically equivalent between subjects with persistent versus self-limiting urinary incontinence. Of the 27 patients with urinary incontinence, 15 (56%) had persistent and 12 (44%) had self-limiting urinary incontinence; 25 (93%) had nocturnal enuresis with (n=11) or without (n=14) daytime symptoms; 2 (7%) had daytime urinary incontinence only. Concomitant medications were not associated with urinary incontinence in this sample (Lin et al, 1999).

4) In one report, urinary incontinence developed in 17 of 57 inpatients after initiation of clozapine therapy. Patients who developed incontinence were significantly more likely to be receiving a typical antipsychotic agent in addition to clozapine, receiving a higher dose of the agent, and to be female. Sixteen of the incontinent patients were treated with ephedrine (25 to 150 milligrams/day) with 12 patients having a complete response to treatment (Fuller et al, 1996).

### 3.3.13.E Urinary retention

1) Incidence: 1% (Prod Info CLOZARIL(R) oral tablets, 2008)

2) In clinical trials (n=842), urinary retention occurred in 1% of patients during clozapine therapy. Elderly patients may be particularly susceptible to the anticholinergic effects of clozapine, such as urinary retention (Prod Info CLOZARIL(R) oral tablets, 2008).

### 3.3.14 Reproductive Effects

#### 3.3.14.A Abnormal ejaculation

- 1) Incidence: 1% (Prod Info [CLOZARIL\(R\)](#) oral tablets, 2008)
- 2) In clinical trials (n=842), abnormal ejaculation occurred in 1% of patients during [clozapine](#) therapy (Prod Info [CLOZARIL\(R\)](#) oral tablets, 2008).

#### 3.3.14.B Priapism

- 1) During postmarketing surveillance, [priapism](#) has been reported in patients who received [clozapine](#) (Prod Info [CLOZARIL\(R\)](#) oral tablets, 2008).

### 3.3.15 Respiratory Effects

#### 3.3.15.A Bronchitis

- 1) Incidence: less than 1% (Prod Info [Clozaril\(R\)](#), 2002)
- 2) In clinical trials, [bronchitis](#) occurred in less than 1% of patients (Prod Info [Clozaril\(R\)](#), 2002).

#### 3.3.15.B Cough

- 1) Incidence: less than 1% (Prod Info [Clozaril\(R\)](#), 2002)
- 2) In clinical trials, cough occurred in less than 1% of patients (Prod Info [Clozaril\(R\)](#), 2002).

#### 3.3.15.C Dyspnea

- 1) Incidence: 1% (Prod Info [Clozaril\(R\)](#), 2002)
- 2) In clinical trials, dyspnea occurred in 1% of patients (n=842) (Prod Info [Clozaril\(R\)](#), 2002).

#### 3.3.15.D Hyperventilation

- 1) Incidence: less than 1% (Prod Info [Clozaril\(R\)](#), 2002)
- 2) In clinical trials, hyperventilation occurred in less than 1% of patients (Prod Info [Clozaril\(R\)](#), 2002).

#### 3.3.15.E Laryngitis

- 1) Incidence: less than 1% (Prod Info [Clozaril\(R\)](#), 2002)
- 2) In clinical trials, [laryngitis](#) occurred in less than 1% of patients (Prod Info [Clozaril\(R\)](#), 2002).

#### 3.3.15.F Nasal congestion

- 1) Incidence: 1% (Prod Info [Clozaril\(R\)](#), 2002)
- 2) In clinical trials, nasal congestion occurred in 1% of patients (n=842) (Prod Info [Clozaril\(R\)](#), 2002).

#### 3.3.15.G Nasal discharge

- 1) Incidence: less than 1% (Prod Info [Clozaril\(R\)](#), 2002)
- 2) In clinical trials, rhinorrhea occurred in less than 1% of patients (Prod Info [Clozaril\(R\)](#), 2002).

#### 3.3.15.H Pain in throat

- 1) Incidence: 1% (Prod Info [Clozaril\(R\)](#), 2002)
- 2) In clinical trials, throat discomfort occurred in 1% of patients (n=842) (Prod Info [Clozaril\(R\)](#), 2002).

**3.3.15.I Pleural effusion****1) Summary**

a) Two cases of pulmonary effusion were reported with [clozapine](#) therapy (Stanislav & Gonzalez-Blanco, 1999; Chatterjee & Safferman, 1997).

**2) LITERATURE REPORTS**

a) [Bilateral pleural effusion](#), accompanied by a fever and papular rash, appeared in a 37-year-old female 9 days after [clozapine](#) initiation and titration to 150 mg/day. Diagnostic findings were consistent with a [drug hypersensitivity](#) reaction, as no infectious or cardiopulmonary etiology was identified. The remainder of her medication regimen had been stable with no recent dose changes. Within a week of [clozapine](#) discontinuation, signs and symptoms resolved (Stanislav & Gonzalez-Blanco, 1999).

b) A 37-year-old male developed right [arm cellulitis](#) after 5 days of [clozapine](#) therapy and a left-sided [pleural effusion](#) after 12 days. [Eosinophilia](#) was also present (white blood cell count of 17,100 cells/mm(3), 23.6% eosinophils). [Clozapine](#) was discontinued and he improved with antibiotics. The patient was rechallenged with [clozapine](#). After 8 days, he again experienced right arm swelling and [chest x-ray](#) showed reemergence of left-sided [pleural effusion](#) (Chatterjee & Safferman, 1997).

3) [Pleural effusion](#) has been voluntarily reported in postmarketing surveillance, a causal relationship could not be determined (Prod Info [Clozaril\(R\)](#), 2002).

**3.3.15.J Pneumonia**

1) Incidence: less than 1% (Prod Info [Clozaril\(R\)](#), 2002)

2) In clinical trials, [pneumonia](#) occurred in less than 1% of patients (Prod Info [Clozaril\(R\)](#), 2002).

**3.3.15.K Pulmonary aspiration**

1) Aspiration has been voluntarily reported in postmarketing surveillance, a causal relationship could not be determined (Prod Info [Clozaril\(R\)](#), 2002).

**3.3.15.L Pulmonary embolism**

1) Incidence: rare

2) A case of bilateral [pulmonary embolism](#) was reported in a 30-year-old man, five months after starting [clozapine](#). He had a sudden onset of shortness of breath and dizziness while walking. He then collapsed on the street and taken to the emergency room. Upon examination he was found to be diaphoretic and tachycardic, with a pulse of 115 beats per minute. Further investigation included a [ventilation-perfusion scan](#), and he was diagnosed with a bilateral [pulmonary embolism](#). The patient was anticoagulated with [heparin](#) then [warfarin](#) and he made a gradual recovery (Maynes, 2000).

3) Between April 1989 and March 2000, 6 cases of [pulmonary embolism](#) and 6 cases of venous [thrombosis](#) were reported during [clozapine](#) therapy. The adverse reaction was fatal in 5 cases. The affected patients were 3 women and 9 men. [Venous thromboembolism](#) (VTE) complications developed within the first 3 months of [clozapine](#) therapy in 8 of the patients. The mean [clozapine](#) dose was 277 mg/day (Hagg & Soderstrom, 2000). After reviewing the available literature on case reports of VTE from the Swedish Adverse Reactions Advisory Committee, the authors suggest that VTE may not be [clozapine](#) associated after all and that other risk factors, such as reduced motor activity, should be taken into account. The authors concluded that an increased risk of VTE seems to be a general property of the antipsychotic drugs (Thomassen et al, 2000).



### 3.3.15.M Respiratory arrest

- 1) Incidence: rare
- 2) [Clozapine](#) has induced orthostatic hypotension severe enough to cause collapse and respiratory arrest. This adverse effect usually occurs following the initial titration or during rapid escalation of the dose (Prod Info [Clozaril\(R\)](#), 2002).

### 3.3.15.N Sneezing

- 1) Incidence: less than 1% (Prod Info [Clozaril\(R\)](#), 2002)
- 2) In clinical trials, sneezing occurred in less than 1% of patients (Prod Info [Clozaril\(R\)](#), 2002).

### 3.3.15.O Wheezing

- 1) Incidence: less than 1% (Prod Info [Clozaril\(R\)](#), 2002)
- 2) In clinical trials, hyperventilation occurred in less than 1% of patients (Prod Info [Clozaril\(R\)](#), 2002).

## 3.3.16 Other

### 3.3.16.A Death

1) Results of a population-based, retrospective cohort study demonstrated that the use of conventional antipsychotics was associated with an even greater risk for death than atypical antipsychotics when administered to elderly patients (aged 66 years and older) with [dementia](#). Atypical versus no antipsychotic use and conventional versus atypical antipsychotic use pair-wise comparisons were made. A total of 27,259 matched pairs were identified and the [dementia](#) cohort was stratified based on place of residence (community versus long-term care facilities). In order to adjust for difference in baseline health status, propensity score matching was used. The primary outcome of the study was all-cause mortality. The risk for death was evaluated at 30, 60, 120, and 180 days after the antipsychotic medications were initially dispensed. There was a statistically significant increase in the risk for death at 30 days associated with new use of atypical antipsychotic medications compared with nonuse in both the community-dwelling cohort (adjusted hazard ratio (HR), 1.31 (95% confidence interval (CI), 1.02 to 1.70); absolute risk difference, 0.2 percentage point) and long-term care cohort (adjusted HR, 1.55 (95% CI, 1.15 to 2.07); absolute risk difference, 1.2 percentage points). For both cohorts, the risk associated with atypical antipsychotics appeared to persist to 180 days. The risk for death associated with conventional antipsychotics was even greater than the risk identified with atypical antipsychotics. At 30 days, the adjusted HR for the community-dwelling cohort was 1.55 (95% CI, 1.19 to 2.02) and 1.26 (95% CI, 1.04 to 1.53) for the long-term care cohort (adjusted risk difference for both was 1.1 percentage points). The risk appeared to persist to 180 days for both groups. Some important limitations to the study include unknown or unmeasured confounders may influence the results and cause of death could not be examined (Gill et al, 2007).

2) Results of a population-based, retrospective cohort study demonstrated comparable to possibly greater risk of death associated with the use of conventional antipsychotic medications in the elderly (aged 65 years and older) compared with atypical antipsychotic medications. The analysis excluded patients with [cancer](#) and included only new users of antipsychotic medications. The primary study outcome was 180-day all-cause mortality. A set of potential confounders was measured based on healthcare utilization data within 6 months before the initiation of antipsychotic medications. Of the 37,241 elderly patients identified, 12,882 and 24,359 received conventional and atypical antipsychotic medications, respectively. The risk of death in the conventional drug group within the first 180 days was 14.1% compared with 9.6% in the atypical drug group (unadjusted mortality ratio, 1.47; 95% confidence interval (CI), 1.39 to 1.56). In the multi-variable analysis which controlled for potential confounders, the adjusted mortality ratio for the risk of death within 180 days for conventional versus atypical drug therapy was 1.32 (95% CI, 1.23 to 1.42).

When the most frequently prescribed conventional antipsychotic drugs were compared with [risperidone](#), the mortality ratio associated with [haloperidol](#) was 2.14 (95% CI, 1.86 to 2.45) and [loxapine](#) was 1.29 (95% CI, 1.19 to 1.40), while there was no difference associated with [olanzapine](#). The increased mortality risk for conventional versus atypical drug therapy was greatest when doses higher (above median) doses were used (mortality ratio 1.67; 95% CI, 1.5 to 1.86) and also during the first 40 days of therapy (mortality ratio 1.6; 95% CI, 1.42 to 1.8). Confirmatory analyses consisting of multi-variable Cox regression, propensity score, and instrumental variable estimation confirmed the results of the study (Schneeweiss et al, 2007).

3) The results of a retrospective cohort study indicate that conventional antipsychotic agents are at least as likely as atypical antipsychotic agents to increase the risk of death among elderly patients 65 years of age or older. The study included 9,142 new users of conventional agents (mean age, 83.2 years) and 13,748 new users of atypical agents (mean age, 83.5 years). A higher adjusted relative risk of death was associated with the use of conventional antipsychotics as compared with atypical antipsychotics at all time points studied after beginning therapy (within 180 days: relative risk) RR, 1.37; 95% confidence interval (CI), 1.27 to 1.49; less than 40 days: RR, 1.56; 95% CI, 1.37 to 1.78; 40 to 79 days: RR, 1.37; 95% CI, 1.19 to 1.59; 80 to 180 days: RR, 1.27; 95% CI, 1.14 to 1.41). In addition, the adjusted risks of death observed in patients with [dementia](#) (RR, 1.29; 95% CI, 1.15 to 1.45), without [dementia](#) (RR, 1.45; 95% CI, 1.30 to 1.63), in a nursing home (RR, 1.26; 95% CI, 1.08 to 1.47), or not in a nursing home (RR, 1.42; 95% CI, 1.29 to 1.56) were also higher with the use of conventional antipsychotic therapy as compared with atypical antipsychotic use. This risk appeared to be dose-related and was greater with the use of higher dose (ie, greater than the median) conventional antipsychotics (RR, 1.73; 95% CI, 1.57 to 1.90). Additional studies which specifically investigate the optimum care of elderly patients requiring antipsychotic therapy are needed so that appropriate guidance regarding therapeutic intervention can be provided (Wang et al, 2005).

### 3.3.16.B Extrapyramidal disease

See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

### 3.3.16.C Fever

1) Incidence: 5% (Prod Info [Clozaril](#)(R), 2002)

2) Fever was reported in 4% to 6% of patients (sometimes along with flu-like symptoms) following therapeutic dosages of [clozapine](#). The fever (100.4 degrees F (38 degrees C)) is usually transient, with a peak occurring within the first 3 weeks of therapy. The fever is generally benign and self-limiting. Temperature elevation appeared to be independent of dose (Prod Info [Clozaril](#)(R), 2002).

### 3.3.16.D Malaise

1) Incidence: less than 1% (Prod Info [Clozaril](#)(R), 2002)

2) Malaise was temporally associated with [clozapine](#) therapy and occurred at a frequency of less than 1% (Prod Info [Clozaril](#)(R), 2002).

### 3.3.16.E Seizure

See Drug Consult reference: PREVENTION OF CLOZAPINE-INDUCED SEIZURES

### 3.3.16.F Withdrawal sign or symptom

1) Summary

- a) Several different kinds of withdrawal symptoms including cholinergic rebound, [dystonias](#), [dyskinesias](#) and worsening of psychotic symptoms have occurred with [clozapine](#) therapy (Tollefson et al, 1999; Delassus-Guenault et al, 1999; Stanilla et al, 1997).
- 2) In a double-blind, placebo-controlled study of 106 patients undergoing elective discontinuation of [clozapine](#), the immediate substitution of [olanzapine](#) 10 mg/day attenuated some withdrawal symptoms. [Clozapine](#) doses were gradually tapered to 300 mg/day or less prior to abrupt discontinuation, followed by randomization to either placebo or [olanzapine](#) for a 3 to 5-day study period. During this time, 24.5% and 7.5% of placebo and olanzapine-treated patients, respectively, experienced a worsening of at least one psychotic sign or symptom ( $p=0.02$ ). This was reflected by significant between-group differences in the Positive and Negative Syndrome Scale total score ( $p=0.04$ ) and general psychopathology subscale ( $p=0.03$ ) as well as the Montgomery-Asberg Depression Rating Scale total score ( $p$  less than 0.001). However, the primary efficacy variable, the Clinical Global Impression Scale-Severity, was statistically similar in both groups. All subjects then entered a 9-week open-label [olanzapine](#) period, with equivalent outcomes. Investigators stress the importance of a gradual taper of [clozapine](#) with possible overlap and/or substitution with [olanzapine](#) to minimize the risk of withdrawal symptoms. [Olanzapine](#) may be preferred over [risperidone](#) or typical antipsychotics because its receptor affinities are similar to those of [clozapine](#) (Tollefson et al, 1999).
- 3) In two case reports, rapid [clozapine](#) tapering from high doses resulted in severe cholinergic rebound symptoms despite substitution with [olanzapine](#). Maintenance [clozapine](#) doses of 700 to 800 mg/day were tapered over only 4 to 7 days, discontinued and replaced by [olanzapine](#) 5 to 10 mg/day. Withdrawal symptoms included severe anxiety, agitation, aggression, nausea, vomiting, diaphoresis, confusion and disorientation, necessitating medical hospitalization in one case. The authors recommend a 2 to 3-week taper period for [clozapine](#) with concomitant anticholinergic therapy (Delassus-Guenault et al, 1999).
- 4) Severe [dystonias](#) and [dyskinesias](#) were experienced by 4 patients withdrawn from [clozapine](#) therapy (Ahmed et al, 1998). Patients were 18 to 60 years old and had a history of extrapyramidal symptoms while receiving high potency and older neuroleptics. In 3 patients [clozapine](#) was discontinued abruptly. Cholinergic rebound was experienced by 2 subjects. Severe limb-axial and neck [dystonias](#), and [dyskinesias](#) were experienced by 3 patients for 5 to 14 days. The [dystonias](#) were so severe in 2 patients that they were unable to ambulate. Significant improvement was seen after 2 restarted [clozapine](#), 1 started [risperidone](#), and 1 started [olanzapine](#).
- 5) Three cases of [acute delirium](#) and [psychosis](#) occurred upon withdrawal of [clozapine](#). The patients involved were male, ages 38, 46, and 63 years, whose [schizophrenia](#) had been controlled on 250 to 600 mg/day for 12 to 18 months. In two patients, [clozapine](#) was abruptly stopped, while the other was weaned off [clozapine](#) over 2 weeks. Withdrawal symptoms (hallucinations, diaphoresis, agitation, disorientation, choreoathetoid movements) appeared within 24 to 48 hours of the last [clozapine](#) dose and resolved upon reinstitution of [clozapine](#). When a prolonged taper of [clozapine](#) is not possible, the authors recommend the temporary use of [thioridazine](#) when transitioning to another antipsychotic agent to counteract cholinergic hyperactivity (Stanilla et al, 1997).
- 6) A withdrawal syndrome occurred in 9 of 13 patients after sudden discontinuation of long-term [clozapine](#) therapy at doses ranging from 50 to 200 mg/day. After sudden discontinuation, patients experienced a severe [relapse](#) requiring hospitalization within 24 to 48 hours. Five patients reported vomiting, sleeplessness, depression, stupor, fatigue, and dizziness. Withdrawal [akathisia](#) was reported by 4 patients. These symptoms regressed when the patient was given [clozapine](#) or disappeared gradually when patients began to receive other neuroleptics (Zapletal et al, 1980).
- 7) Difficulty in switching patients from other neuroleptics to [clozapine](#) has been reported. In 7 patients, unspecific restlessness, psychotic symptoms, and extrapyramidal symptoms which required hospitalization were seen for an average of 4 weeks after withdrawal of neuroleptics and starting [clozapine](#) (Mauthe et al, 1980).

### 3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

#### A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category B (Prod Info CLOZARIL(R) oral tablets, 2010) (All Trimesters)

a) Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal-reproduction studies have shown adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).

2) Australian Drug Evaluation Committee's (ADEC) Category: C(Australian Drug Evaluation Committee, 1999)

a) Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Unknown

4) Clinical Management

a) There are no adequate and well-controlled studies of clozapine use during pregnancy in humans. However, third-trimester antipsychotic drug exposure has been associated with extrapyramidal and/or withdrawal symptoms in neonates. Limited human data from case reports indicate no complications during pregnancy or delivery and no adverse effects on the infant when clozapine is administered during pregnancy. Animal studies have not demonstrated adverse effects due to clozapine use during gestation in rats and rabbits. In consideration of maintaining the lowest effective dose of any drug during pregnancy and because animal studies are not always predictive of human response, clozapine should be used during pregnancy only if clearly needed (Prod Info CLOZARIL(R) oral tablets, 2010).

5) Literature Reports

a) There are no adequate and well-controlled studies of clozapine use in pregnant women. Maternal use of antipsychotic drugs during the third trimester of pregnancy has been associated with an increased risk of neonatal extrapyramidal and/or withdrawal symptoms (eg, agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder) following delivery. Severity of these adverse effects have ranged from cases that are self-limiting to cases that required prolonged periods of hospitalization and ICU care. In animal studies, there was no evidence of fetal harm when rats and rabbits were exposed to clozapine at approximately 2 to 4 times the human dose (Prod Info CLOZARIL(R) oral tablets, 2010).

b) Two case reports described uncomplicated pregnancies and vaginal term deliveries resulting in healthy infants when clozapine 200 mg/day was used during the pregnancies of 2 women with schizophrenia. In both cases, breast feeding was not recommended. In the first case, the patient was taking clozapine 400 mg/day. One year later, the patient wanted to conceive. Subsequently, clozapine was tapered off to the point of psychotic symptoms to determine the lowest effective dose. Prior to pregnancy, her BMI was 23.6 and serum folate level was 8.2 nanograms/mL. No psychotic symptoms occurred during gestation. The newborn's height of 52 cm and weight of 2900 g were normal. APGAR scores were 9 and 10 in minute 1 and 5, respectively. WBC count was

normal with no neonatal history of seizures. In a subsequent pregnancy 1.5 years later, the patient was still taking [clozapine](#) 200 mg/day. Routine follow-up during pregnancy revealed no [gestational diabetes](#), orthostatic hypotension, [agranulocytosis](#), or psychotic symptoms. The second child was 50 cm and 3000 g with APGAR scores of 10 in minutes 1 and 5. In the second case, a woman had been experiencing auditory hallucinations for which she was initiated on [clozapine](#) 400 mg/day while tapering off of other drugs that were not working. She improved significantly and wanted a second child. Her BMI was 24.1. Birth control or [clozapine](#) dose reduction in the event of pregnancy was recommended. The patient presented to an outpatient clinic reporting that she had delivered healthy twins who were 51 and 49 cm and 3100 and 2940 g with APGAR scores in minute 1 and 5 of 9 and 10, respectively, for one twin and 10 for the other. WBC count was not monitored during pregnancy. No seizures or [agranulocytosis](#) were recorded (Duran et al, 2008).

c) A case report described an uncomplicated pregnancy and delivery resulting in a healthy infant who exhibited normal development, except for speech, when [clozapine](#) was used during pregnancy in a 30-year-old woman with [schizophrenia](#). The mother had been maintained on [clozapine](#) 100 mg/day for 6 months when she became pregnant. Laboratory tests for blood glucose, [hemoglobin](#), and WBC count were within normal limits. The 100-mg daily [clozapine](#) dose was maintained throughout her pregnancy. Weight gain was normal and no psychotic exacerbations occurred during gestation. A term delivery (9 months and 2 days) resulted in a healthy baby girl with a normal weight of 2.95 kg and no perinatal complications. The patient was maintained on the same [clozapine](#) dose while breastfeeding her infant until 1 year of age. The infant achieved normal developmental milestones, with the exception of speech. At the age of 1 year, she began using consonants and began using combined syllables at the age of 18 months. She spoke only 6 to 8 words at 2 years of age and would speak only 12 to 15 words until 3 years of age. She was also [stuttering](#). At 4 years of age, she developed speaking skills with small sentences of 2 or 3 words and she could repeat small sentences. She was able to speak fluently by the end of 5 years. Local pathology was ruled out and audiometric assessment was within normal limits. The mother-child relationship was not impaired and there was no evidence of familial [phonological disorder](#) or a bilingual environment (Mendhekar, 2007).

d) Cases of [clozapine](#) use during pregnancy (150 to 625 mg/day) have not resulted in fetal abnormalities (Dickson & Hogg, 1998; Stoner et al, 1997). A case report described a 30-year-old female who was treated with [clozapine](#) throughout her pregnancy. The patient delivered a female infant at 39 weeks gestation with abnormal findings including a cephalhematoma, [hyperpigmentation](#) folds, and a coccygeal dimple, all of which were resolving within 2 days of delivery. At 8 days old, the infant was reported to have a seizure and developed [gastroenteritis](#), both of which resolved. At 2 years of age, the child was reported to be healthy with no physical problems (Stoner et al, 1997). Another case report described a 32-year-old female who was treated with [clozapine](#) throughout her pregnancy. She delivered a female at 40 weeks gestational age with no reported abnormalities except a low-grade fever which resolved prior to hospital discharge (Stoner et al, 1997).

e) A case report described an infant born to a mother treated with [clozapine](#) 100 mg per day until the last 9 weeks of pregnancy, at which time the dose was decreased to 50 mg/day. The infant girl weighed 3600 g at birth and had Apgar scores of 5 at 1 minute and 8 at 5 minutes. The infant had normal psychomotor development up to 6 months of age. Maternal [clozapine](#) plasma levels were measured monthly during pregnancy, the day of delivery, one day after delivery when the mother began lactating, and one week after delivery. While taking 100 mg/day, the mother's [clozapine](#) plasma levels were 38 to 55 nanograms (ng)/mL; at 50 mg/day, the level was 15.4 ng/mL. When the infant was delivered, the maternal, amniotic, and fetal plasma levels were 14.1 ng/mL, 11.6 ng/mL, 27 ng/mL, respectively. The accumulation of drug in the fetal plasma can be explained by the higher concentration of albumin in fetal blood which binds [clozapine](#), an acidic, lipophilic drug, and by ion trapping in the fetal compartment which results in a pH gradient in the fetus (Barnas et al, 1994).



**B) Breastfeeding**

1) American Academy of Pediatrics Rating: Drugs for which the effect on nursing infants is unknown but may be of concern. (Anon, 2001)

2) Thomson Lactation Rating: Infant risk cannot be ruled out.

a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

**3) Clinical Management**

a) Human data showing the effects, if any, of [clozapine](#) on the nursing infant are limited. A case report demonstrated a milk/plasma ratio of greater than 2.5 in a woman taking [clozapine](#) 100 mg/day. The high milk/plasma ratio was attributed to the high lipid solubility and lipophilic properties of [clozapine](#) (Barnas et al, 1994a). Another case report described a problem with speech development in an infant who had been breastfed for 1 year while her mother was maintained on a daily 100-mg dose of [clozapine](#). However, it is not possible to determine whether the speech difficulty was a result of postnatal exposure to [clozapine](#) (Mendhekar, 2007). Animal studies have indicated that [clozapine](#) may be excreted in breast milk. Therefore, breastfeeding should be avoided during [clozapine](#) treatment (Prod Info [CLOZARIL](#)(R) oral tablets, 2010).

**4) Literature Reports**

a) A case report described an uncomplicated pregnancy and delivery resulting in a healthy infant who exhibited normal development, except for speech, when [clozapine](#) was used during pregnancy and lactation in a 30-year-old woman with [schizophrenia](#). The mother had been maintained on [clozapine](#) 100 mg/day for 6 months when she became pregnant. Laboratory tests for blood glucose, [hemoglobin](#), and WBC count were within normal limits. The 100-mg daily [clozapine](#) dose was maintained throughout her pregnancy. Weight gain was normal and no psychotic exacerbations occurred during gestation. A term delivery (9 months and 2 days) resulted in a healthy baby girl with a normal weight of 2.95 kg and no perinatal complications. The patient was maintained on the same [clozapine](#) dose while breastfeeding her infant until 1 year of age. The infant achieved normal developmental milestones, with the exception of speech. At the age of 1 year, she began using consonants. At 18 months, she began using combined syllables. She spoke only 6 to 8 words at 2 years of age and would speak only 12 to 15 words until 3 years of age. She was also [stuttering](#). At 4 years of age, she developed speaking skills with small sentences of 2 or 3 words and she could repeat small sentences. She was able to speak fluently by the end of 5 years. Local pathology was ruled out and audiometric assessment was within normal limits. The mother-child relationship was not impaired and there was no evidence of familial [phonological disorder](#) or a bilingual environment (Mendhekar, 2007).

b) A case report described a healthy infant born to a mother treated with [clozapine](#) 100 mg/day until the last 9 weeks of pregnancy, at which time the dose was decreased to 50 mg/day. The infant girl weighed 3600 g at birth and had Apgar scores of 5 at 1 minute and 8 at 5 minutes. She had normal psychomotor development up to 6 months of age. Maternal [clozapine](#) plasma levels were measured monthly during pregnancy, the day of delivery, one day after delivery when the mother began lactating, and one week after delivery. While taking 100 mg/day, the mother's [clozapine](#) plasma level was 38 to 55 nanograms (ng)/mL; at 50 mg/day, her level was 15.4 ng/mL. When the infant was delivered, the maternal, amniotic, and fetal plasma levels were 14.1 ng/mL, 11.6 ng/mL, 27 ng/mL, respectively. The day after delivery, the concentration of [clozapine](#) in the maternal plasma was 14.7 ng/mL and the first portion of the breast milk contained 63.5 ng/mL. At one week postdelivery, the



mother was taking [clozapine](#) 100 mg/day; the breast milk concentration of drug measured 115.6 ng/mL and plasma level measured 41.4 ng/mL. The authors postulated that [clozapine](#) accumulates in the breast milk because of the high lipid concentration of breast milk (Barnas et al, 1994a).

## 5) Drug Levels in Breastmilk

### a) Parent Drug

#### 1) Milk to Maternal Plasma Ratio

a) 2.8 to 4.3 (Barnas et al, 1994a)

## 3.5 Drug Interactions

### 3.5.1 Drug-Drug Combinations

#### 3.5.1.A Aprindine

- 1) Interaction Effect: increased plasma concentrations of [clozapine](#) and or class I antiarrhythmic agents
- 2) Summary: Coadministration of [clozapine](#) with other drugs that are metabolized by cytochrome P450 2D6, such as class I antiarrhythmics, should be approached with caution (Prod Info [Clozaril\(R\)](#), 2002g).
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Concomitant use of [clozapine](#) with other drugs metabolized by cytochrome P450 2D6, such as class I antiarrhythmic agents, may require lower doses than usually prescribed for either [clozapine](#) or the class I antiarrhythmic.
- 7) Probable Mechanism: competitive substrate inhibition

#### 3.5.1.B Belladonna

- 1) Interaction Effect: excessive anticholinergic activity (severe dry mouth, constipation, decreased urination, excessive sedation, blurred vision)
- 2) Summary: The anticholinergic activity of the active alkaloids present in belladonna may predispose the patient to excessive anticholinergic activity if taken with [clozapine](#). Belladonna contains L-hyoscyamine, [atropine](#), and [scopolamine](#) with a total alkaloid content of at least 0.3% in the leaves and 0.5% in the roots (Blumenthal et al, 1998). Because belladonna is typically available as a homeopathic preparation, the clinical severity of the interaction with [clozapine](#) is unknown. Caution is advised.
- 3) Severity: minor
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Excessive anticholinergic activity may be manifested by dry mouth, constipation, urinary retention, [tachycardia](#), decreased sweating, mydriasis, blurred vision, elevated temperature, muscular weakness, and sedation. If such effects are noted, belladonna should be discontinued immediately. In severe cases, [paralytic ileus](#), confusion, [psychoses](#), agitation, delusions, [delirium](#), and paranoia may be encountered as well as [tachycardia](#), [dysrhythmia](#), and [hypertension](#). In severe cases, immediate medical attention should be obtained.
- 7) Probable Mechanism: additive anticholinergic effect

### 3.5.1.C Belladonna Alkaloids

- 1) Interaction Effect: excessive anticholinergic activity (severe dry mouth, constipation, decreased urination, excessive sedation, blurred vision)
- 2) Summary: The anticholinergic activity of the active alkaloids present in belladonna may predispose the patient to excessive anticholinergic activity if taken with [clozapine](#). Belladonna contains L-hyoscyamine, [atropine](#), and [scopolamine](#) with a total alkaloid content of at least 0.3% in the leaves and 0.5% in the roots (Blumenthal et al, 1998). Because belladonna is typically available as a homeopathic preparation, the clinical severity of the interaction with [clozapine](#) is unknown. Caution is advised.
- 3) Severity: minor
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Excessive anticholinergic activity may be manifested by dry mouth, constipation, urinary retention, [tachycardia](#), decreased sweating, mydriasis, blurred vision, elevated temperature, muscular weakness, and sedation. If such effects are noted, belladonna should be discontinued immediately. In severe cases, [paralytic ileus](#), confusion, [psychoses](#), agitation, delusions, [delirium](#), and paranoia may be encountered as well as [tachycardia](#), [dysrhythmia](#), and [hypertension](#). In severe cases, immediate medical attention should be obtained.
- 7) Probable Mechanism: additive anticholinergic effect

### 3.5.1.D Benztropine

- 1) Interaction Effect: excessive anticholinergic effects (sedation, constipation, dry mouth)
- 2) Summary: The use of antipsychotics and anticholinergics may increase the incidence of ileus, [hyperpyrexia](#), or neurologic deficits. In addition, the concurrent use of these drugs may decrease the gastrointestinal absorption of selected antipsychotics. Anticholinergic drugs that pass into the central nervous system may antagonize antipsychotic effects (Linnoila et al, 1980; Mann & Boger, 1978).
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Use this combination only when clearly indicated. Monitor for excessive anticholinergic effects. Dosage adjustments may be required.
- 7) Probable Mechanism: additive anticholinergic effects

### 3.5.1.E Buspirone

- 1) Interaction Effect: an increased risk of [gastrointestinal bleeding](#) and [hyperglycemia](#)
- 2) Summary: A 33-year old male who was taking [clozapine](#) for more than a year without adverse effects, but developed [gastrointestinal bleeding](#) and severe [hyperglycemia](#) when [buspirone](#) therapy was also instituted, has been reported (Good, 1997). Since [clozapine](#) can cause [gastric ulcer](#) and [hyperglycemia](#) by itself, it is possible that [buspirone](#) augmented the serum level of [clozapine](#), either by enzyme inhibition or by displacing [clozapine](#) from its binding sites.
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Caution should be observed when [clozapine](#) and [buspirone](#) are coadministered. Monitor blood glucose levels and watch for signs and symptoms of bleeding, especially from the gastrointestinal tract.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) A 33-year old institutionalized paranoid schizophrenic male was placed on [clozapine](#) 600 mg daily for hallucinations and serious assaultiveness. A series of other medications failed to control his feelings of anxiety, so [buspirone](#) therapy was initiated at a dose of 5 mg three times daily. His [clozapine](#) serum level was 390 ng/mL (range 100-700 ng/mL) prior to [buspirone](#) therapy. One month after [buspirone](#) was started, the dose was increased to 20 mg daily, and the patient began to complain of nausea and epigastric pain. After an episode of coffee-grounds emesis, he was transferred to the intensive care unit, where he was found to have severe [acidosis](#). His blood glucose level was over 1300 mg/dL, and hematocrit had dropped to 31 mL/dL. Both the [clozapine](#) and [buspirone](#) were discontinued. An [upper gastrointestinal series](#) did not reveal a source of the bleeding, and the patient required [insulin](#) therapy until his blood glucose level eventually returned to normal. [Clozapine](#) was reinitiated because of his assaultiveness, and he had no recurrence of adverse effects (Good, 1997).

### 3.5.1.F Carbamazepine

- 1) Interaction Effect: an increased risk of [bone marrow suppression](#), asterixis, or decreased serum [clozapine](#) levels
- 2) Summary: [Clozapine](#) and [carbamazepine](#) both have the potential to cause [bone marrow suppression](#), including [agranulocytosis](#) (Prod Info [Clozaril](#)(R), 2002I). Asterixis (flapping tremor) has also been reported in patients undergoing concurrent therapy with [carbamazepine](#) and [clozapine](#) (Rittmannsberger, 1996a). In addition, a therapeutic drug monitoring study revealed significantly lower [clozapine](#) concentrations when [carbamazepine](#) was added to therapy (Jerling et al, 1994c). The mechanism may be due to [carbamazepine](#) induction of [clozapine](#) metabolism through cytochrome P450 3A4. Controlled studies are needed to further evaluate the pharmacokinetic and clinical effects of combining these agents.
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Avoid concurrent use; an alternative anticonvulsant agent should be considered. If coadministration of these agents is necessary, monitor patients for decreased response to [clozapine](#) and [agranulocytosis](#). Lower doses of either [clozapine](#) or [carbamazepine](#) may be required.
- 7) Probable Mechanism: additive bone marrow-suppressive effects and [neurotoxicity](#); induction of [clozapine](#) metabolism
- 8) Literature Reports

- a) One [agranulocytosis](#) fatality has been reported in association with the use of a multi-drug regimen which included [clozapine](#), [carbamazepine](#), [clonazepam](#), [benztropine](#), and [lithium](#) (Gerson & Lieberman JA Friedenber, 1991). This case exhibited [pancytopenia](#) which is not characteristic of clozapine-induced [agranulocytosis](#).
- b) Over a three-year period, some drug combinations caused a greater risk of asterixis (flapping tremor) in patients on a regimen of multiple psychopharmacologic agents (Rittmannsberger, 1996). With regard to the agents [carbamazepine](#), [clozapine](#), and [lithium](#), incidence of asterixis was greatest in those patients that were on at least two of these three agents. Out of ten patients developing asterixis, five patients received [carbamazepine](#) and [clozapine](#) as part of multi-drug therapy, and in two cases [carbamazepine](#) and [clozapine](#) were the sole psychopharmacologic agents. In all cases serum levels of all the drugs were within normal therapeutic ranges, suggesting an additive effect of combination therapy rather than the effect of a single agent.
- c) Therapeutic drug monitoring data showed a 50% lower [clozapine](#) concentration/dose (C/D) ratio when concurrent [carbamazepine](#) was taken compared to [clozapine](#) alone. The [clozapine](#) C/D ratio was inversely correlated with the dose of [carbamazepine](#). An additional analysis of

eight patients confirmed that upon addition of [carbamazepine](#) to the drug regimen, [clozapine](#) concentrations decreased significantly. The mean C/D ratio during monotherapy was 1.21 and during [cotherapy](#) with [carbamazepine](#) fell to 0.30. The change in [clozapine](#) metabolism was suggested to be due to [carbamazepine](#) induction of cytochrome P450 3A4 (Jerling et al, 1994b).

### 3.5.1.G [Cimetidine](#)

- 1) Interaction Effect: an increased risk of [clozapine](#) side effects (dizziness, vomiting, hypotension, [bone marrow suppression](#))
- 2) Summary: Concomitant administration of drugs known to inhibit the activity of cytochrome P450 isozymes may increase the plasma levels of [clozapine](#), potentially resulting in adverse effects (Prod Info [Clozaril](#)(R), 2002a). In a case report the concomitant use of [clozapine](#) and [cimetidine](#) resulted in elevated serum levels of [clozapine](#) and subsequent side effects (Szymanski et al, 1991a).
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: With concurrent use, monitor patients for [clozapine](#) toxicity. Consider selecting another H2 antagonist (eg, [ranitidine](#) or [famotidine](#)) that has less potential to alter drug metabolism or switching to another anti-ulcer medication such as [sucralfate](#).
- 7) Probable Mechanism: [cimetidine](#) inhibits cytochrome P450-mediated [clozapine](#) metabolism
- 8) Literature Reports

a) An elevation in the serum level of [clozapine](#) and subsequent side effects developed following the administration of [cimetidine](#) in a patient receiving [clozapine](#) 900 mg/day. The patient did not experience any side effects with the concomitant administration of [cimetidine](#) 800 mg/day. However, within 3 days following an increase to [cimetidine](#) 1200 mg/day, marked diaphoresis, dizziness, vomiting, severe orthostatic hypotension, and generalized weakness developed. [Cimetidine](#) was discontinued and the [clozapine](#) dose was reduced to 200 mg/day; symptoms gradually resolved over 5 days. [Clozapine](#) was reinitiated over 1 week to 900 mg/day. The patient continued to experience epigastric distress; therefore, [ranitidine](#) 150 mg twice daily was instituted and no interaction has been identified over a 3-month follow-up (Szymanski et al, 1991).

### 3.5.1.H [Ciprofloxacin](#)

- 1) Interaction Effect: increased [clozapine](#) serum concentrations and increased risk of side effects (sedation, incoordination, slurred speech, seizures, hematologic abnormalities)
- 2) Summary: Concomitant administration of drugs known to inhibit the activity of cytochrome P450 isozymes, such as [ciprofloxacin](#), may increase the plasma levels of [clozapine](#), potentially resulting in adverse effects (Brouwers et al, 2009; Prod Info [CLOZARIL](#)(R) tablets, 2005a).
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Monitor patients for signs and symptoms of [clozapine](#) intoxication (sedation, incoordination, slurred speech, seizures, hematologic abnormalities). Doses of [clozapine](#) may need to be reduced when [ciprofloxacin](#) is added to therapy.
- 7) Probable Mechanism: inhibition of cytochrome P450 3A4 by [ciprofloxacin](#) resulting in delayed [clozapine](#) metabolism
- 8) Literature Reports

a) Coadministration of [ciprofloxacin](#) and [clozapine](#) led to elevated [clozapine](#) plasma level in a 46-year-old male presented with [urosepsis](#). History included smoking, [caffeine](#) use, and treatment

at a psychiatric facility with [citalopram](#), [lorazepam](#), [valproic acid](#), and [clozapine](#). He was treated with a 5-day course of IV [ciprofloxacin](#) 400 mg twice daily and [amoxicillin](#) while on maintenance therapy of [clozapine](#) 900 mg daily for [paranoid schizophrenia](#), and was discharged after 4 days in good condition. He returned 3 days later with suspected [rhabdomyolysis](#), but did not report any pain. Lab results indicated creatine phosphokinase (CPK) levels of 195,000 units per liter, lactic dehydrogenase (LDH) of 6687 units per liter, [aspartate aminotransferase](#) (AST) 845 units per liter, [alanine aminotransferase](#) (ALT) of 93 units per liter, and a urine test positive for myoglobin. [Clozapine](#) treatment was stopped and high-volume alkaline diuresis started. Three days after the end of [ciprofloxacin](#) treatment and one day after stopping [clozapine](#), the patient's [clozapine](#) plasma concentration was 890 nanograms/mL, higher than the recommended therapeutic concentration of 350 to 600 ng/mL. Five days after stopping [clozapine](#), the [clozapine](#) plasma concentration was undetectable. LDH, AST, and ALT concentrations returned to normal by day 18, and CPK levels returned to normal by day 28. The patient did not show signs of worsening psychotic symptoms after the cessation of [clozapine](#); however, [clozapine](#) was restarted 2 weeks after discharge. The Drug Interaction Probability Scale (DIPS) score was 5, indicating a probable reaction between the [clozapine](#) and the [ciprofloxacin](#) (Brouwers et al, 2009).

b) Coadministration of [ciprofloxacin](#) and [clozapine](#) led to elevated [clozapine](#) plasma level in a 58-year-old male presented with [delirium](#) and suspected [urinary tract infection](#) or [pneumonia](#). History included smoking, [caffeine](#) use, and treatment at a psychiatric facility with [valproic acid](#), [hydrochlorothiazide](#), [clonazepam](#), and [clozapine](#) 300 mg per day. Lab results before the addition of [ciprofloxacin](#) indicated normal [aspartate aminotransferase](#) (AST; 10 units/L) and [alanine aminotransferase](#) (ALT; 13 units/L) levels, and his [clozapine](#) plasma concentration was 850 nanograms/mL. He was treated with IV [ciprofloxacin](#) 200 mg twice daily. AST and ALT levels slightly increased (46 and 74 units/liter, respectively), and [ciprofloxacin](#) was stopped after 2 days due to the suspected drug-drug interaction between [ciprofloxacin](#) and [clozapine](#). Three days after the start of [ciprofloxacin](#) treatment, the patient's [clozapine](#) plasma concentration was 1720 ng/mL although he did not show signs of [rhabdomyolysis](#) or other [clozapine](#)-induced adverse effects. He was discharged after 5 days. The Drug Interaction Probability Scale (DIPS) score was 6, indicating a probable reaction between the [clozapine](#) and the [ciprofloxacin](#) (Brouwers et al, 2009).

### 3.5.1.I Citalopram

1) Interaction Effect: an increased risk of [clozapine](#) toxicity (sedation, seizures, hypotension)

2) Summary: Coadministration of [clozapine](#) with other drugs that are metabolized by cytochrome P450 2D6, such as antidepressants, should be approached with caution (Prod Info [Clozaril](#)(R), 2002j). Five hospitalized patients who had been receiving a constant dose of [clozapine](#) for at least two weeks were started on [citalopram](#) 20 mg daily. Plasma [clozapine](#) levels were closely monitored for 14 days after the start of [citalopram](#). Out of the five participants, one patient experienced an increase in their [clozapine](#) level from 0.70 mg/L to 1.16 mg/L. Plasma [clozapine](#) levels did not change in one patient, but the other three patients experienced a slight decline. Overall, [clozapine](#) mean serum levels were 1.13 mg/L prior to [citalopram](#), 1.07 mg/L following one week of coadministration, and 0.93 mg/L following two weeks of concurrent administration. The ratio of [clozapine](#) to norclozapine remained much the same during the study. These results suggest that [citalopram](#) use is safe in patients receiving [clozapine](#), although further studies are needed to verify this hypothesis (Taylor et al, 1998).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor the therapeutic efficacy of [clozapine](#) and for any evidence of toxicity, particularly when the daily [clozapine](#) dose exceeds 300 mg or 3.5 mg/kg. Lower [clozapine](#) dosage may be required in some clinical situations.

7) Probable Mechanism: inhibition by [citalopram](#) of N-dealkylation and N-oxidation of [clozapine](#) via the cytochrome P450 2D6 enzymatic pathway

#### 8) Literature Reports

a) In a case report, Borba and Henderson describe a 39-year-old white male with a 20-year history of DSM-IV [schizoaffective disorder](#), depressive type, who was referred for a trial of [clozapine](#) after failing various antipsychotic and antidepressant medications. Prior to switching to [clozapine](#) 400 mg/day, the patient's medications included [lithium](#) 900 mg/day, [risperidone](#) 3 mg/day, and [bupropion](#) 300 mg/day. Improvement in positive and negative symptoms occurred with [clozapine](#). [Citalopram](#) dosage was 20 mg/day for two weeks then 40 mg/day. The patient experienced worsening sedation, new onset fatigue, [enuresis](#), [hypersalivation](#) and mild confusion. The [citalopram](#) dose was reduced to 20 mg/day which resulted in complete resolution of symptoms within two weeks. The patient has continued with the combination of [clozapine](#) 400 mg/day and [citalopram](#) 20 mg/day with good results. The authors conclude that this case report suggests higher serum concentrations of [clozapine](#) may result when given with [citalopram](#) 40 mg/day. Inhibition of metabolism of [clozapine](#) occurs with [citalopram](#) 40 mg/day, resulting in higher serum concentrations compared with [citalopram](#) 20 mg/day. It has been documented that other selective serotonin reuptake inhibitors (SSRIs) elevate serum [clozapine](#) levels by inhibiting CYP1A2 and CYP3A3/4. Presumably, inhibition of CYP1A2 or CYP3A3/4 enzymes with [citalopram](#) may be dose related (Borba & Henderson, 2000).

### 3.5.1.J Dehydroepiandrosterone

1) Interaction Effect: reduced effectiveness of [clozapine](#)

2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/deciliter (mcg/dL) are conducive to optimal treatment of patients with [psychosis](#) (Howard, 1992a). In case reports, patients have been resistant to antipsychotics when DHEA levels were elevated (Howard, 1992a). Patients being treated with [clozapine](#) should avoid DHEA supplementation.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and [clozapine](#). If DHEA is elevated, treatment with [dexamethasone](#) 1 mg orally per day may be used to normalize DHEA levels.

7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness to [clozapine](#)

#### 8) Literature Reports

a) A 24-year-old female diagnosed with [schizophrenia](#) was resistant to daily doses of [haloperidol](#) 20 milligrams (mg), [fluphenazine](#) 40 mg, [lithium](#) carbonate 1200 mg, and [lithium](#) carbonate 900 mg plus [thioridazine](#) 300 mg. The patient appeared Cushingoid with moon face, acne, facial hair, abdominal hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA) measured as part of an endocrine panel was 725 micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). [Dexamethasone](#) 1 mg orally at bedtime resulted in substantial improvement within one week. The patient appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. At two weeks, a repeated DHEA level was within normal range (328 mcg/dL). The author concluded that elevated DHEA levels were associated with severe [psychosis](#) resistant to conventional antipsychotic therapy (Howard, 1992).

b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accompanied by heavy use of LSD, hashish, barbiturates, and alcohol. His mental status



included bizarre, disorganized, delusional thinking, auditory and visual hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combativeness. He was diagnosed with [chronic paranoid schizophrenia](#); [schizophrenia](#), chronic undifferentiated type, and [schizoaffective disorder](#), excited type. He was resistant to daily doses of [trifluoperazine](#) 40 mg, [chlorpromazine](#) 400 mg, and [imipramine](#) 100 mg. He was also resistant to combination therapy with [chlorpromazine](#) 400 mg with [thiothixene](#) 80 mg, [thioridazine](#) 1000 mg, [perphenazine](#) 48 mg with [lithium](#) carbonate 1200 mg, [clonazepam](#) 4 mg, and [carbamazepine](#) 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day suppression test with [dexamethasone](#) 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, [psychosis](#) improved and the patient was well-oriented, conversational, and was making good eye contact. Once [dexamethasone](#) was discontinued, rapid decompensation and florid [psychosis](#) ensued despite "substantial amounts of psychotropic medications." DHEA increased to 536 mcg/dL. The author concluded that elevated DHEA levels were associated with florid [psychosis](#) resistant to conventional antipsychotic therapy (Howard, 1992).

### 3.5.1.K Droperidol

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Any drug known to have the potential to prolong the QT interval should not be used together with [droperidol](#). Possible pharmacodynamic interactions can occur between [droperidol](#) and potentially arrhythmogenic agents such as neuroleptics that prolong the QT interval (Prod Info [Inapsine](#)(R), 2001).
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of [droperidol](#) and agents that prolong the QT interval, such as neuroleptics, is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

### 3.5.1.L Encainide

- 1) Interaction Effect: increased plasma concentrations of [clozapine](#) and or class I antiarrhythmic agents
- 2) Summary: Coadministration of [clozapine](#) with other drugs that are metabolized by cytochrome P450 2D6, such as class I antiarrhythmics, should be approached with caution (Prod Info [Clozaril](#)(R), 2002g).
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Concomitant use of [clozapine](#) with other drugs metabolized by cytochrome P450 2D6, such as class I antiarrhythmic agents, may require lower doses than usually prescribed for either [clozapine](#) or the class I antiarrhythmic.
- 7) Probable Mechanism: competitive substrate inhibition

### 3.5.1.M Erythromycin

- 1) Interaction Effect: increased [clozapine](#) serum concentrations and risk of side effects (sedation, incoordination, slurred speech, seizures, hematologic abnormalities)
- 2) Summary: Coadministered [erythromycin](#) may inhibit [clozapine](#) metabolism, resulting in increased [clozapine](#) serum concentrations and [clozapine](#) toxicity (Prod Info [Clozaril](#)(R), 2002i; Cohen et al, 1996a; Funderburg et al, 1994a). Elevated levels of [clozapine](#) have been associated with somnolence, disorientation, dizziness, nausea, seizures, and [leukocytosis](#). It is not known if similar effects will occur when other macrolide antibiotics are given concomitantly with [clozapine](#).

- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor patients for signs and symptoms of [clozapine](#) intoxication (sedation, incoordination, slurred speech, seizures, hematologic abnormalities). Doses of [clozapine](#) may need to be reduced when [erythromycin](#) is added to therapy. Alternatively, consider using [azithromycin](#), which is less likely to interfere with [clozapine](#) metabolism, or a non-macrolide antibiotic.
- 7) Probable Mechanism: inhibition by [erythromycin](#) of hepatic cytochrome P450 3A4 metabolism of [clozapine](#)
- 8) Literature Reports

a) A 32-year-old male was being treated with [clozapine](#) 800 mg daily for [schizophrenia](#). A week after beginning [erythromycin](#) 250 mg four times a day for [pharyngitis](#), he experienced a tonic-clonic seizure followed by a period of [postictal confusion](#). Shortly after the seizure, his [clozapine](#) serum concentration was 1300 mcg/mL. Both [erythromycin](#) and [clozapine](#) were discontinued. Two days later, low-dose [clozapine](#) therapy was initiated and gradually increased to the former dose. With a daily [clozapine](#) dose of 800 mg, his serum concentration was 700 mcg/mL (Funderburg et al, 1994).

b) A 34-year-old male with [schizophrenia](#) was stabilized for three months on a regimen of [clozapine](#) 600 mg daily, [thiothixene](#) 10 mg three times daily, [divalproex](#) sodium 1000 mg three times daily, and [propranolol](#) 20 mg three times daily. Three days before admission, he had started [erythromycin](#) 333 mg three times a day for a lower respiratory infection. The day after beginning [erythromycin](#), the patient experienced increased somnolence, incoordination, and difficulty walking. Two days later, he had slurred speech, increasing disorientation, and [incontinence of urine](#) and stool. On admission, his white blood cell count was  $31 \times 10^9/L$  and his [clozapine](#) serum concentration was 1150 mcg/L. [Clozapine](#) and [erythromycin](#) were discontinued, and intravenous [acyclovir](#), [ampicillin](#), and [ceftriaxone](#) were administered for suspected CNS infection. Four days later, treatment with [clozapine](#) was resumed, with the dose gradually increased to 600 mg daily. His [clozapine](#) serum concentration was 385 mcg/mL and his [leukocyte](#) count was normal. The authors postulated that the mechanism of this interaction was inhibition by [erythromycin](#) of P450 isoenzymes (including CYP2D6 and CYP3A) responsible for [clozapine](#) metabolism (Cohen et al, 1996).

c) [Erythromycin](#) was not found to inhibit the metabolism of a single dose of [clozapine](#) in twelve healthy male volunteers. Each participant received a single dose of [clozapine](#) 12.5 mg alone or in combination with [erythromycin](#) 1500 mg daily in a randomized, crossover manner. No significant differences were observed in the [clozapine](#) area under the concentration-time curve (AUC), half-life, maximum concentration (C<sub>max</sub>), time to C<sub>max</sub> (t<sub>max</sub>), or apparent oral clearance. The authors suggest that cytochrome P450 3A4 (CYP3A4) only plays a minor role in [clozapine](#) metabolism (Hagg et al, 1999). However, [erythromycin](#) steady-state was not reached in this study, and doses of [clozapine](#) used are typically much higher than the starting dose of 12.5 mg.

### 3.5.1.N [Flecainide](#)

- 1) Interaction Effect: increased plasma concentrations of [clozapine](#) and or class I antiarrhythmic agents
- 2) Summary: Coadministration of [clozapine](#) with other drugs that are metabolized by cytochrome P450 2D6, such as class I antiarrhythmics, should be approached with caution (Prod Info [Clozaril](#)(R), 2002g).
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: probable

6) Clinical Management: Concomitant use of [clozapine](#) with other drugs metabolized by cytochrome P450 2D6, such as class I antiarrhythmic agents, may require lower doses than usually prescribed for either [clozapine](#) or the class I antiarrhythmic.

7) Probable Mechanism: competitive substrate inhibition

### 3.5.1.O [Fluoxetine](#)

1) Interaction Effect: an increased risk of [clozapine](#) toxicity (sedation, seizures, hypotension)

2) Summary: With concurrent administration of [fluoxetine](#), increased serum [clozapine](#) concentrations have been reported (Prod Info [Clozaril](#)(R), 2002e; Centorrino et al, 1994a; Centorrino et al, 1996a; Spina et al, 1998a). Certain adverse effects associated with [clozapine](#) are dose-dependent, including sedation (Ayd, 1974) and seizures (Haller & Binder, 1990), and might be expected to occur with concurrent use of these medications.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor the therapeutic efficacy of [clozapine](#) and for any evidence of toxicity, particularly when the daily [clozapine](#) dose exceeds 300 mg or 3.5 mg/kg. Lower [clozapine](#) dosage may be required in some clinical situations.

7) Probable Mechanism: inhibition by [fluoxetine](#) of N-dealkylation and N-oxidation of [clozapine](#) via the cytochrome P450 2D6 enzymatic pathway

8) Literature Reports

a) Subjects receiving concurrent [clozapine](#) and [fluoxetine](#) had 76% higher serum [clozapine](#) concentrations and 61% higher metabolite concentrations on average compared with controls receiving only [clozapine](#). The mean ratio of total drug level ([clozapine](#) plus metabolites) to dose was 60% higher and the mean ratio of concentrations to dose was 75% higher in patients receiving [clozapine](#) and [fluoxetine](#) compared with concentrations in patients receiving [clozapine](#) alone (Centorrino et al, 1994).

b) A study evaluated the serum concentrations of [clozapine](#) and norclozapine, the major metabolite, when given in combination with the selective serotonin reuptake inhibitors (SSRIs) [fluoxetine](#), [paroxetine](#), and [sertraline](#). Eighty outpatients receiving [clozapine](#) all had been diagnosed with [schizophrenia](#) or major affective disorder, and 40 of these patients were receiving an SSRI in combination with [clozapine](#). Of these 40 patients, 14 were receiving [fluoxetine](#), 10 were receiving [sertraline](#), and 16 were receiving [paroxetine](#) therapy. Among the patients on SSRI therapy, serum concentrations of [clozapine](#) and norclozapine were 41.1% and 44.8% higher, respectively, than in matched patients who were not receiving an SSRI. The ratio of [clozapine](#) plus norclozapine concentration to dose was also 37.7% higher in patients receiving SSRIs, indicating [clozapine](#) impaired clearance. The differences between the three SSRIs were minor, and the study groups were too limited for an accurate statistical comparison between the individual SSRIs (Centorrino et al, 1996).

c) A 44-year-old male receiving [fluoxetine](#) and [clozapine](#) was found dead in his yard. The dates of the prescriptions and the number of tablets which remained indicated that he had been taking his medications as prescribed. Autopsy results showed a high therapeutic [fluoxetine](#) concentration (0.7 mcg/mL) and also a high therapeutic norfluoxetine concentration (0.6 mcg/mL). [Fluoxetine](#) found in his gastric contents also indicated that the medication was being taken as directed. The [clozapine](#) blood concentration was in the lethal concentration range (4.9 mcg/mL), but the [clozapine](#) in the gastric contents suggested that the [clozapine](#) was being taken as prescribed and that the patient had not consumed a large overdose amount prior to his death. Other pathological findings included [pulmonary edema](#), visceral vascular congestion, [paralytic ileus](#), [gastroenteritis](#), and [eosinophilia](#),

which are all consistent with [clozapine](#) toxicity. The combined central nervous system, respiratory, and cardiovascular depression caused by these two drugs was sufficient to result in the death of this patient, and his death was ruled to be a [clozapine overdose](#) due to a fatal drug interaction (Ferslew et al, 1998).

**d)** Ten institutionalized schizophrenic patients stabilized on [clozapine](#) therapy for at least one month participated in a prospective study to evaluate the effect of [fluoxetine](#) on [clozapine](#) pharmacokinetics. [Fluoxetine](#) 20 mg once daily was administered for eight consecutive weeks. Mean plasma [clozapine](#) concentrations increased from 348 ng/mL to 550 ng/mL (58%) at week 8. Plasma levels of norclozapine were also increased by 36% (from 280 ng/mL to 381 ng/mL). [Clozapine](#) N-oxide levels rose from 89 ng/mL at baseline to 128 ng/mL, representing a 38% increase. However, these increases in [clozapine](#) and metabolite plasma concentrations were not associated with significant changes in efficacy or safety (Spina et al, 1998).

### 3.5.1.P Fluvoxamine

- 1) Interaction Effect: increased serum [clozapine](#) concentrations
- 2) Summary: Coadministration of [clozapine](#) with [fluvoxamine](#) has been reported to result in increased [clozapine](#) levels and worsening of psychotic symptoms (Prod Info [Clozaril](#)(R), 2002k; Chong et al, 1997c; Jerling et al, 1994a). Extrapyramidal symptoms have also been reported with this drug combination (Kuo et al, 1998a). [Fluvoxamine](#), a potent inhibitor of CYP1A2, may decrease metabolism of [clozapine](#), resulting in increased serum concentrations (Chong et al, 1997c; Wetzel et al, 1998a).
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Clinicians should be aware of a potential interaction between [clozapine](#) and [fluvoxamine](#). If these drugs are given concurrently, monitor patients for increased serum [clozapine](#) concentrations, worsening of [psychosis](#), and the development of extrapyramidal symptoms. Downward dosage adjustments of [clozapine](#) may be necessary.
- 7) Probable Mechanism: inhibition of cytochrome P450 1A2-mediated [clozapine](#) metabolism
- 8) Literature Reports

**a)** Therapeutic drug monitoring data showed higher [clozapine](#) concentration/dose ratios in three of four patients when concurrent [fluvoxamine](#) was used compared with [clozapine](#) alone. In two of these patients, [clozapine](#) concentrations were 5 to 10 times higher when [fluvoxamine](#) was coadministered. One patient experienced adverse effects, including sedation and [urinary incontinence](#). Inhibition of the CYP1A2 enzyme by [fluvoxamine](#) was thought to be the mechanism in this drug interaction (Jerling et al, 1994).

**b)** One study presented two case reports in which addition of a selective serotonin reuptake inhibitor (SSRI) to [clozapine](#) therapy resulted in exacerbation of psychotic symptoms. The first patient, a 26-year old woman with [schizophrenia](#), had been taking [clozapine](#) 175 mg per day. Other medications included [propranolol](#) for [tachycardia](#) and trihexyphenidyl for [hypersalivation](#). After marked improvement in psychotic symptoms but continued compulsive behavior, [sertraline](#) 50 mg per day was added. Within four weeks, the patient's obsessive-compulsive symptoms and psychotic symptoms worsened. Plasma [clozapine](#) concentrations increased from 325 ng/mL before [sertraline](#) therapy to 695 ng/mL after [sertraline](#) therapy. Patient 2, a 24-year old woman with [schizophrenia](#), was placed on a regimen of [clozapine](#) 500 mg per day which was later increased to 600 mg per day. After [fluvoxamine](#) 50 mg per day was started as adjunctive treatment, the patient's [clozapine](#) level rose from 1146 ng/mL before [fluvoxamine](#) treatment to 2750 ng/mL after 28 days of [fluvoxamine](#) treatment. During this time the patient's compulsive symptoms remained unchanged, but psychotic symptoms worsened. The authors postulated that the worsening of psychotic

symptoms could be due to SSRI inhibition of [clozapine](#) metabolism by cytochrome P450 isozymes, or an imbalance of the serotonergic and dopaminergic blockade caused by coadministration the two drugs (Chong et al, 1997b).

c) [Fluvoxamine](#) significantly increased serum levels of [clozapine](#) in 16 patients with [schizophrenia](#). [Clozapine](#) 2.5 to 3 mg/kg/day was given for 14 days, then [fluvoxamine](#) 50 mg daily was added for 14 days. Serum concentrations of [clozapine](#) and two metabolites were measured on days 1, 7, and 14. The increase in [clozapine](#) serum concentration was approximately 3-fold when given with [fluvoxamine](#) compared to [clozapine](#) alone (Wetzel et al, 1998).

d) Two patients experienced the onset of extrapyramidal symptoms (EPS) when [fluvoxamine](#) was added to an existing regimen that included [clozapine](#). The first patient, a 46-year-old male, was stabilized on [clozapine](#) 400 mg daily for more than a year when [fluvoxamine](#) 25 mg daily was started. No signs of EPS were present before [fluvoxamine](#) therapy, and the [clozapine](#) plasma level was 686.2 ng/mL. Four days after [fluvoxamine](#) was initiated, the patient experienced rigidity and an Extrapyramidal Symptom Rating Scale (ESRS) score of 6. Three weeks later, the ESRS had increased to 8 and the [clozapine](#) level was 817.9 ng/mL. [Fluvoxamine](#) was discontinued, and the ESRS score and [clozapine](#) level decreased to 1 and 686.8 ng/mL, respectively, three weeks later. The second patient, a 46-year-old female, was maintained on [clozapine](#) 600 mg daily for more than two years with a plasma level of 1292.5 ng/mL and no signs of EPS. [Fluvoxamine](#) was started at 25 mg daily and six days later she developed moderate [akathisia](#) and tremors (ESRS of 7). Three weeks and six weeks into combination therapy, her [clozapine](#) plasma levels were 1438.2 ng/mL and 1548.9 ng/mL, respectively. The ESRS increased to 9, but the patient preferred the combination therapy due to the efficacy in alleviating psychotic symptoms (Kuo et al, 1998).

### 3.5.1.Q [Fosphenytoin](#)

1) Interaction Effect: decreased [clozapine](#) plasma levels associated with marked worsening of [psychosis](#)  
 2) Summary: [Fosphenytoin](#) is a prodrug of [phenytoin](#) and the same interactions that occur with [phenytoin](#) are expected to occur with [fosphenytoin](#) (Prod Info [Cerebyx](#)(R), 1999). Two case reports (Miller, 1991d) demonstrate that the addition of [phenytoin](#) to [clozapine](#) therapy can reduce steady-state plasma concentrations of [clozapine](#) by 65% to 85%, resulting in increased psychotic symptoms. Subsequent increases in [clozapine](#) dosage may be necessary.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: When adding [fosphenytoin](#) therapy to patients stabilized on [clozapine](#), monitor patient closely for worsening of psychotic symptoms. If needed, increase the [clozapine](#) dose cautiously on basis of psychotic symptoms.

7) Probable Mechanism: increased metabolism of [clozapine](#) due to induction of cytochrome P-450 enzymes by [fosphenytoin](#)

8) Literature Reports

a) Two 29-year-old schizophrenic patients were stabilized on [clozapine](#) therapy. Their [clozapine](#) plasma concentrations decreased and psychotic symptoms markedly worsened after the addition of [phenytoin](#) for seizure activity. [Phenytoin](#) reduced [clozapine](#) plasma concentrations by 65% to 85% and necessitated an increase in [clozapine](#) dosage. The author's possible explanations for the decrease in [clozapine](#) plasma concentrations were a) induction of cytochrome P-450 enzymes by [phenytoin](#), causing increased [clozapine](#) metabolism, b) decreased [clozapine](#) absorption due to [phenytoin](#), and/or c) decreased protein binding of [clozapine](#) making more free drug available for metabolism. If the deterioration in clinical status was not related to the decrease in [clozapine](#) plasma levels, Miller's possible explanations were rebound [psychosis](#) after abruptly decreasing



clozapine at the time of seizure activity, spontaneous fluctuation in illness, postictal exacerbation of preexisting psychosis, or postictal psychosis. The author recommends that clinicians closely monitor clozapine patients for worsening of psychotic symptoms when phenytoin is added to therapy (Miller, 1991c).

### 3.5.1.R Guarana

1) Interaction Effect: increased clozapine levels, (leukopenia, agranulocytosis, and seizures) or increased guarana levels, (headache, insomnia, restlessness, diuresis, tachycardia)

2) Summary: The primary ingredient of guarana is caffeine. Caffeine inhibits CYP1A2, a major metabolic pathway for clozapine, thereby decreasing clozapine metabolism with resultant increased clozapine levels (Hagg et al, 2000a; Carrillo et al, 1998a). Patients who consume caffeine, especially acutely, may be at increased risk for clozapine toxicity. A case report has described an acute psychotic exacerbation in a patient taking clozapine who ingested caffeine acutely (Vainer & Chouinard, 1994a). Patients taking clozapine should take caffeine-containing products with caution to maintain a consistent intake.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Ideally, patients should avoid caffeine-containing products such as guarana as well as coffee, tea, and cola during clozapine treatment. Patients who are unwilling to discontinue caffeine intake should be instructed to maintain consistent intake, and advised of the consequences of abrupt discontinuation (i.e., decreased clozapine levels and decreased effectiveness). Conversely, if a patient has been stabilized on clozapine and initiates a significant intake of caffeine, clozapine metabolism will likely be decreased, resulting in increased clozapine blood levels. Such patients will then be at increased risk for clozapine toxicity that may manifest as leukopenia, agranulocytosis, and seizures.

7) Probable Mechanism: caffeine component of guarana may inhibit metabolism of clozapine or clozapine may also inhibit the metabolism of caffeine

8) Literature Reports

a) In 12 healthy, nonsmoking subjects, caffeine intake increased clozapine area under the curve (AUC) following a single dose of clozapine in a randomized, crossover trial. Subjects refrained from other medication use during and 2 weeks prior to the study. Clozapine was administered as a 12.5 milligram (mg) dose. Dietary caffeine intake was allowed during the caffeine phase but not during the clozapine control phase, and was registered and estimated. Total caffeine intake during the caffeine phase ranged from 500-700 mg on day 1, and 400-1000 mg on day 2 (mean 550 mg/day). In one subject, clozapine AUC was doubled with concomitant caffeine intake, indicating individual variation. Overall, clozapine AUC was increased 19% as a result of caffeine intake (p equal to 0.05), with a range from -14% to +97%. Clozapine clearance was decreased 14% as a result of caffeine intake (p equal to 0.05), with a range from -49% to +7% (Hagg et al, 2000).

b) In a study of 7 hospitalized patients (six men and one woman) averaging 31.0 +/- 5.5 years (range: 25-41 years) with a DSM-IV diagnosis of schizophrenia, clozapine levels decreased when caffeine was removed from the diet. All patients received monotherapy with clozapine at 271 +/- 102 milligrams/day (mg/day). Clozapine, norclozapine, and clozapine-N-oxide were assayed in plasma by high-performance liquid chromatography. Assays were conducted at three time points: with concomitant intake of caffeine, 5 days after caffeine withdrawal, and 2 weeks after rechallenge with habitual caffeine intake (mean caffeine intake: 296.4 +/- 354.8 mg; range: 150-1100 mg daily). Clozapine levels decreased from 486 nanograms/milliliter (ng/mL) during initial concomitant intake to 306 ng/mL (-47%) (p less than 0.02) 5 days after a caffeine-free diet. Clozapine-N-oxide levels decreased from 66 to 49 ng/mL (-31%) (p less than 0.03). All parameters returned to initial values after 2 weeks of resumption of caffeine intake (Carrillo et al, 1998).



- c) In a study of 14 healthy volunteers, [clozapine](#) metabolism was found to co-vary with CYP1A2 activity as determined by concomitant [caffeine](#) metabolism. Subjects were administered [caffeine](#) 150 mg as an oral tablet with [clozapine](#) 10 mg orally. N1- and N7-demethylation indices of [caffeine](#) correlated with [clozapine](#) clearance ( $r$  (s) equal to 0.89 and 0.85;  $p$  equal to 0.0013 and 0.0023, respectively). The authors conclude that 70% of the variance of [clozapine](#) clearance was accounted for by [caffeine](#) N3-demethylation reflecting CYP1A2 activity. There was no correlation between the area under the curve (AUC) for [clozapine](#) and the [caffeine](#) indices of xanthine oxidase ( $r$ (s) equal to -0.32) or N-acetyl transferase ( $r$ s equal to -0.33) activity (Bertilsson et al, 1994).
- d) [Supraventricular tachycardia](#) (SVT) was reported in a 66-year-old woman administered [clozapine](#) and [caffeine](#) while receiving [electroconvulsive therapy](#) (ECT). The patient suffered from severe, recurrent, affect [psychosis](#) necessitating ECT. During her first course of ECT, the duration of seizures decreased, requiring [caffeinesodium benzoate](#) 1000 mg (titrated from an initial dose of 125 mg). Although [arrhythmias](#) are a known side effect of ECT, none occurred, including none during augmentation with [caffeine](#). Despite an initial response, the patient relapsed and was started on [clozapine](#), titrated to a dosage of 300 mg daily. After one week, ECT was re-instituted with [caffeinesodium benzoate](#) titrated to 500 mg by the ninth treatment. The patient developed SVT with a heart rate of 180 beats/minute. The patient responded to [verapamil](#) 5 mg intravenously, converting to [sinus tachycardia](#) at 102 beats/minute and recovered uneventfully. Interestingly, 1000 mg intravenous [caffeine](#) augmentation was tolerated during the first course of therapy but 500 mg was not tolerated during the course of therapy accompanied by [clozapine](#) administration. This is suggestive of a caffeine-clozapine interaction (Beale et al, 1994).
- e) A 39-year-old man with [paranoid schizophrenia](#) with long-standing refractoriness to neuroleptics was treated with [clozapine](#) titrated up to 150 mg daily within 6 months of initiation. [Clozapine](#) was taken with two cups of coffee and the patient experienced a short-lasting acute psychotic exacerbation characterized by marked anxiety, agitation, insomnia, weakness, headaches, generalized stiffness, and intense [paranoid ideation](#). These acute reactions were completely prevented when water replaced coffee. The acute episodes resumed when he took 200 mg/day [clozapine](#) with a caffeinated cola (40-50mg [caffeine](#) in each 12-ounce bottle). When taken with a decaffeinated cola beverage, the patient had no [acute psychotic episodes](#) (Vainer & Chouinard, 1994).

### 3.5.1.S [Hydromorphone](#)

- 1) Interaction Effect: an increase in CNS or [respiratory depression](#)
- 2) Summary: The concomitant use of [hydromorphone](#) and other CNS depressants, such as antipsychotics, may result in additive CNS depressant effects, including [respiratory depression](#), hypotension, profound sedation, and coma. When administering [hydromorphone](#) and an antipsychotic together, dose reduction of one or both of the medications should be considered (Prod Info EXALGO(R) extended release oral tablets, 2010).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [hydromorphone](#) and other CNS depressants, such as antipsychotics, may result in [respiratory depression](#), hypotension, profound sedation, and coma. When concomitant use is required, dose reduction of one or both medications should be considered (Prod Info EXALGO(R) extended release oral tablets, 2010).
- 7) Probable Mechanism: additive effects

### 3.5.1.T [Lithium](#)

- 1) Interaction Effect: weakness, [dyskinesias](#), increased extrapyramidal symptoms, [encephalopathy](#), and brain damage
- 2) Summary: An encephalopathic syndrome followed by irreversible brain damage has occurred in a few patients treated with [lithium](#) plus a [dopamine-2](#) antagonist, particularly [haloperidol](#). A causal relationship between these events and the concomitant administration of a [dopamine-2](#) antagonist and [lithium](#) has not been established (Prod Info [LITHOBID](#)(R) slow-release oral tablets, 2005). Coadministration of [lithium](#) and a number of antipsychotic drugs has caused a wide variety of encephalopathic symptoms, brain damage, extrapyramidal symptoms, and [dyskinesias](#) in isolated case reports. In most cases, these effects have occurred with therapeutic [lithium](#) levels (Amdisen, 1982; Prakash, 1982; Addonizio et al, 1988a). However, many series and trials have reported using such combinations with no severe adverse consequences (Goldney & Spence, 1986). The mechanism is not fully understood, but chronic [lithium](#) treatment decreases neostriatal dopaminergic activity, probably through a direct action on the G protein and the capacity of the G proteins, once activated, to stimulate adenylyl cyclase (Carli et al, 1994). Hyperglycemic reactions have also occurred during combined phenothiazine and [lithium](#) use (Zall et al, 1968).
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor patients closely for any signs of toxicity or extrapyramidal symptoms, especially if high doses of [dopamine-2](#) antagonists, particularly [haloperidol](#), and [lithium](#) are used. Serum [lithium](#) levels should be monitored periodically. Some clinicians advocate maintaining levels in the low therapeutic range.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

- a) Concomitant [haloperidol](#) and [lithium](#) therapy has resulted in symptoms of [encephalopathy](#), confusion, extrapyramidal symptoms, and fever in several patients with mania (Cohen & Cohen, 1974; Loudon & Waring, 1976; Thomas, 1979). Irreversible [neurological injuries](#) have been reported (Sandyk & Hurwitz, 1983; Keitner & Rahman, 1984).
- b) Seizures, [encephalopathy](#), [delirium](#), and abnormal EEG occurred in four patients during combined [lithium](#) and [thioridazine](#) therapy (Spring, 1979). Serum [lithium](#) levels were below 1 mEq/L at the time of the toxic reaction in all cases. All patients had previously tolerated [lithium](#) in combination with another phenothiazine. Three of these patients developed symptoms within eight days of initiating combination therapy.
- c) The addition of [lithium](#) to [neuroleptic therapy](#) exacerbated extrapyramidal symptoms (EPS) in a small study (Addonizio et al, 1988). The patients had received at least five days of treatment with either oral [thiothixene](#), [haloperidol](#), or [fluphenazine](#) in mean doses of 607.5 [chlorpromazine](#) equivalents prior to initiation of the [lithium](#) and were experiencing drug-induced extrapyramidal symptoms. Oral [lithium](#) was added when clinically indicated in sufficient doses to achieve a therapeutic serum concentration. The maximum levels attained were 0.65 to 1.27 mEq/L. The EPS ratings increased in all ten patients following the addition of [lithium](#). However, only three patients developed marked symptoms and no patient developed [lithium](#) toxicity. Significantly increased symptoms included gait, shoulder shaking, elbow rigidity, and tremor.
- d) Ten patients treated with [clozapine](#) and [lithium](#) were studied (Blake et al, 1992). Of the ten patients, four experienced significant neurologic effects, including jerking of limbs, [facial spasms](#) and tics, tremor of hands and arms, tongue twitching, and stumbling gait. One of these also experienced [delirium](#). These effects reversed when [lithium](#) was discontinued or given at a lower dose. On rechallenge, one of two patients suffered recurrence of symptoms. By keeping serum [lithium](#) no greater than 0.5 mEq/L, [clozapine](#) could be safely coadministered.

e) **Chlorpromazine** serum levels can be significantly reduced in the presence of **lithium** treatment. If used concurrently, abrupt cessation of **lithium** may result in rebound elevation of **chlorpromazine** levels, resulting in **chlorpromazine** toxicity. In patients on a lithium-chlorpromazine combination, abrupt withdrawal of the **lithium** may precipitate **chlorpromazine** cardiotoxicity. In this report, such toxicity was manifested as sudden **ventricular fibrillation** associated with prolongation of the QTc interval. Hypotension and EPS are also possible in this situation (Stevenson et al, 1989).

f) However, other data do not support that such adverse events are frequent or indeed causally related to combination therapy. Combination of **dopamine** antagonist antipsychotic drugs and **lithium** have been used successfully in many patients with **manic-depressive illness**. It has been proposed that the interaction may only become significant with very high doses of one or both drugs or with failure to discontinue dosing in the presence of toxic symptoms (Miller & Menninger, 1987).

g) A 69-year-old patient with oxygen-dependent **chronic obstructive pulmonary disorder** and a 25-year history of **bipolar disorder** was started on **risperidone** 3 mg for the treatment of new-onset auditory and visual hallucinations. She had also been maintained on a regimen of **lithium** (450 mg daily) for more than 10 years. In addition, she was given **amantadine** (100 mg twice daily) for tremor. Three weeks after the start of **risperidone**, the patient experienced a decline in mental status in addition to dizziness, worsening tremors, nausea and vomiting, polyuria, depression, and visual and auditory hallucinations. She was then admitted to the hospital for **delirium**. Her **lithium** serum level was 1.36 mEq/L at the time of the admission. All medications were discontinued. Although her **lithium** level decreased to 0.41 mEq/L, she continued to experience profound **delirium**, tremors, lethargy, and hallucinations for almost one week. After she started to respond to commands, she was restarted on **lithium** (300 mg at bedtime) because of the onset of mild **hypomania**. Five days later, she was discharged with a regimen of **lithium** and low-dose **lorazepam** for treatment of insomnia. It is suggested that **delirium** could have been caused by the concurrent use of **lithium** and **risperidone**. Other factors could also have caused **delirium**, such as the patient's serum **lithium** level and the underlying **pulmonary pathology**. In addition, **amantadine**, which facilitates the release of presynaptic **dopamine** and has a mild anticholinergic effect, may have contributed (Chen & Cardasis, 1996).

### 3.5.1.U **Lorazepam**

1) Interaction Effect: CNS depression

2) Summary: Two cases have been reported in which concomitant use of **clozapine** and **lorazepam** resulted in marked sedation, **excessive salivation**, and ataxia (Cobb et al, 1991). The manufacturer advises caution when giving **clozapine** with a benzodiazepine (Prod Info **Clozaril**(R), 1997).

3) Severity: minor

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Monitor for signs of intoxication (eg, marked sedation, dizziness, ataxia, weakness, decreased cognition or motor performance, **excessive salivation**). If symptoms are present, reduce **lorazepam** dose.

7) Probable Mechanism: additive

### 3.5.1.V **Lorcainide**

1) Interaction Effect: increased plasma concentrations of **clozapine** and or class I antiarrhythmic agents

2) Summary: Coadministration of **clozapine** with other drugs that are metabolized by cytochrome P450 2D6, such as class I antiarrhythmics, should be approached with caution (Prod Info **Clozaril**(R), 2002g).

3) Severity: moderate

- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Concomitant use of [clozapine](#) with other drugs metabolized by cytochrome P450 2D6, such as class I antiarrhythmic agents, may require lower doses than usually prescribed for either [clozapine](#) or the class I antiarrhythmic.
- 7) Probable Mechanism: competitive substrate inhibition

### 3.5.1.W Mate

- 1) Interaction Effect: inhibition of [clozapine](#) metabolism (increasing the risk for [leukopenia](#), [agranulocytosis](#), and seizures) or inhibition of mate metabolism (headache, insomnia, restlessness, diuresis, [tachycardia](#))
- 2) Summary: One of the primary ingredients of mate is [caffeine](#). [Caffeine](#) inhibits CYP1A2, a major metabolic pathway for [clozapine](#), thereby decreasing [clozapine](#) metabolism with resultant increased [clozapine](#) levels (Hagg et al, 2000c; Carrillo et al, 1998c). Patients who consume [caffeine](#), especially acutely, may be at increased risk for [clozapine](#) toxicity. A case report has described an acute psychotic exacerbation in a patient taking [clozapine](#) who ingested [caffeine](#) acutely (Vainer & Chouinard, 1994c). Patients taking [clozapine](#) should take caffeine-containing products with caution to maintain a consistent intake.
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Ideally, patients should avoid caffeine-containing products such as mate as well as coffee, tea, and cola during [clozapine](#) treatment. Patients who are unwilling to discontinue [caffeine](#) intake should be instructed to maintain consistent intake, advising them of the consequences of abrupt discontinuation (i.e., decreased [clozapine](#) levels and decreased effectiveness). Conversely, if a patient has been stabilized on [clozapine](#) and initiates a significant intake of [caffeine](#), [clozapine](#) metabolism will likely be decreased, resulting in increased [clozapine](#) blood levels. Such patients will then be at increased risk for [clozapine](#) toxicity that may manifest as [leukopenia](#), [agranulocytosis](#), and seizures.
- 7) Probable Mechanism: [caffeine](#) inhibits CYP1A2 activity and can increase [clozapine](#) levels; [caffeine](#) was also found to inhibit [clozapine](#) clearance
- 8) Literature Reports

a) In 12 healthy, nonsmoking subjects, [caffeine](#) intake increased [clozapine](#) area under the curve (AUC) following a single dose of [clozapine](#) in a randomized, crossover trial. Subjects refrained from other medication use during and 2 weeks prior to the study. [Clozapine](#) was administered as a 12.5 milligram (mg) dose. Dietary [caffeine](#) intake was allowed during the [caffeine](#) phase but not during the [clozapine](#) control phase, and was registered and estimated. Total [caffeine](#) intake during the [caffeine](#) phase ranged from 500-700 mg on day 1, and 400-1000 mg on day 2 (mean 550 mg/day). In one subject, [clozapine](#) AUC was doubled with concomitant [caffeine](#) intake, indicating individual variation. Overall, [clozapine](#) AUC was increased 19% as a result of [caffeine](#) intake (p equal to 0.05), with a range from -14% to +97%. [Clozapine](#) clearance was decreased 14% as a result of [caffeine](#) intake (p equal to 0.05), with a range from -49% to +7% (Hagg et al, 2000b).

b) In a study of 7 hospitalized patients (six men and one woman) averaging 31.0 +/- 5.5 years (range: 25-41 years) with a DSM-IV diagnosis of [schizophrenia](#), [clozapine](#) levels decreased when [caffeine](#) was removed from the diet. All patients received monotherapy with [clozapine](#) at 271 +/- 102 milligrams/day (mg/day). [Clozapine](#), norclozapine, and clozapine-N-oxide were assayed in plasma by [high-performance liquid chromatography](#). Assays were conducted at three time points: with concomitant intake of [caffeine](#), 5 days after [caffeine](#) withdrawal, and 2 weeks after rechallenge with habitual [caffeine](#) intake (mean [caffeine](#) intake: 296.4 +/- 354.8 mg; range: 150-1100 mg daily). [Clozapine](#) levels decreased from 486 nanograms/milliliter (ng/mL) during initial concomitant

intake to 306 ng/mL (-47%) (p less than 0.02) 5 days after a caffeine-free diet. In a similar fashion, clozapine-N-oxide levels decreased from 66 to 49 ng/mL (-31%) (p less than 0.03). All parameters returned to initial values after 2 weeks of resumption of caffeine intake (Carrillo et al, 1998b).

c) In a study of 14 healthy volunteers, clozapine metabolism was found to co-vary with CYP1A2 activity as determined by concomitant caffeine metabolism. Subjects were administered caffeine 150 mg as an oral tablet with clozapine 10 mg orally. N1- and N7-demethylation indices of caffeine correlated with clozapine clearance (rs equal to 0.89 and 0.85; p equal to 0.0013 and 0.0023, respectively). The authors conclude that 70% of the variance of clozapine clearance was accounted for by caffeine N3-demethylation reflecting CYP1A2 activity. There was no correlation between the area under the curve (AUC) for clozapine and the caffeine indices of xanthine oxidase (rs equal to -0.32) or N-acetyl transferase (rs equal to -0.33) activity (Bertilsson et al, 1994a).

d) Supraventricular tachycardia (SVT) was reported in a 66-year-old woman administered clozapine and caffeine while receiving electroconvulsive therapy (ECT). The patient suffered from severe, recurrent, affect psychosis necessitating ECT. During her first course of ECT, the duration of seizures decreased, requiring caffeine-sodium benzoate 1000 mg (titrated from an initial dose of 125 mg). Although arrhythmias are a known side effect of ECT, none occurred, including none during augmentation with caffeine. Despite an initial response, the patient relapsed and was started on clozapine, titrated to a dosage of 300 mg daily. After one week, ECT was re-instituted with caffeine-sodium benzoate titrated to 500 mg by the ninth treatment. The patient developed SVT with a heart rate of 180 beats/minute. The patient responded to verapamil 5 mg intravenously, converting to sinus tachycardia at 102 beats/minute and recovered uneventfully. Interestingly, 1000 mg intravenous caffeine augmentation was tolerated during the first course of therapy but 500 mg was not tolerated during the course of therapy accompanied by clozapine administration. This is suggestive of a caffeine-clozapine interaction (Beale et al, 1994a).

e) A 39-year-old man with paranoid schizophrenia with long-standing refractoriness to neuroleptics was treated with clozapine titrated up to 150 mg daily within 6 months of initiation. Clozapine was taken with two cups of coffee and the patient experienced a short-lasting acute psychotic exacerbation characterized by marked anxiety, agitation, insomnia, weakness, headaches, generalized stiffness, and intense paranoid ideation. These acute reactions were completely prevented when water replaced coffee. The acute episodes resumed when he took 200 mg/day clozapine with a caffeinated cola (40-50mg caffeine in each 12-ounce bottle). When taken with a decaffeinated cola beverage, the patient had no acute psychotic episodes (Vainer & Chouinard, 1994b).

f) Caffeine-induced reinforcement of dopaminergic enhancement may predispose some patients to exacerbations of psychosis. Caffeine elimination does not appear to improve or worsen schizophrenia. Chronic use of caffeine may lead to tolerance of adverse effects (Hughes et al, 1998).

### 3.5.1.X Metoclopramide

- 1) Interaction Effect: an increased risk of extrapyramidal reactions or neuroleptic malignant syndrome
- 2) Summary: Concomitant use of metoclopramide with antipsychotic agents may increase the risk of extrapyramidal symptoms, such as tardive dyskinesia or neuroleptic malignant syndrome, and is contraindicated (Prod Info REGLAN(R) oral tablets, 2009). If concurrent therapy is required, monitor patients for signs and symptoms of extrapyramidal reactions or neuroleptic malignant syndrome (fever, sweating, confusion, muscle stiffness). Discontinue metoclopramide if patient develops signs and symptoms of extrapyramidal reactions. Injection of diphenhydramine 50 mg intramuscularly or benztropine 1 to 2 mg intramuscularly may reverse the extrapyramidal reactions (Prod Info METOZOLV ODT orally disintegrating tablets, 2009).
- 3) Severity: contraindicated
- 4) Onset: unspecified



5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [metoclopramide](#) with antipsychotic agents is contraindicated (Prod Info [REGLAN](#)(R) oral tablets, 2009). If concurrent therapy is required, monitor patients for signs and symptoms of extrapyramidal reactions or [neuroleptic malignant syndrome](#) (fever, sweating, confusion, muscle stiffness). Discontinue [metoclopramide](#) if patient develops signs and symptoms of extrapyramidal reactions or [neuroleptic malignant syndrome](#). Injection of [diphenhydramine](#) 50 mg intramuscularly or [benztropine](#) 1 to 2 mg intramuscularly may reverse the extrapyramidal reactions (Prod Info METOZOLV ODT orally disintegrating tablets, 2009).

7) Probable Mechanism: unknown

### 3.5.1.Y Milnacipran

1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)

2) Summary: Concomitant use of milnacipran and an antipsychotic may result in [hypertension](#), coronary artery vasoconstriction or [serotonin syndrome](#), which may be life-threatening. When concomitant use of milnacipran and an antipsychotic is required, caution should be used. If symptoms of [serotonin syndrome](#) develop (eg, restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea), treatment should be immediately discontinued and the appropriate supportive therapy initiated (Prod Info SAVELLA(R) oral tablets, 2010).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of milnacipran and an antipsychotic may result in [hypertension](#) and coronary artery vasoconstriction through additive serotonergic effects. Therefore, use caution when coadministering these agents. If symptoms of [serotonin syndrome](#) develop, discontinue treatment immediately and institute the appropriate supportive symptomatic treatment (Prod Info SAVELLA(R) oral tablets, 2010).

7) Probable Mechanism: additive serotonergic effect

### 3.5.1.Z Nefazodone

1) Interaction Effect: increased [clozapine](#) plasma concentrations and [clozapine](#) toxicity (sedation, seizures, hypotension)

2) Summary: A study reported [clozapine](#) concentrations increased by an average of 19 mcg/L (4% of baseline) and noreclozapine concentrations increased by 46 mcg/L (16% of baseline) (Taylor et al, 1999a). Concomitant administration of [nefazodone](#) resulted in decreased clearance resulting in elevated plasma concentrations of [clozapine](#) and noreclozapine in a 40-year-old male. Seven days after initiation of treatment with [nefazodone](#), the patient was increasingly anxious, increasingly dizzy and had mild hypotension. [Nefazodone](#) dose reduction resolved the patient's hypotension and other symptoms. [Nefazodone](#) may cause a modest, dose-dependent reduction in the clearance of both [clozapine](#) and noreclozapine, with resultant increases in serum concentrations. The author suggests that this effect may be due to [nefazodone](#) inhibition of the cytochrome P450 3A4 isoenzyme. Caution is suggested when prescribing [nefazodone](#) concomitantly with [clozapine](#) (Khan & Preskorn, 2001a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable



6) Clinical Management: Monitor the therapeutic efficacy of [clozapine](#) and for any evidence of toxicity, particularly when the daily [clozapine](#) dose exceeds 300 mg or 3.5 mg/kg. Lower [clozapine](#) dosage may be required in some clinical situations.

7) Probable Mechanism: inhibition of cytochrome P450-mediated [clozapine](#) metabolism by [nefazodone](#)

#### 8) Literature Reports

a) Concomitant administration of [nefazodone](#) may result in decreased clearance resulting in elevated plasma concentrations of [clozapine](#) and noreclozapine. A 40-year-old male with a history of [schizophrenia](#) was successfully treated with [clozapine](#) and [risperidone](#) for several years. After experiencing persistent negative symptoms, [nefazodone](#) was initiated at 200 mg/day for seven days and then increased to 300 mg/day. Seven days later, the patient reported increased anxiety and dizziness. Physical exam revealed mild hypotension. An increase in plasma concentrations and decrease in clearance of both [clozapine](#) and noreclozapine was documented. [Nefazodone](#) dose was reduced to 200 mg/day and, within one week, the patient's symptoms and hypotension resolved. [Nefazodone](#) may cause a modest, dose-dependent reduction in the clearance of both [clozapine](#) and noreclozapine, with resultant increases in serum concentrations. The author suggests that this effect may be due to [nefazodone](#) inhibition of the cytochrome P450 3A4 isoenzyme. Caution is suggested when prescribing [nefazodone](#) concomitantly with [clozapine](#) (Khan & Preskorn, 2001).

b) Six patients receiving a stable dose of [clozapine](#) for at least two weeks were selected to begin [nefazodone](#) therapy at 100 mg twice daily for one week and then 200 mg daily for two more weeks. The overall changes in [clozapine](#) pharmacokinetics were minimal when [nefazodone](#) was coadministered. [Clozapine](#) concentrations increased by an average of 19 mcg/L (4% of baseline) and noreclozapine concentrations increased by 46 mcg/L (16% of baseline). Cytochrome P450 3A4 (CYP3A4) has been postulated to play a significant role in the metabolism of [clozapine](#). [Nefazodone](#) is an inhibitor of CYP3A4. Because this study failed to show a significant interaction between these two drugs, CYP3A4 may play only an insignificant role in the metabolism of [clozapine](#), or alternative routes of metabolism may be activated when CYP3A4 is inhibited (Taylor et al, 1999).

#### 3.5.1.AA Nicotine

1) Interaction Effect: decreased plasma [clozapine](#) levels

2) Summary: Concomitant administration of agents known to induce cytochrome P450 enzymes such as nicotine, may decrease the plasma levels of [clozapine](#). This may result in a decrease in effectiveness of a previously effective [clozapine](#) dose (Prod Info [Clozaril](#)(R), 2002d).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Observe patients for signs and symptoms of decreased [clozapine](#) efficacy when nicotine is added to [clozapine](#).

7) Probable Mechanism: induction of cytochrome P450-mediated [clozapine](#) metabolism by nicotine

#### 3.5.1.AB Norfloxacin

1) Interaction Effect: increased [clozapine](#) serum concentrations

2) Summary: In vitro studies have shown that quinolones, including [norfloxacin](#), are CYP1A2 inhibitors. Concomitant use with [clozapine](#), a CYP1A2 substrate, may result in increased [clozapine](#) serum levels when given in usual doses. Caution is advised if these agents are used together. Monitor patients closely for signs and symptoms of [clozapine](#) intoxication (Prod Info [NOROXIN](#)(R) oral tablets, 2006).

3) Severity: moderate

4) Onset: unspecified

- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [clozapine](#) and [norfloxacin](#) may result in increased [clozapine](#) serum levels when given in usual doses. Use caution if these agents are used together and monitor patients closely (Prod Info [NOROXIN\(R\)](#) oral tablets, 2006). Signs and symptoms of [clozapine](#) intoxication may include sedation, incoordination, slurred speech, seizures, hematologic abnormalities.
- 7) Probable Mechanism: inhibition of CYP1A2-mediated [clozapine](#) metabolism

### 3.5.1.AC [Paroxetine](#)

- 1) Interaction Effect: an increased risk of [clozapine](#) toxicity (sedation, seizures, hypotension)
- 2) Summary: Increased serum concentrations of [clozapine](#) and its metabolites have been observed when it is given with serotonin reuptake inhibitors; however, other published reports describe [paroxetine](#) having no effect on serum concentrations of [clozapine](#) or its metabolites (Prod Info [Clozaril\(R\)](#), 2002n; Centorrino et al, 1996e; Wetzel et al, 1998c).
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor for signs of [clozapine](#) toxicity or serum concentrations when [paroxetine](#) is given concomitantly.
- 7) Probable Mechanism: decreased [clozapine](#) metabolism
- 8) Literature Reports

a) [Paroxetine](#) had no significant effect on serum levels of [clozapine](#) in 14 patients with [schizophrenia](#). [Clozapine](#) 2.5 to 3 mg/kg/day was given for 14 days, then [paroxetine](#) 20 mg daily was added for 14 days. Serum concentrations of [clozapine](#) and two metabolites were measured on days 1, 7, and 14. Over the course of this study there was no significant difference in serum concentrations of [clozapine](#) or its metabolites (Wetzel et al, 1998b).

b) Serum concentrations of [clozapine](#) and norclozapine, the major metabolite, were evaluated when given in combination with the selective serotonin reuptake inhibitors (SSRIs) [fluoxetine](#), [paroxetine](#), and [sertraline](#). Eighty outpatients receiving [clozapine](#) all had been diagnosed with [schizophrenia](#) or major affective disorder, and 40 of these patients were receiving an SSRI in combination with [clozapine](#). Of these 40 patients, 14 were receiving [fluoxetine](#), 10 were receiving [sertraline](#), and 16 were receiving [paroxetine](#) therapy. Among the patients on SSRI therapy, serum concentrations of [clozapine](#) and norclozapine were 41.1% and 44.8% higher, respectively, than in matched patients who were not receiving an SSRI. The ratio of [clozapine](#) plus norclozapine concentration to dose was also 37.7% higher in patients receiving SSRIs, indicating [clozapine](#) impaired clearance. The differences between the three SSRIs were minor, and the study groups were too limited for an accurate statistical comparison between the individual SSRIs (Centorrino et al, 1996d).

### 3.5.1.AD [Perphenazine](#)

- 1) Interaction Effect: increased plasma concentrations of [clozapine](#) and or the phenothiazine
- 2) Summary: Coadministration of [clozapine](#) with other drugs that are metabolized by cytochrome P450 2D6, such as phenothiazines, should be approached with caution (Prod Info [Clozaril\(R\)](#), 2002b).
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Concomitant use of [clozapine](#) with other drugs metabolized by cytochrome P450 2D6, such as phenothiazines, may require lower doses than usually prescribed for either [clozapine](#) or the phenothiazine.

## 7) Probable Mechanism: competitive substrate inhibition

**3.5.1.AE Phenobarbital**

- 1) Interaction Effect: decreased [clozapine](#) plasma levels associated with marked worsening of [psychosis](#)
- 2) Summary: [Clozapine](#) levels have been reported to be markedly elevated when [phenobarbital](#) therapy was discontinued (Lane et al, 1998a). Two case reports (Miller, 1991) demonstrate that the addition of [phenytoin](#), another enzyme inducer, to [clozapine](#) therapy can reduce steady-state plasma concentrations of [clozapine](#) by 65% to 85%, resulting in increased psychotic symptoms. [Phenobarbital](#) is capable of inducing multiple cytochrome P450 enzyme systems, including CYP1A2 and CYP3A4. Because [clozapine](#) is metabolized primarily by CYP1A2, a significant interaction with [phenobarbital](#) is possible (Lane et al, 1998a). A study conducted with 22 schizophrenic patients revealed 35% lower [clozapine](#) concentrations when given concurrently with [phenobarbital](#), versus [clozapine](#) administration alone. In addition, the [clozapine](#) N-oxide metabolite concentrations were 64% higher, supporting the theory that [phenobarbital](#) induces [clozapine](#) metabolism (Facciola et al, 1998a).
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: When adding [phenobarbital](#) therapy to patients stabilized on [clozapine](#), monitor patient closely for worsening of psychotic symptoms. If needed, increase the [clozapine](#) dose cautiously on the basis of psychotic symptoms. Conversely, when discontinuing [phenobarbital](#), levels of [clozapine](#) may increase significantly.
- 7) Probable Mechanism: increased metabolism of [clozapine](#) due to induction of cytochrome P450 enzymes by [phenobarbital](#)
- 8) Literature Reports

a) A 26-year-old male schizophrenic patient was stabilized on [clozapine](#) 300 mg twice daily when he experienced a seizure. [Phenobarbital](#) 60 mg daily was initiated, and the [clozapine](#) dose was decreased to 400 mg daily over a period of two months because of the patient's stable mental status. One month after the [clozapine](#) dose was at 400 mg daily, the plasma levels for [clozapine](#) and its major metabolites, desmethylclozapine and clozapine-N-oxide were 346 ng/mL, 241 ng/mL, and 65 ng/mL, respectively. [Phenobarbital](#) therapy was tapered off over one month. Two and four weeks after the discontinuation of [phenobarbital](#), the [clozapine](#), desmethylclozapine, and clozapine-N-oxide levels were 608 ng/mL and 602 ng/mL, 253 ng/mL and 280 ng/mL, and 87 ng/mL and 96 ng/mL, respectively. The increase in the plasma levels of [clozapine](#) and its metabolites may be due to the fact that [phenobarbital](#) is an inducer of cytochrome P450 1A2 enzymes, and discontinuing [phenobarbital](#) slowed the metabolism of [clozapine](#) (Lane et al, 1998).

b) Steady-state plasma concentrations of [clozapine](#) and its two major metabolites were compared in 22 schizophrenic patients. Patients were distributed into two groups, either receiving [clozapine](#) monotherapy, or [clozapine](#) plus [phenobarbital](#). The two groups were matched for age, sex, body weight, and daily dosage of [clozapine](#). The group receiving combined therapy demonstrated mean plasma concentrations of [clozapine](#) which were 35% lower than the monotherapy group. In addition, the mean [clozapine](#) N-oxide metabolite concentrations were 64% higher in the combined therapy group. The authors concluded that these findings support the theory that [phenobarbital](#) induces metabolism of [clozapine](#), and recommended careful monitoring of [clozapine](#) plasma concentrations when combined with [phenobarbital](#) (Facciola et al, 1998).

**3.5.1.AF Phenylalanine**

- 1) Interaction Effect: increased incidence of [tardive dyskinesia](#)

2) Summary: Taking [phenylalanine](#) concomitantly with certain neuroleptic drugs may exacerbate [tardive dyskinesia](#) (Gardos et al, 1992a). Abnormal [phenylalanine](#) metabolism in certain patients may lead to [phenylalanine](#) accumulation in the brain and in turn, reduced brain availability of other large neutral amino acids. This may interfere with the synthesis of catecholamines (Gardos et al, 1992a).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Caution is advised if [phenylalanine](#) is administered with a neuroleptic agent. Monitor the patient closely for signs of [tardive dyskinesia](#).

7) Probable Mechanism: reduced brain availability of other large neutral amino acids and interference with catecholamine synthesis

8) Literature Reports

a) [Phenylalanine](#) tended to increase the incidence of [tardive dyskinesia](#) in patients taking neuroleptics in an open study. Three groups of patients were studied: (1) patients with [unipolar depression](#) with [tardive dyskinesia](#) (n=11), (2) patients with no [tardive dyskinesia](#) with current or past exposure to greater than or equal to 100 milligrams (mg) of a [chlorpromazine](#) equivalent for at least 3 months (n=10), and (3) patients with no [tardive dyskinesia](#) not previously exposed to a neuroleptic drug (n=10). Neuroleptic agents were taken during the study by 6 patients in group 1, and 5 patients in group 2. Patients received powdered [phenylalanine](#) 100 mg/kilogram dissolved in orange juice after an overnight fast. Blood samples were obtained just prior to [phenylalanine](#) administration and 2 hours after administration. Three patients in group 1 (with [tardive dyskinesia](#)) had the highest postloading [phenylalanine](#) plasma levels, this group as a whole had higher (though nonsignificant) mean [phenylalanine](#) levels than the other groups. [Tardive dyskinesia](#) score (measured using the [Abnormal Involuntary Movements Scale \(AIMS\)](#)) nonsignificantly increased in group 1. Postloading [phenylalanine](#) level and postloading AIMS scores were significantly positively correlated in group 1 (rs=0.347, p less than 0.05; Spearman correlation coefficient 0.543, p less than 0.05). Postloading [phenylalanine](#) level and baseline AIMS scores demonstrated a trend toward correlation (rs=0.246, p=0.092; Spearman correlation coefficient 0.679, p less than 0.05). In all patients, [phenylalanine](#) loading increased plasma [phenylalanine](#) levels approximately eight-fold, and plasma tyrosine increased 2.5 times as a result of conversion of [phenylalanine](#) to tyrosine. Plasma levels of competing large neutral amino acids such as tryptophan decreased slightly (Gardos et al, 1992).

### 3.5.1.AG [Phenytoin](#)

1) Interaction Effect: decreased [clozapine](#) plasma levels associated with marked worsening of [psychosis](#)

2) Summary: Concomitant administration of drugs known to induce cytochrome P450 enzymes may decrease the [clozapine](#) plasma levels, resulting in a decrease in effectiveness of a previously effective [clozapine](#) dose (Prod Info [Clozaril\(R\)](#), 2002m). Two case reports (Miller, 1991b) demonstrate that the addition of [phenytoin](#) to [clozapine](#) therapy can reduce steady-state plasma concentrations of [clozapine](#) by 65% to 85%, resulting in increased psychotic symptoms. Subsequent increases in [clozapine](#) dosage may be necessary.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When adding [phenytoin](#) therapy to patients stabilized on [clozapine](#), monitor patient closely for worsening of psychotic symptoms. If needed, increase the [clozapine](#) dose cautiously on basis of psychotic symptoms. Conversely, when [phenytoin](#) is discontinued, levels of [clozapine](#) may significantly increase.

- 7) Probable Mechanism: increased metabolism of [clozapine](#) due to induction of cytochrome P-450 enzymes by [phenytoin](#)
- 8) Literature Reports

a) Two 29-year-old schizophrenic patients were stabilized on [clozapine](#) therapy. Their [clozapine](#) plasma concentrations decreased and psychotic symptoms markedly worsened after the addition of [phenytoin](#) for seizure activity. [Phenytoin](#) reduced [clozapine](#) plasma concentrations by 65% to 85% and necessitated an increase in [clozapine](#) dosage. The author's possible explanations for the decrease in [clozapine](#) plasma concentrations were a) induction of cytochrome P-450 enzymes by [phenytoin](#), causing increased [clozapine](#) metabolism, b) decreased [clozapine](#) absorption due to [phenytoin](#), and/or c) decreased protein binding of [clozapine](#) making more free drug available for metabolism. If the deterioration in clinical status was not related to the decrease in [clozapine](#) plasma levels, Miller's possible explanations were rebound [psychosis](#) after abruptly decreasing [clozapine](#) at the time of seizure activity, spontaneous fluctuation in illness, postictal exacerbation of preexisting [psychosis](#), or postictal [psychosis](#). The author recommends that clinicians closely monitor [clozapine](#) patients for worsening of psychotic symptoms when [phenytoin](#) is added to therapy (Miller, 1991a).

### 3.5.1.AH [Propafenone](#)

- 1) Interaction Effect: increased plasma concentrations of [clozapine](#) and or class I antiarrhythmic agents
- 2) Summary: Coadministration of [clozapine](#) with other drugs that are metabolized by cytochrome P450 2D6, such as class I antiarrhythmics, should be approached with caution (Prod Info [Clozaril](#)(R), 2002g).
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Concomitant use of [clozapine](#) with other drugs metabolized by cytochrome P450 2D6, such as class I antiarrhythmic agents, may require lower doses than usually prescribed for either [clozapine](#) or the class I antiarrhythmic.
- 7) Probable Mechanism: competitive substrate inhibition

### 3.5.1.AI [Quinidine](#)

- 1) Interaction Effect: increased plasma concentrations of [clozapine](#)
- 2) Summary: Coadministration of [clozapine](#) and [quinidine](#) should be approached with caution. Quinidine inhibits cytochrome P450 2D6, the isozyme that also metabolizes [clozapine](#) (Prod Info [Clozaril](#)(R), 2002f).
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Concomitant use of [clozapine](#) with drugs that inhibit cytochrome P450 2D6, such as [quinidine](#), should be approached with caution.
- 7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of [clozapine](#) by [quinidine](#).

### 3.5.1.AJ [Rifampin](#)

- 1) Interaction Effect: subtherapeutic concentrations of [clozapine](#) and decreased [clozapine](#) efficacy
- 2) Summary: Concomitant administration of drugs known to induce cytochrome P450 enzymes may decrease the [clozapine](#) plasma levels, resulting in a decrease in effectiveness of a previously effective [clozapine](#) dose (Prod Info [CLOZARIL](#)(R) oral tablets, 2005). Case reports have shown subtherapeutic

clozapine concentrations, with decreased clozapine efficacy during concomitant administration with rifampin (Joos et al, 1998; Peritogiannis et al, 2007).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Use caution when prescribing rifampin to patients who take clozapine as there have been reports of decreased clozapine levels and efficacy with concomitant use (Joos et al, 1998; Peritogiannis et al, 2007). Monitor clozapine levels when rifampin therapy is added, changed, or discontinued.

7) Probable Mechanism: induction of CYP450-mediated clozapine metabolism by rifampin

8) Literature Reports

a) A 33-year-old male schizophrenic patient was controlled on clozapine therapy for a few years when a chest X-ray revealed an opacity in the right lower quadrant. Rifampin, isoniazid, and pyrazinamide therapy was instituted for suspected tuberculosis. Within three and a half weeks, the patient became restless and sleepless, and clozapine serum concentrations were found to have significantly decreased to a subtherapeutic range. The dose of clozapine was increased from 400 mg daily to 600 mg daily without clinical improvement of the patient's psychosis. Rifampin therapy was substituted with ciprofloxacin when the opportunistic infection was found to be mycobacterium xenopi, and within three days the clozapine serum concentration increased back to a therapeutic level (Joos et al, 1998).

b) A case report described loss of clozapine efficacy following concomitant rifampin administration in a 30-year-old male schizophrenic. The patient had been initiated on clozapine for paranoid schizophrenia. Following problems with clozapine's adverse events (sedation, hypersalivation) at therapeutically successful doses, he had been controlled on clozapine therapy for 3 months at 300 mg daily when he was diagnosed with pulmonary tuberculosis. The patient was started on rifampin monotherapy at 600 mg daily. Two weeks later, the patient no longer complained of sedation and hypersalivation, but his psychotic symptoms worsened. At the end of the month, his psychopathology was as severe as when clozapine was first initiated. The dose of clozapine was increased to 550 mg daily with only mild improvement. However, the patient complained of no adverse events and was compliant with therapy. Following discontinuation of rifampin after 6 months of therapy, sedation and hypersalivation reappeared within 1 week. The dose of clozapine was not decreased to below 500 mg daily due to the marked improvement in the patient's psychotic symptoms. Induction of the CYP450-mediated clozapine metabolism was postulated as a probable mechanism. However, clozapine plasma levels were not available for confirmation due to laboratory difficulties (Peritogiannis et al, 2007).

### 3.5.1.AK Risperidone

1) Interaction Effect: decreased risperidone clearance

2) Summary: The manufacturer reports that clozapine may decrease risperidone clearance with chronic combined use (Prod Info Risperdal(R) Consta(TM), 2003).

3) Severity: minor

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Monitor patients for increased adverse effects of risperidone when these drugs are given concurrently.

7) Probable Mechanism: unknown

### 3.5.1.AL Ritonavir



- 1) Interaction Effect: increased [clozapine](#) plasma concentrations and [clozapine](#) toxicity (sedation, seizures, hypotension)
- 2) Summary: When coadministering [ritonavir](#) with [clozapine](#), a cytochrome P450 3A4 substrate, substantial increases in concentrations of [clozapine](#) may occur, possibly requiring a dosage reduction of [clozapine](#) (less than 50%) (Prod Info [Norvir\(R\)](#), 2000).
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor the therapeutic efficacy of [clozapine](#) and for any evidence of toxicity, particularly when the daily [clozapine](#) dose exceeds 300 mg or 3.5 mg/kg. Lower [clozapine](#) dosage may be required in some clinical situations.
- 7) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated [clozapine](#) metabolism by [ritonavir](#)

### 3.5.1.AM [Saquinavir](#)

- 1) Interaction Effect: increased risk of QT and/or PR interval prolongation
- 2) Summary: [Clozapine](#) use has been associated with ECG repolarization changes, which usually normalize upon discontinuation of therapy (Prod Info [FAZACLO\(R\)](#) orally disintegrating tablets, 2010). Prolongation of the QT and PR intervals were observed with ritonavir-boosted [saquinavir](#) therapy and rare cases of [torsade de pointes](#) were reported in postmarketing evaluations. Due to the potential for additive effects on the QT and/or PR interval, concomitant use of ritonavir-boosted [saquinavir](#) and [clozapine](#) should be considered only when no alternatives are available and the potential benefits outweigh the potential risks. Do not initiate concomitant therapy in patients with a baseline QT interval of greater than 450 milliseconds. In patients with a baseline QT interval of less than 450 milliseconds, perform an on-treatment ECG approximately 3 to 4 days after therapy is initiated. During concomitant therapy, if a subsequent QT interval reading is greater than 480 milliseconds or has increased by more than 20 milliseconds from baseline, evaluate whether to discontinue either [clozapine](#) or ritonavir-boosted [saquinavir](#) or both (Prod Info [INVIRASE\(C\)](#) oral capsules, tablets, 2010).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Due to the potential for additive effects on the QT and/or PR interval, caution is advised if ritonavir-boosted [saquinavir](#) is coadministered with [clozapine](#). These drugs should be used concomitantly only when no alternatives are available and the potential benefits outweigh the potential risks. Do not initiate concomitant therapy in patients with a baseline QT interval of greater than 450 milliseconds. In patients with a baseline QT interval of less than 450 milliseconds, perform an on-treatment ECG approximately 3 to 4 days after therapy is initiated. During concomitant therapy, if a subsequent QT interval reading is greater than 480 milliseconds or has increased by more than 20 milliseconds from baseline, evaluate whether to discontinue either [clozapine](#) or ritonavir-boosted [saquinavir](#) or both (Prod Info [INVIRASE\(C\)](#) oral capsules, tablets, 2010).
- 7) Probable Mechanism: additive effects on QT and/or PR interval prolongation

### 3.5.1.AN [Sertraline](#)

- 1) Interaction Effect: an increased risk of [clozapine](#) toxicity (sedation, seizures, hypotension)
- 2) Summary: Coadministration of [clozapine](#) with [sertraline](#) has been reported to result in increased [clozapine](#) concentrations and worsening of psychotic symptoms (Prod Info [Clozaril\(R\)](#), 2002h; Chong et al, 1997a; Centorrino et al, 1996c). Clozapine is metabolized by the cytochrome P450 2D6 isoenzyme (CYP2D6). Sertraline is considered a moderate to weak inhibitor of this isoenzyme, in addition to being metabolized by CYP2D6 itself (Prod Info [Zoloft\(R\)](#), 1999; DeVane, 1994). Cytochrome P450 3A4 may

also be involved with [clozapine](#) metabolism, and [sertraline](#) also inhibits CYP3A4 (Chong & Remington, 1998).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor the therapeutic efficacy of [clozapine](#) and for any evidence of toxicity, particularly when the daily [clozapine](#) dose exceeds 300 mg or 3.5 mg/kg. Lower [clozapine](#) dosage may be required in some clinical situations.

7) Probable Mechanism: decreased [clozapine](#) metabolism

8) Literature Reports

a) Two case reports revealed the exacerbation of psychotic symptoms with the addition of a selective serotonin reuptake inhibitor (SSRI) to [clozapine](#). The first patient, a 26-year old woman with [schizophrenia](#), had been taking [clozapine](#) 175 mg per day. Other medications included [propranolol](#) for [tachycardia](#) and trihexyphenidyl for [hypersalivation](#). After marked improvement in psychotic symptoms but continued compulsive behavior, [sertraline](#) 50 mg per day was added. Within four weeks, the patient's obsessive-compulsive symptoms and psychotic symptoms worsened. Plasma [clozapine](#) concentrations increased from 325 ng/mL before [sertraline](#) therapy to 695 ng/mL after [sertraline](#) therapy. Patient 2, a 24-year old woman with [schizophrenia](#), was placed on a regimen of [clozapine](#) 500 mg per day which was later increased to 600 mg per day. After [fluvoxamine](#) 50 mg per day was started as adjunctive treatment, the patient's [clozapine](#) level rose from 1146 ng/mL before [fluvoxamine](#) treatment to 2750 ng/mL after 28 days of [fluvoxamine](#) treatment. During this time the patient's compulsive symptoms remained unchanged, but psychotic symptoms worsened. The authors postulated that the worsening of psychotic symptoms could be due to SSRI inhibition of [clozapine](#) metabolism by cytochrome P450 isozymes, or an imbalance of the serotonergic and dopaminergic blockade caused by coadministration of the two drugs (Chong et al, 1997).

b) A study evaluated the serum concentrations of [clozapine](#) and norclozapine, the major metabolite, when given in combination with the selective serotonin reuptake inhibitors (SSRI) [fluoxetine](#), [paroxetine](#), and [sertraline](#). Eighty outpatients receiving [clozapine](#) all had been diagnosed with [schizophrenia](#) or major affective disorder, and 40 of these patients were receiving an SSRI in combination with [clozapine](#). Of these 40 patients, 14 were receiving [fluoxetine](#), 10 were receiving [sertraline](#), and 16 were receiving [paroxetine](#) therapy. Among the patients on SSRI therapy, serum concentrations of [clozapine](#) and norclozapine were 41.1% and 44.8% higher, respectively, than in matched patients who were not receiving an SSRI. The ratio of [clozapine](#) plus norclozapine concentration to dose was also 37.7% higher in patients receiving SSRIs, indicating [clozapine](#) impaired clearance. The differences between the three SSRIs were minor, and the study groups were too limited for an accurate statistical comparison between the individual SSRIs (Centorrino et al, 1996b).

### 3.5.1.AO St John's Wort

1) Interaction Effect: reduced [clozapine](#) efficacy

2) Summary: This interaction is based on in vitro information that St. John's Wort induced CYP1A2 enzymes, and a case report of a patient experiencing reduced blood [theophylline](#) concentrations and loss of efficacy (Nebel et al, 1999). Since [clozapine](#) is metabolized by CYP1A2 enzymes, like [theophylline](#), [clozapine](#) may be similarly affected. If St. John's Wort and [clozapine](#) are taken together, their dosages should be consistently administered, recognizing that increased dosages of [clozapine](#) may be required. Discontinuation of St. John's Wort should be done carefully as side effects of [clozapine](#) may increase and dose reduction may be required.

- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid concomitant use of [clozapine](#) with St. John's Wort. If patients elect to remain on St. John's Wort, they should maintain consistent dosing. [Clozapine](#) dosage may need to be increased. Patients should not discontinue St. John's Wort without first consulting their clinician as downward adjustments in [clozapine](#) dose may be necessary as well as monitoring for increased side effects of [clozapine](#) (e.g. decreased white blood cell count, increased salivation, orthostatic hypotension, [tachycardia](#), sedation, seizures).
- 7) Probable Mechanism: induction of cytochrome P450 1A2 enzymes by St. John's Wort

#### 3.5.1.AP Thioridazine

- 1) Interaction Effect: increased plasma concentrations of [clozapine](#) and or the phenothiazine
- 2) Summary: Coadministration of [clozapine](#) with other drugs that are metabolized by cytochrome P450 2D6, such as phenothiazines, should be approached with caution (Prod Info [Clozaril\(R\)](#), 2002b).
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Concomitant use of [clozapine](#) with other drugs metabolized by cytochrome P450 2D6, such as phenothiazines, may require lower doses than usually prescribed for either [clozapine](#) or the phenothiazine.
- 7) Probable Mechanism: competitive substrate inhibition

#### 3.5.1.AQ Tramadol

- 1) Interaction Effect: an increased risk of seizures
- 2) Summary: Seizures have been reported in patients using [tramadol](#). The manufacturer of [tramadol](#) states that combining neuroleptic medications with [tramadol](#) may enhance the risk of seizures (Prod Info [Ultram\(R\)](#), 1998).
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Caution should be used if [tramadol](#) is to be administered to patients receiving [neuroleptic therapy](#). If possible, avoid this combination, especially in patients with underlying conditions that might predispose to seizures.
- 7) Probable Mechanism: unknown

#### 3.5.1.AR Vandetanib

- 1) Interaction Effect: an increased risk of QT interval prolongation and [Torsades de pointes](#)
- 2) Summary: Vandetanib can prolong the QT interval in a concentration-dependent manner. [Torsades de pointes](#), [ventricular tachycardia](#), and sudden death have been reported in patients taking vandetanib. The concomitant administration of vandetanib and other drugs that prolong the QT interval should be avoided. If these drugs must be coadministered, monitor ECG more frequently. If the corrected QT interval (Fridericia; QTcF) is greater than 500 milliseconds, discontinue therapy until QTcF returns to less than 450 milliseconds. Dosing can then be resumed at a reduced dose (Prod Info [CAPRELSA\(R\)](#) oral tablets, 2011).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use of vandetanib and drugs that prolong the QT interval as it may result in additive effects on the QT interval and an increased risk of **Torsades de pointes** and **ventricular tachycardia**. If these agents must be given together, monitor ECG more frequently. If the corrected QT interval (Fridericia; QTcF) is greater than 500 milliseconds, discontinue therapy until QTcF returns to less than 450 milliseconds and can then resume at a reduced dose (Prod Info CAPRELSA(R) oral tablets, 2011).

7) Probable Mechanism: additive effects on the QT interval prolongation

### 3.5.1.AS Venlafaxine

1) Interaction Effect: increased serum concentrations of **clozapine** and **venlafaxine**

2) Summary: Coadministration of **clozapine** with other drugs that are metabolized by cytochrome P450 2D6, such as antidepressants, should be approached with caution (Prod Info **Clozaril**(R), 2002c). The hepatic P450IID6 isoenzyme is apparently involved with **clozapine** metabolism. **Venlafaxine** is a weak inhibitor of this isoenzyme, in addition to being metabolized by cytochrome P450IID6 itself (Prod Info **Effexor**(R) XR, 1999; Ellingrod & Perry, 1994). With clozapine-venlafaxine coadministration, both agents may competitively inhibit the other's metabolism resulting in enhanced serum concentrations of both. Controlled studies are needed to validate these expectations and to document the clinical impact.

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Monitor patients receiving concurrent **clozapine** and **venlafaxine** for signs of **clozapine** toxicity (dizziness, sedation, vomiting, hypotension, hematologic abnormalities) and **venlafaxine** toxicity (somnolence). Doses of either or both medications may need to be reduced.

7) Probable Mechanism: decreased **clozapine** and **venlafaxine** metabolism

### 3.5.1.AT Zotepine

1) Interaction Effect: increased risk of seizures

2) Summary: Zotepine used concurrently with neuroleptics may increase the risk of seizures (Prod Info Nipolept(R), 1994; Hori et al, 1992).

3) Severity: major

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Monitoring for seizures is particularly important in those patients who: (1) are taking large doses of zotepine; (2) have a history of seizure disorders; (3) are of young age; or (4) have a past history of **brain injury**.

7) Probable Mechanism: unknown

## 3.5.2 Drug-Food Combinations

### 3.5.2.A Caffeine

1) Interaction Effect: an increased risk of **clozapine** toxicity (sedation, seizures, hypotension)

2) Summary: **Caffeine** may significantly inhibit the metabolism of **clozapine** when ingested in quantities ranging from 400 mg to 1000 mg daily. Caffeine is metabolized by cytochrome P450 1A2 (CYP1A2) enzymes, which are also responsible for the metabolism of **clozapine**. Because of dose-dependent **caffeine** pharmacokinetics, **clozapine** clearance is reduced when **caffeine** is ingested in moderate to high quantities (Prod Info **Clozaril**(R), 2002o; Hagg et al, 2000e).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Patients receiving [clozapine](#) therapy should be advised to avoid changes in habitual [caffeine](#) intake. Variations in [caffeine](#) ingestion should be considered when [clozapine](#) concentrations fluctuate.

7) Probable Mechanism: inhibition of cytochrome P450 1A2-mediated [clozapine](#) metabolism

8) Literature Reports

a) Twelve healthy nonsmoking male volunteers took part in an investigation to determine whether [caffeine](#) affects the pharmacokinetics of [clozapine](#). In both phases of the randomized cross-over study, single doses of [clozapine](#) 12.5 mg were administered after an overnight fast. During the [caffeine](#) phase, subjects received [caffeine](#) 100 mg as an oral tablet in addition to dietary [caffeine](#) intake. The mean [caffeine](#) ingestion was 550 mg daily. The [clozapine](#) area under the concentration-time curve (AUC) increased by 19% while the oral clearance decreased by 14% during the [caffeine](#) phase. However, in one subject, the AUC was nearly doubled, indicating that certain individuals may be more predisposed to this interaction than others (Hagg et al, 2000d).

## 4.0 Clinical Applications

[Monitoring Parameters](#)

[Patient Instructions](#)

[Place In Therapy](#)

[Mechanism of Action / Pharmacology](#)

[Therapeutic Uses](#)

[Comparative Efficacy / Evaluation With Other Therapies](#)

### 4.1 Monitoring Parameters

#### A) Therapeutic

##### 1) Physical Findings

a) Decrease in signs and symptoms of [psychoses](#)

b) One small study (n=15) suggests that weight gain is a predictor of long-term (21 months) [clozapine](#) efficacy in treatment-resistant schizophrenic patients. Further studies are needed (Jalenques et al, 1996).

##### 2) SERUM LEVEL

a) A decrease of 40% or more in the plasma level of [clozapine](#) from baseline values (baseline value determined when patient was free from positive symptoms for at least 4 months) for an extended period may be a predictor of [relapse](#) of schizophrenic [psychosis](#). Eight of 12 patients who exhibited such "at-risk" plasma [clozapine](#) levels for more than 8.6 months during the study period (12% of the study interval) had [relapses](#), while 2 of 11 patients who exhibited "at-risk" plasma levels for less than 8.6 months relapsed. [Relapse](#) rates were the same for the 2 groups for the first 2 years but after that increased rapidly in the group with the longer exposure to "at risk" plasma [clozapine](#) levels (Gaertner et al, 2001).

#### B) Toxic

##### 1) Laboratory Parameters

a) [AGRANULOCYTOSIS](#)

**1)** A white blood cell (WBC) count and an absolute neutrophil count (ANC) should be obtained before beginning therapy. Do not start therapy if the WBC count is less than 3500 cells/cubic millimeter (mm<sup>3</sup>), if the ANC is less than 2000 cells/mm<sup>3</sup>, or if the patient has a history of a myeloproliferative disorder or previous clozapine-induced granulocytopenia or agranulocytosis (Prod Info CLOZARIL(R) Tablets, 2005)). Sandoz Australia guidelines prohibit initiation of clozapine treatment in patients with a WBC count less than  $3 \times 10^9$  cells/L and/or a neutrophil count less than  $1.5 \times 10^9$  cells/L (Prod Info Clozaril(R) Australia, 1996).

**2)** Repeat WBC counts and ANC should be obtained weekly during the first 6 months of clozapine therapy. If the WBC count remains greater than or equal to 3500cells/mm<sup>3</sup> and the ANC remains greater than or equal to 2000cells/mm<sup>3</sup>, then WBC and ANC may be monitored every 2 weeks for the next 6 months. Thereafter, if acceptable WBC counts and ANC have been maintained during the second 6 months of continuous therapy, WBC count and ANC can be monitored every 4 weeks. Weekly WBC counts and ANC should be continued for at least 4 weeks after the discontinuation of clozapine or until WBC count is greater than or equal to 3500/mm<sup>3</sup> and ANC is greater than or equal to 2000/mm<sup>3</sup> (Prod Info CLOZARIL(R) Tablets, 2005).

**3)** For interruptions in therapy, the following guidelines should be used for reinitiation of monitoring white blood cell counts (see below for guidelines on restarting therapy with specific abnormal blood counts) (Prod Info Clozaril(R), 2002):

Length of Therapy	Length of Break	History of Abnormal Blood Event (WBC less than 3500 cells/mm <sup>3</sup> or ANC less than 2000 cells/mm <sup>3</sup> )	Reco (*red perm coun equal is gr 2000
Less than 6 months	Less than 1 month	No	Cont week Rest testin Wee then week Wee mon to ev mon Wee then week Wee mon for 6 to ev
Less than 6 months	Greater than 1 month	No	
6 to 12 months	Less than 1 month	No	
6 to 12 months	Greater than 1 month	No	
Greater than 12 months	Less than 1 month	No	
Greater than 12 months	Greater than 1 month	No	

\* Transition to reduced monitoring frequency only if all WBC  $\geq 3500$  AND  $\geq 2000$

**4)** If there is a substantial drop in WBC or ANC after starting therapy, a repeat WBC count and ANC should be done. A substantial drop is considered to be a single drop or cumulative drop within a 3-week period of 3000 more in the WBC count or 1500 or more of ANC. If the



repeat WBC count and ANC reveal a total WBC count between 3000 and 3500 cells/mm(3) and an ANC above 2000 cells/mm(3), WBC counts and ANC should be monitored twice weekly (Prod Info CLOZARIL(R) Tablets, 2005); (Prod Info Clozaril(R) Australia, 1996).

5) If mild leukopenia (WBC count is 3000/mm(3) or greater but less than 3500/mm(3)) and/or mild granulocytopenia (ANC is 1000/mm(3) or greater but less than 1500/mm(3)) develop, monitoring should be twice-weekly until WBC count is greater than 3500/mm(3) and ANC is greater than 2000/mm(3). At this point, return to previous monitoring (Prod Info CLOZARIL(R) Tablets, 2005).

6) If moderate leukopenia (WBC count is 2000/mm(3) or greater but less than 3000/mm(3)) and/or moderate granulocytopenia (ANC is 1000/mm(3) or greater but less than 1500/mm(3)) develop, therapy should be interrupted. Monitor daily until WBC are greater than 3000/mm(3) and ANC is greater than 1500/mm(3), then twice-weekly until WBC is greater than 3500/mm(3) and ANC is greater than 2000/mm(3). Rechallenge may occur when WBC are greater than 3500/mm(3) and ANC is greater than 2000/mm(3). If rechallenged, monitor weekly for 1 year before returning to the usual monitoring schedule of every 2 weeks for 6 months and then every 4 weeks indefinitely (Prod Info CLOZARIL(R) Tablets, 2005).

7) If the total WBC count falls below 2000 cells/mm(3) and/or the ANC falls below 1000 cells/mm(3), clozapine therapy should be discontinued and patient should not be rechallenged. WBC counts and ANC should be monitored daily until WBC are greater than 3000 cells/mm(3) and the ANC returns to levels above 1500 cells/mm(3). Twice-weekly WBC counts and ANC should be taken until the total WBC counts return to levels above 3500 cells/mm(3) and ANC return to levels above 2000/mm(3). After WBC are greater than 3500/mm(3), monitor weekly (Prod Info CLOZARIL(R) Tablets, 2005).

#### **b) PLASMA LEVEL**

1) If an infectious, hypersensitivity, or inflammatory process is suspected, clozapine plasma levels should be closely monitored and the clozapine dose may need to be reduced by up to 50%. Toxic clozapine levels of 1100 to 2400 micrograms/liter (mcg/L) have been reported in several cases. However, toxic effects are possible at plasma levels of 1000 mcg/L and higher; and adverse effects are twice as likely at concentrations above 350 mcg/L (de Leon & Diaz, 2003; Haack et al, 2003).

### **2) Physical Findings**

#### **a) AGRANULOCYTOSIS**

1) Monitor for any signs of infection including lethargy, weakness, fever, or sore throat (Prod Info CLOZARIL(R) Tablets, 2005).

#### **b) CARDIOMYOPATHY**

1) Signs and symptoms suggestive of cardiomyopathy include: exertional dyspnea, fatigue, orthopnea, paroxysmal nocturnal dyspnea and peripheral edema. If the diagnosis of cardiomyopathy is confirmed, discontinue clozapine unless the benefit to the patient clearly outweighs the risk (Prod Info CLOZARIL(R) Tablets, 2005).

#### **c) DIABETES MELLITUS**

1) Monitor patients with an established diagnosis of diabetes mellitus for worsening of glucose control during treatment with an atypical antipsychotic. Patients with risk factors

for diabetes mellitus (ie, obesity, family history of diabetes) who are beginning treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically throughout treatment (Prod Info CLOZARIL(R) Tablets, 2005).

**d) HYPERGLYCEMIA**

**1)** Monitor patients for signs and symptoms of hyperglycemia (ie, polydipsia, polyuria, polyphagia, and weakness). Patients who exhibit symptoms of hyperglycemia during atypical antipsychotic treatment should undergo fasting blood glucose testing. In some instances, hyperglycemia has resolved when the atypical antipsychotic was stopped; however, some patients required ongoing antidiabetic treatment despite discontinuation of the suspect medication (Prod Info CLOZARIL(R) Tablets, 2005).

**e) MYOCARDITIS**

**1)** If tachycardia develops, particularly during the first month of treatment, monitor closely for signs of myocarditis. Patients who present with unexplained fatigue, dyspnea, tachypnea, fever, chest pain, palpitations, ST-T wave abnormalities, arrhythmias, or other signs or symptoms of heart failure should also be evaluated for myocarditis (Prod Info CLOZARIL(R) Tablets, 2005).

**f) SEIZURE ACTIVITY**

**1)** Patients who receive clozapine should be monitored for seizure activity, especially if there is a history of seizures or predisposing factors (Prod Info CLOZARIL(R) Tablets, 2005).

**3) IMPORTANT NOTE**

**a)** In the United States, the Clozaril(R) Patient Management System was phased out in May 1991 (Anon, 1991). Information on monitoring for [agranulocytosis](#) is available from the manufacturer (Prod Info [CLOZARIL\(R\) Tablets](#), 2005).

**4.2 Patient Instructions**

**A) Clozapine (By mouth)**

**Clozapine**

Treats [schizophrenia](#). Also used to prevent risk of suicidal behavior from occurring again in patients with [schizophrenia](#) or [schizoaffective disorder](#).

When This Medicine Should Not Be Used:

You should not use this medicine if you have had an [allergic reaction](#) to [clozapine](#). You should not use this medicine if you have certain blood problems, a [bone marrow disorder](#), uncontrolled seizures ([epilepsy](#)), bowel blockage, certain nervous system problems, or certain heart problems. Do not breastfeed while you are using this medicine.

How to Use This Medicine:

Tablet, Dissolving Tablet

Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed several times in order to find out what works best for you. Do not use more medicine or use it more often than your doctor tells you to.

You may take this medicine with or without food.

Drink extra fluids so you will pass more urine while you are using this medicine. This will keep your kidneys working well and help prevent kidney problems.

If you are using the disintegrating tablet, make sure your hands are dry before you handle the tablet. Do not open the blister pack that contains the tablet until you are ready to take it. Remove the tablet from the blister pack by [peeling](#) back the foil, then taking the tablet out. Do not push the tablet through the foil. Place the tablet in your mouth. It should melt quickly. After the tablet has melted, swallow or take a drink of water. The disintegrating tablets may also be chewed.

#### If a Dose is Missed:

If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next dose, wait until then to use the medicine and skip the missed dose. Do not use extra medicine to make up for a missed dose.

If for any reason you stop taking [clozapine](#) for longer than 2 days, do not start back on the same dose. Ask your doctor what dose you should take.

#### How to Store and Dispose of This Medicine:

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.

Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after you have finished your treatment. You will also need to throw away old medicine after the expiration date has passed.

Keep all medicine away from children and never share your medicine with anyone.

#### Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

There are many other drugs that can interact with [clozapine](#). Make sure your doctor knows about all other medicines you are using.

Make sure your doctor knows if you are using [carbamazepine](#) ([Tegretol](#)®), [cimetidine](#) ([Tagamet](#)®), [ciprofloxacin](#) ([Cipro](#)®), [erythromycin](#) ([Ery-tab](#)®), [fluvoxamine](#) ([Luvox](#)®), [paroxetine](#) ([Paxil](#)®), [phenytoin](#) ([Dilantin](#)®), [quinidine](#), or [rifampin](#) ([Rifadin](#)®, [Rimactane](#)®). Tell your doctor if you are using [atropine](#), [dicyclomine](#) ([Bentyl](#)®), [glycopyrrolate](#) ([Robinul](#)®), [hyoscyamine](#) ([Cystospaz](#)®), [propantheline](#) ([Pro-Banthine](#)®), or [scopolamine](#) ([Transderm Scop](#)®).

Make sure your doctor knows if you are also using medicine to lower blood pressure (such as [atenolol](#), [hydrochlorothiazide](#) [[HCTZ](#)], [lisinopril](#), [metoprolol](#), [quinapril](#), [Accupril](#)®, [Cozaar](#)®, [Diovan](#)®, [Lotrel](#)®, [Norvasc](#)®, [Toprol](#)®, or [Zestril](#)®) or medicine for heart rhythm problems (such as [flecainide](#), [encainide](#), [propafenone](#), [Rythmol](#)®, or [Tambocor](#)®).

Tell your doctor if you are also using other medicine to treat mental illness (such as [chlorpromazine](#), [haloperidol](#), [risperidone](#), [thioridazine](#), [Haldol](#)®, [Mellaril](#)®, [Risperdal](#)®, or [Thorazine](#)®), medicine to treat anxiety (such as [alprazolam](#), [clonazepam](#), [Ativan](#)®, [Valium](#)®, or [Xanax](#)®), medicine for nausea or vomiting (such as [prochlorperazine](#), [promethazine](#), [Compazine](#)®, or [Phenergan](#)®), or medicine to treat depression (such as [citalopram](#), [fluoxetine](#), [sertraline](#), [venlafaxine](#), [Celexa](#)®, [Effexor](#)®, [Prozac](#)®, or [Zoloft](#)®). Tell your doctor if you are smoking tobacco or drinking caffeine-containing products.

Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and allergy medicine, narcotic pain relievers, and sedatives.

Do not drink alcohol while you are using this medicine.

#### Warnings While Using This Medicine:

Make sure your doctor knows if you are pregnant or if you ever had [neuroleptic malignant syndrome](#) (NMS). Tell your doctor if you have [kidney disease](#), liver disease (including [hepatitis](#)), blood vessel problems, [heart disease](#), [heart failure](#), heart rhythm problems, low blood pressure, lung disease, an enlarged prostate, or a problem with your bowels (such as constipation). Tell your doctor if you have [glaucoma](#), if you have ever had a head injury, or if you have a history of seizures or [stroke](#).

Tell your doctor if you have [diabetes](#), because this medicine may raise your blood sugar.

Tell your doctor if you have [phenylketonuria](#). The orally disintegrating tablet contains [phenylalanine](#), which can make this condition worse.

This medicine lowers the number of some [types of blood](#) cells in your body. Because of this, you may bleed or get infections more easily. To help with these problems, avoid being near people who are sick or have infections. Wash your hands often. Stay away from rough sports or other situations where you could be bruised, cut, or injured. Brush and floss your teeth gently. Be careful when using sharp objects, including razors and fingernail clippers.

This medicine can cause drowsiness or seizures. Avoid driving, swimming, climbing, using machines, or doing anything else that could be dangerous if you are not alert. You may also feel lightheaded when getting up suddenly from a lying or sitting position, so stand up slowly.

Stop using this medicine and contact your doctor as soon as possible if you have chest pain or discomfort, a fast heartbeat, trouble breathing, or fever and chills. These can be symptoms of a very serious problem with your heart.

Your doctor will need to check your blood at regular visits while you are using this medicine. Be sure to keep all appointments. If you do not have your scheduled blood test, you may not be given your next week's supply of this medicine.

This medicine is not approved to treat behavior disorders in older people who have [dementia](#). Using this medicine to treat this problem could increase the risk of death. This risk has not been shown for the approved uses of this medicine.

Stop using this medicine and contact your doctor as soon as possible if you have chest pain or discomfort, a fast heartbeat, trouble breathing, or fever and chills. These can be symptoms of a very serious problem with your heart.

Check with your doctor right away if you are having convulsions (seizures); difficulty with breathing; fast heartbeat; high fever; high or low blood pressure; increased sweating; [loss of bladder control](#); severe muscle stiffness; unusually pale skin; or tiredness. These could be symptoms of a serious condition called [neuroleptic malignant syndrome](#) (NMS).

[Tardive dyskinesia](#) (a movement disorder) may occur and may not go away after you stop using the medicine. Stop using this medicine and check with your doctor right away if you have any of the following symptoms while taking this medicine: lip smacking or puckering, puffing of the cheeks, rapid or worm-like movements of the tongue, uncontrolled chewing movements, or uncontrolled movements of the arms and legs.

Stop using this medicine and check with your doctor right away if you have pain or tenderness in the upper stomach; pale stools; dark urine; loss of appetite; nausea; unusual tiredness or weakness; or yellow eyes or skin. These could be symptoms of a serious liver problem.

Make sure any doctor or dentist who treats you knows that you are using this medicine. You may need to stop using this medicine several days before having surgery or medical tests.

Do not stop using this medicine suddenly without asking your doctor. You may need to slowly decrease your dose before stopping it completely.

#### Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

- Keep all medicine away from children and never share your medicine with anyone.
- Blistering, red, or [peeling](#) skin rash.
- Constant muscle movement that you cannot control, often in your face, lips, tongue, jaw, arms, or legs.
- Dark-colored urine or pale stools.
- Fever with chills, cough, sore throat, and body aches.
- Fever with sweating, confusion, uneven heartbeat, or muscle stiffness.
- Lightheadedness, dizziness, or fainting.
- Nausea, vomiting, loss of appetite, or pain in your upper stomach.
- Pain in your lower leg (calf).
- Seizures or tremors.
- Swelling in your hands, ankles, or feet.
- Weak and rapid heartbeat, tiredness, chest pain, fever, or trouble breathing.
- Yellowing of your skin or the whites of your eyes.

If you notice these less serious side effects, talk with your doctor:

- Blurred vision or vision problems.
- Constipation, upset stomach.
- Dry mouth, increased sweating.
- Excess saliva or drooling.
- Feeling of constant movement of self or surroundings.
- Headache.
- Sleepiness or unusual drowsiness.
- Trouble sleeping.
- Weight gain.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

#### 4.3 Place In Therapy

A) Current users of atypical antipsychotic drugs (including [clozapine](#)) and typical antipsychotic drugs had a similar dose-dependent risk of sudden cardiac death, according to a retrospective cohort of 93,300 adult users of antipsychotic drugs and 186,600 matched controls. The study included patients age 30 to 74 years (mean 45.7 +/- 11.8 years) with similar cardiovascular risk at baseline who had at least one filled prescription and had 1 outpatient visit in each of the 2 preceding years. Sudden cardiac death was defined as occurring in the community and excluded deaths of patients admitted to the hospital, non-sudden deaths, deaths due to extrinsic causes, or causes not related to ventricular [tachyarrhythmia](#). Current use was defined as the interval between the time the prescription was filled and the end of the day's supply. Low and high doses was defined as comparable to less than 100 milligrams (mg) of [chlorpromazine](#), and doses comparable to [chlorpromazine](#) 300 mg or greater, respectively. The adjusted rate of sudden cardiac death (incidence-rate ratio) in current users of atypical antipsychotic drugs in 79,589 person-years was 2.26 (95% CI, 1.88 to 2.72, p less than 0.001) which was similar to the risk in current users of typical antipsychotic drugs in 86,735 person-years which was 1.99 (95% CI, 1.68 to 2.34, p less than 0.001). The risk of sudden cardiac death in current [clozapine](#) users in 4654 person-years was 3.67 (95% CI, 1.94 to 6.94, p less than 0.001). The risk of sudden cardiac death significantly increased with increasing dose in both the typical and atypical antipsychotic drug groups. In atypical antipsychotic use, the incidence rate ratio increased from 1.59 (95% CI, 1.03 to 2.46) in low-dose use to 2.86 (95% CI, 2.25 to 3.65) in high-dose use. To limit the effects of confounding of the study results, there was a secondary analysis performed in a cohort of patients matched by propensity score, which resulted in a similar risk of sudden death as the primary cohort analysis (Ray et al, 2009). In an editorial in The

New England Journal of Medicine, it has been suggested that antipsychotic drugs continue to be used in patients with clear evidence of benefit, but in vulnerable populations with cardiac risk profiles (eg, elderly patients), there should be an age-dependent justification required prior to administration. It has also been suggested (although not formally tested) that ECGs be performed before and shortly after initiation of antipsychotic therapy to screen for existing or emergent QT interval prolongation (Schneeweiss & Avorn, 2009).

**B)** Clozapine is considered to be an atypical antipsychotic agent because of its limited propensity to cause extrapyramidal adverse effects often associated with other antipsychotic agents. The drug has demonstrated efficacy in the therapy of treatment-resistant schizophrenic patients (Conley, 1998; Bablenis et al, 1989).

**C)** Because of the higher risk of agranulocytosis, clozapine should be reserved for those treatment-resistant patients who have not responded to adequate trials of other antipsychotic agents (Prod Info Clozaril(R), 2002). Prior to the initiation of clozapine treatment, patients should be given at least two trials, each with a different standard drug product for schizophrenia at an adequate dose and for an adequate duration to insure safety and efficacy (Prod Info CLOZARIL(R) tablets, 2005). Clozapine may also be useful in patients who cannot tolerate other antipsychotics because of their associated extrapyramidal symptoms or in patients with tardive dyskinesia (Conley, 1998).

**D)** A number of studies by different investigators (Kane et al, 1988; Conley et al, 1988; Mattes, 1989) showed that treatment resistant schizophrenic patients responded to clozapine. Clozapine is a useful addition to therapy for long-term treatment of schizophrenia despite the risks and the need for frequent blood tests. Clozapine improves both positive and negative symptoms, and may improve organization of thoughts, and certain aspects of cognitive function (Conley, 1998).

See Drug Consult reference: FIRST- VS SECOND-GENERATION ANTIPSYCHOTIC AGENTS FOR SCHIZOPHRENIA

#### 4.4 Mechanism of Action / Pharmacology

##### A) MECHANISM OF ACTION

1) Clozapine is a neuroleptic agent with a tricyclic structure that is similar to the antidepressant dibenzepine.

2) Clozapine exhibits relatively potent serotonergic S<sub>2</sub>-, serotonergic S<sub>3</sub>-, alpha-1-adrenergic, histamine H<sub>1</sub>-, and muscarinic antagonism activity, and appears to induce preferential blockade of dopamine D<sub>1</sub>- (versus dopamine D<sub>2</sub>-) and D<sub>4</sub> receptors in vivo (Kumar & Brecher, 1999; Shaikh et al, 1993; Fitton & Heel, 1990). Although the exact mechanism of action of clozapine has not been established, it has been suggested that the antipsychotic effects of clozapine might be related to central dopamine D<sub>1</sub>- or a combination of dopamine D<sub>1</sub>- and D<sub>2</sub>- receptor blockade with serotonergic, S<sub>2</sub>-receptor antagonism possibly playing a supplementary role. It has been postulated that the therapeutic effects of neuroleptics are mediated by mesolimbic and mesocortical dopaminergic pathways, while the neostriatum is associated with extrapyramidal side effects of these drugs. The low incidence of extrapyramidal side effects of clozapine might be attributable to a selective action on mesolimbic dopaminergic receptors (Fitton & Heel, 1990; Gudelsky et al, 1989).

3) A positive correlation was seen for the overall score on the Scale for the Assessment of Positive Symptoms (p=0.02) (and for the subscores for hallucination (p=0.02), and delusion (p=0.001)), and prolactin release as evoked by d-fenfluramine. The prolactin response to d-fenfluramine is a highly specific test of 5-HT function. The authors hypothesize that this 5-HT antagonism is therefore relevant to clozapine's efficacy in alleviating hallucinations and to the positive symptoms of schizophrenia (Jones et al, 1998).

4) A high degree of D<sub>2</sub> dopamine receptor blockade by antipsychotic drugs is usually necessary for clinical response. However, about 30% of schizophrenic patients do not respond. To test this assumption, one author compared clinical response with central D<sub>2</sub> dopamine receptor availability measured by I-123 iodobenzamide single photon emission tomography in two groups of schizophrenic patients. Six patients on typical antipsychotics showed poor therapeutic response despite D<sub>2</sub> receptor blockade. Significant clinical improvement occurred in all 10 patients on the antipsychotic clozapine, but at a lower level of D<sub>2</sub> blockade



by the drug. These findings suggest a more complex relation between D2 blockade and clinical efficacy than was previously thought (Pilowsky et al, 1992).

**5) Positron emission tomography (PET)** has been used for quantification of D2 receptor occupancy induced by antipsychotic drugs in the basal ganglia. The classical neuroleptics have their antipsychotic effects mediated by a blockade of D2 receptors. In clozapine-treated patients, the D2 receptor occupancy was low, thus classifying it as an "atypical" antipsychotic. PET and the radioligand (11-C)N-methylspiperone were used to determine cortical 5-HT<sub>2</sub> receptor occupancy in three psychotic patients treated with 125, 175, and 200 milligrams of clozapine daily (Nordstrom et al, 1993). The results show that clinical treatment with clozapine induces a high 5-HT<sub>2</sub> receptor occupancy in psychotic patients at a low clozapine dosage. In another study, a very high degree of serotonin 5-HT<sub>2a</sub> receptor blockade was found with both clozapine and high doses of chlorpromazine. This lead the authors to hypothesize that it is actually the difference in the dopamine D(2) receptor occupancy that accounts for the differences in clinical properties between clozapine and the typical antipsychotic drugs (Trichard et al, 1998).

**6) Dopamine D4 receptors** have greater affinity for clozapine than for any other antipsychotic. The D4 receptor occurs in at least 7 polymorphic forms and can be rapidly identified. These polymorphic forms may influence the receptor to clozapine. It is concluded that response to clozapine is not pharmacogenetically dichoromous (Shaikh et al, 1993).

**7) Results on assessing clozapine's effect on dopamine and serotonin metabolites** have been inconsistent. The dopamine-serotonin relationship was reappraised in a group of 19 neuroleptic refractory and intolerant schizophrenic patients treated with clozapine (Szymanski et al, 1993). Only a small change in cerebrospinal fluid and plasma homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) levels was found. The modest relationship between HVA and 5-HIAA and treatment response suggests the involvement of both neurotransmitters in the pathophysiology of schizophrenia.

**8) The plasma levels of dopamine, norepinephrine, and their metabolites homovanillic acid (HVA) and 3-methoxy-4-hydroxyphenylglycol (MHPG)** were measured in eight schizophrenic patients treated with clozapine for 12 weeks. They found the plasma levels of HVA and MHPG decreased during the initial weeks of treatment in responders, but not in nonresponders; and plasma levels of dopamine and norepinephrine increased in both responders and nonresponders to clozapine treatment (Green et al, 1993).

**9) It has been well established with other clinically active neuroleptics that elevations in serum prolactin occur** (Langer et al, 1977; Meltzer et al, 1978). This is believed to result from the blockade of dopamine receptors in the pituitary. One study reported that the degree of acute prolactin elevation in man following the parenteral administration of a neuroleptic drug appeared to be highly correlated with the milligram for milligram antipsychotic potency (Langer et al, 1977). However, various reports (Sachar et al, 1976; Nair et al, 1979; Meltzer et al, 1979) have shown that clozapine may cause no increase or only a minimal increase of prolactin secretion in man. They observed a 17% elevation in basal serum prolactin levels but also saw a marked inhibition of growth hormone response to 0.75 mg apomorphine which was administered subcutaneously in 6 of 7 subjects. In one study, data suggest that clozapine can block dopamine receptors responsible for apomorphine growth hormone effect without effecting the pituitary dopamine receptors involved in prolactin response. Ten schizophrenic male patients received a maximum clozapine dose of 100 mg/day and a total of 200 mg during the 3-day study (Nair et al, 1979). Based on this, one author has suggested that this may indicate a difference between the hypothalamic and pituitary dopamine receptors (Meltzer et al, 1979).

**10) Clozapine differed from haloperidol, chlorpromazine, and fluphenazine in that clozapine produced only a brief elevation of serum prolactin but a marked increase of corticosterone and ACTH.** Moreover, it increased the activity of tuberoinfundibular dopamine neurons. In view of the lack of propensity of clozapine to induce extrapyramidal symptoms, it has been hypothesized that clozapine selectively affects mesocorticolimbic dopamine function (Owen et al, 1993; Gudelsky et al, 1989). It has been proposed that schizophrenia may involve a dysregulation of 5-HT-2 and D-2-mediated neurotransmission and that a more

normal balance in serotonergic and dopaminergic neurotransmission is at least partially restored by [clozapine](#) (Meltzer, 1989).

11) [Clozapine](#) is highly anticholinergic and stimulates higher human brain anticholinergic activity than [risperidone](#) (Tracy et al, 1998). However, it may still be less than other traditional neuroleptics such as [haloperidol](#).

## B) REVIEW ARTICLES

- 1) Optimization of [clozapine](#) therapy has been reviewed (Naber, 1999; Conley, 1998a).
- 2) The pharmacokinetics and pharmacodynamics of [clozapine](#) have been reviewed in patients with [schizophrenia](#) (Jann et al, 1993).
- 3) [Clozapine](#) and [agranulocytosis](#) has been reviewed (Pirmohamed & Park, 1997; Feldman, 1996).
- 4) [Clozapine](#) for the treatment of [psychosis](#) in [Parkinson's disease](#) has been reviewed (Auzou et al, 1996).
- 5) A comprehensive review of [clozapine's](#) use in treating movement disorders, including [Parkinson's disease](#), essential tremor, [Huntington's disease](#) and [tardive dyskinesia](#) is available (Factor & Friedman, 1997).
- 6) Evaluations of the clinical studies on new drug therapies for treatment-resistant [schizophrenia](#) (Kane, 1996) and [schizoaffective disorder](#) have been reviewed (Keck et al, 1996).
- 7) The use of atypical antipsychotic medications in adults (Markowitz et al, 1999; Brown et al, 1999), older adults (Chan et al, 1999), and children (Lewis, 1998; Toren et al, 1998) has been reviewed.
- 8) A review on [clozapine](#) use in [schizophrenia](#) has been included in the American Psychiatric Association's Practice Guideline for the Treatment of Patients with [Schizophrenia](#) (Anon, 1997).
- 9) Review articles evaluating the adverse effect profiles of [clozapine](#) (Miller, 2000) along with other antipsychotic agents in the elderly (Masand, 2000) and in [bipolar disorder](#) (Zarate, 2000) are available.
- 10) A review of published, comparative data of [clozapine](#) versus other atypical antipsychotic agents is available (Fleischhacker, 1999).

## 4.5 Therapeutic Uses

### 4.5.A [Anorexia nervosa](#)

See Drug Consult reference: [ANOREXIA NERVOSA - DRUG THERAPY](#)

### 4.5.B [Dementia](#)

See Drug Consult reference: BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF [DEMENTIA](#)

### 4.5.C [Parkinson's disease](#)

See Drug Consult reference: [PARKINSON'S DISEASE - DRUG OVERVIEW](#)

### 4.5.D [Parkinson's disease - Psychotic disorder](#)

#### 1) Overview

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

#### 2) Summary:

See Drug Consult reference: THERAPY OF PSYCHOTIC DISTURBANCES IN PARKINSONIAN PATIENTS

#### 3) Adult:

a) The authors of a review article recommend [clozapine](#) as the second-line antipsychotic for patients with Parkinson's-associated [psychosis](#). Two controlled trials plus numerous open studies and case reports attest to the efficacy and safety of [clozapine](#) for this indication. Daily [clozapine](#) doses are much

lower (6.25 to 50 milligrams) than required for [schizophrenia](#). The major advantage of [clozapine](#) in this setting is its lack of parkinsonian adverse effects. However, the risk of [agranulocytosis](#) coupled with the expense and inconvenience of weekly blood monitoring prompted the authors to consider [quetiapine](#) as the first-line antipsychotic despite relatively limited efficacy data (Friedman & Factor, 2000).

**b)** In a double-blind, placebo-controlled trial (n=60), [clozapine](#) improved [drug-induced psychosis](#) in patients with [Parkinson's disease](#), even though the patients continued to take antiparkinsonian drugs. [Clozapine](#) did not worsen the symptoms of [Parkinson's disease](#) and actually decreased motor tremor. Subjects (mean age: 71 years, disease duration: 10 years) were randomized to 4 weeks of therapy with either placebo or [clozapine](#), titrated from 6.25 milligrams (mg)/day to a maximum of 50 mg/day. At a mean dose of 25 mg/day, [clozapine](#) produced significant improvements in the Clinical Global Impression (CGI) scale (in comparison to placebo, p less than 0.001) and the Brief Psychiatric Rating Scale (BPRS) (in comparison to placebo, p=0.02). Changes (from baseline) in total score and motor score on the Unified [Parkinson's Disease](#) Rating Scale (UPDRS) were not statistically different for [clozapine](#) and placebo, but the improvement in tremor score was significantly better with [clozapine](#) than with placebo (p=0.02). Three patients withdrew from the [clozapine](#) group: one because of [leukopenia](#), one because of [myocardial infarction](#), and one because of sedation. Three patients in the placebo group discontinued the study (Anon, 1999a). In a 12-week, open label extension of this trial, 52 patients were all given [clozapine](#), starting with 6.25 mg per day, with no ceiling dose. Those patients who had received placebo in the double-blind portion of the trial improved to a degree similar to that of the patients originally randomized to [clozapine](#). Improvement was maintained in both groups through week 16. [Clozapine](#) did not worsen motor scores. The average dose of [clozapine](#) was 28.8 mg/day, similar to that in the double-blind portion of the study, when there was a 50 mg ceiling. Of the original 60 patients, 6 patients died and another 12 were hospitalized. The most common cause was pulmonary (usually [pneumonia](#)). The relation of the high morbidity and mortality to [clozapine](#) treatment is uncertain (Factor et al, 2001).

**c)** In a retrospective chart review, 172 patients with [Parkinson's disease](#) at 4 centers benefited from [clozapine](#) (mean dose 31.4 milligrams; mean duration 16.7 months). Visual hallucinations that were present in 114 of the patients improved in 89.5% with [clozapine](#) therapy. Auditory hallucinations, present in 9 patients had an 89% improvement rate. Delusions in 64 patients showed an improvement rate of 91%. [Clozapine](#) was discontinued in 40 patients (23%) due to adverse affects. [Agranulocytosis](#) was not seen at any site (Trosch et al, 1998a).

**d)** Patients with [Parkinson's disease](#) (n=49) received [clozapine](#) (16 to 31 milligrams/day) with 3 of 49 patients (6%) having complete relief of their psychotic symptoms. Improvement was seen in 76% of patients at 3 months, in 70% at 6 months, in 84% at 12 months, and in 70% at 18 months. Similar results were reported in 18 additional patients with [Parkinson's disease](#) and [psychosis](#) (Wagner et al, 1996; Lew & Waters, 1993; Wolk & Douglas, 1992; Friedman & Lannon, 1989).

#### 4.5.E [Schizophrenia](#), Treatment-resistant

##### FDA Labeled Indication

##### 1) Overview

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

##### 2) Summary:

##### 3) Adult:

##### a) General Information

**1)** Results from short- and long-term retrospective, noncomparative studies indicate that 30% to 60% of patients with treatment-resistant [schizophrenia](#) show a marked improvement with [clozapine](#) as compared to previous standard antipsychotic agents (Alvarez et al, 1997; Fitton

& Heel, 1990a). Positive schizophrenic symptoms, mainly hallucinations, delusions, unusual thought content, psychomotor hyperactivity, hostility and aggression appear to be significantly alleviated by [clozapine](#) (Keck et al, 2000; Volavka, 1999; Lindstrom, 1988), possibly even better than with [haloperidol](#) (Buchanan et al, 1998). Some evidence suggests that [clozapine](#) may decrease comorbid depressive symptoms, substance abuse and suicidal behavior (Keck et al, 2000; Zimmet et al, 2000; Volavka, 1999; Meltzer, 1999). In comparative studies of patients refractory to classic antipsychotics, [clozapine](#) (less than or equal to 900 milligrams/day) had significant superior overall antipsychotic efficacy (in terms of Brief Psychiatric Rating Scale score) to [chlorpromazine](#) (less than or equal to 1800 milligrams/day) over a 6-week treatment period (Conley et al, 1988a; Herrera et al, 1988; Kane et al, 1988b). Results from various studies in treatment-resistant [schizophrenia](#) indicate that patients intolerant to classic neuroleptics and presenting [tardive dyskinesia](#)/extrapyramidal side effects have improved response to [clozapine](#) therapy (greater than or equal to 3 months' duration) when compared to previous antipsychotic therapy (Lieberman et al, 1994; Kane et al, 1994; Maier, 1992; Davies et al, 1991; Meltzer et al, 1990; Meltzer et al, 1989). Patients have continued to improve even after 5 to 10 years of therapy with [clozapine](#) (Lindstrom & Lundberg, 1997).

2) Combination therapies of [clozapine](#) and [fluoxetine](#), and [clozapine](#), [risperidone](#), and [paroxetine](#) have been used successfully in refractory [schizophrenia](#) (Patel et al, 1997; Cassady & Thaker, 1992). The combination of [clozapine](#) and [paroxetine](#) was effective in [schizophrenia](#) with comorbid obsessive-compulsive symptoms in a case report (Strous et al, 1999). Combination [clozapine](#) and [electroconvulsive therapy](#) has also been used (James & Gray, 1999).

3) In a comparison of responders and non-responders, characteristics which were associated with response to [CLOZAPINE](#) included (1) lower severity of illness at baseline according to the Clinical Global Impressions-Severity of Illness (CGI-S) scale, (2) lower baseline level of negative symptoms as assessed on the Scale for the Assessment of Negative Symptoms (SANS), and (3) lower level of acute extrapyramidal symptoms at baseline. After controlling for the foregoing characteristics, a higher total score on the Brief Psychiatric Rating Scale (BPRS) was predictive of a positive response to [clozapine](#). Patient history did not influence response to [clozapine](#). Subjects in this study (n=37) were partially treatment-refractory outpatients diagnosed with [schizophrenia](#) or [schizoaffective disorder](#) (DSM-III-R), of which 22 (59%) responded to [clozapine](#) given for 29 weeks (ie, showed a 20% decrease in BPRS [psychosis](#) factor scores). Targeted [clozapine](#) dose titration was to reach 500 milligrams (mg)/day by the end of week 5 (minimum 250 mg/day; maximum 850 mg/day) (Umbricht et al, 1994a).

#### b) Single Drug Therapy

1) A reduction in left caudate nucleus volume (CNV) was correlated with improvement in positive symptoms and general symptoms of [schizophrenia](#), though not in negative symptoms, in patients who had been unresponsive to conventional antipsychotropic drugs but who responded to [clozapine](#). Treatment with conventional antipsychotropic drugs was associated with an increase in left CNV in this population of 28 patients. Treatment was switched to [clozapine](#) (mean dose 346 milligrams/day) and CNV was assessed again at 24 weeks and 52 weeks of treatment. In responders to [clozapine](#), but not in nonresponders, left (but not right) CNV was significantly reduced by 24 weeks (p less than 0.005). The change in CNV between weeks 24 and 52 was not significant. Scores on the Positive and Negative Syndrome scale showed significant improvement at 24 weeks compared to baseline scores (p less than 0.001) and continued to improve through week 52 (p less than 0.01 for comparison to 24-week scores). These results suggest that the caudate nucleus may play a role in the positive and general symptoms of [schizophrenia](#) (Scheepers et al, 2001).

2) In a prospective, 12-month study, [clozapine](#) elicited therapeutic responses in 68% of 50 inpatients with [schizophrenia](#). Subjects were refractory to at least 2 adequate trials of [antipsychotic drug therapy](#), in addition to a 6-week trial of [haloperidol](#) or [perphenazine](#) just prior to study entry. [Clozapine](#) was initiated at 25 milligrams (mg)/day, then titrated slowly to 400 to 450 mg/day within 3 weeks. Doses were advanced as necessary every 6 weeks thereafter to a maximum of 900 mg/day. The average onset and dose for therapeutic response were 82 days and 468 mg/day, respectively. Investigators concluded that an 8-week trial is sufficient to assess response after a dose change (Conley et al, 1997).

3) Fifty percent of treatment-refractory patients and 76% of treatment-intolerant patients had a favorable response to [clozapine](#). The clinical responses of 84 schizophrenic patients who were either intolerant or refractory to other neuroleptic agents were evaluated for a period of up to 52 weeks (Lieberman et al, 1994). The authors suggested that predictors of a good response to [clozapine](#) include the presence of extrapyramidal side effects during previous treatment with classic neuroleptics and a diagnosis of [paranoid schizophrenia](#).

4) Data from a retrospective review (n=33) support the efficacy and tolerability of [clozapine](#) in patients with [mental retardation](#) and comorbid treatment-resistant psychotic illness. All had failed three or more traditional antipsychotics with or without mood stabilizers and required hospitalization for acute exacerbation. Patients categorized as having mild (58%), moderate (39%) or severe (3%) [mental retardation](#) were initiated on [clozapine](#) 25 milligrams (mg)/day and titrated to a median dose of 400 mg/day. After a mean inpatient stay of 40 days, the average Clinical Global Impression (CGI)-Improvement score indicated much improvement, while the mean CGI-Efficacy Index score indicated decided improvement, partial symptom remission and no or minimal adverse effects. The clinical benefits were sustained for a mean follow-up of 25 months (Antonacci & de Groot, 2000). Four out of five mentally retarded patients responded to [clozapine](#) therapy with progressive improvement in psychopathology, social functioning and ability to participate in daily activities. [Clozapine](#) was studied in a group of five patients with treatment-resistant [schizophrenia](#) or [schizoaffective disorder](#) and borderline intellectual function or [mental retardation](#) (Sajatovic et al, 1994).

#### 4) Pediatric:

a) [Clozapine](#) has been reported to be effective in the treatment of young adolescents (ages 12 to 17 years) with severe symptoms of [schizophrenia](#) refractory to other neuroleptics (Turpeinen, 1996; Frazier et al, 1994; Jacobsen et al, 1994; Towbin et al, 1994). Usual side effects were observed, with precautionary measures taken to avoid seizures and [agranulocytosis](#).

b) [Clozapine](#) has been successful in treating 4 children (ages 10 to 12) with [schizophrenia](#). Early onset schizophrenic patients generally do not respond well to treatment with other conventional neuroleptics (Mozes et al, 1994).

c) In an open trial of 11 adolescents (ages 12 to 17 years) with childhood-onset [schizophrenia](#) refractory to other neuroleptic agents, [clozapine](#) was given as an initial dose of 12.5 to 25 milligrams/day and increased every 4 days by one or two times the starting dose. The dose was advanced based on clinical response and the emergence of adverse effects to a maximal possible dose of 900 milligrams/day. The mean dose at week 6 of the trial was 370.5 milligrams/day (Frazier et al, 1994).

#### 4.5.F [Schizophrenia](#) - Suicidal behavior, Recurrent

##### FDA Labeled Indication

##### 1) Overview

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

##### 2) Summary:



### 3) Adult:

a) In the International Suicide Prevention Trial (InterSePT), [clozapine](#) was shown to be more effective than [olanzapine](#) in reducing suicidal behavior in high-risk, adult, patients with [schizophrenia](#) or [schizoaffective disorder](#). Men and women between the ages of 18 to 65 years, at high risk of committing suicide, were recruited to participate in this 2-year, prospective, randomized, international, parallel group, study. The endpoints in this study included significant suicide attempts (including completed suicides) or hospitalization due to imminent suicide risk (type 1 events) or ratings of "much worse" or "very much worse" on the Clinical Global Impression of Suicide Severity (CGI-SS) scale (type 2 events). Of the total sample of 980 patients enrolled in the study, 62% (609) were diagnosed as having [schizophrenia](#) and 38% (371) were diagnosed with [schizoaffective disorder](#). Twenty-seven percent (263) of these patients were considered treatment resistant. The patients were divided into two treatment groups ([clozapine](#) or [olanzapine](#)) and did not differ significantly in terms of age, sex, race, diagnosis, treatment resistance, number of previous suicide attempts, or baseline concomitant medications. Both groups had weekly or biweekly clinical contact. Dropout rates for the two groups were similar with 192 discontinuing treatment with [clozapine](#) and 187 with [olanzapine](#). [Clozapine](#) showed a hazard ratio of 0.76 (95% CI, 0.58-0.97) for type 1 events ( $p=0.03$ ) and 0.78 (95% CI, 0.61-0.99) for type 2 events ( $p=.04$ ) compared to [olanzapine](#). The most frequently reported adverse events for the [olanzapine](#) group were weight gain, somnolence, dry mouth, and dizziness, while [salivary hypersecretion](#), somnolence, weight gain, and dizziness were the most frequently reported adverse events reported for the [clozapine](#) group. The overall number of adverse events did not differ significantly between the two groups. Decreased white blood cell counts occurred in 5.8% of clozapine-treated patients and in 0.8% of olanzapine-treated patients, but there were no reports of [agranulocytosis](#) or deaths due to [granulocytopenia](#) in either group. There was a total of 8 suicide deaths in the two groups (5 [clozapine](#) and 3 [olanzapine](#)). The mean daily [olanzapine](#) dosage was 16.6 +/- 6.4 mg and the mean daily [clozapine](#) dosage was 274.2 +/- 155.0 mg (Meltzer et al, 2003a).

b) It has been reported that [clozapine](#) reduces the risk of suicide by 75% to 80%. The International Suicide Prevention Trial (InterSePT) is a prospective study investigating the effect of [clozapine](#) (300 mg to 900 mg daily) versus [olanzapine](#) (10 mg to 20 mg daily) on suicidal rates of patients with [schizophrenia](#) (Meltzer et al, 2000).

#### 4.5.G Tardive dyskinesia

See Drug Consult reference: [TARDIVE DYSKINESIA - DRUG THERAPY](#)

### 4.6 Comparative Efficacy / Evaluation With Other Therapies

#### 4.6.A Chlorpromazine

##### 4.6.A.1 Schizophrenia

a) [Clozapine](#) was more effective and induced fewer adverse effects than [chlorpromazine](#) for the treatment of [schizophrenia](#) (Claghorn et al, 1987). One hundred fifty-one schizophrenic patients were enrolled in a double-blind, randomized, placebo-controlled multicenter study. Each patient received either [clozapine](#) 150 to 900 milligrams/day or [chlorpromazine](#) 300 to 1800 milligrams/day over a 28-day period. Eleven [chlorpromazine](#) patients compared with one [clozapine](#) patient were dropped from the study due to extrapyramidal side effects. As measured by the Brief Psychiatric Rating and Clinical Global Impression scales, [clozapine](#) was superior to [chlorpromazine](#) (Claghorn et al, 1987).

b) In a double-blind follow-up for a year following the initiation of a clinical trial comparing [chlorpromazine](#) and [clozapine](#), a higher percentage of [clozapine](#) patients were evaluated as clinically recovered as compared with [chlorpromazine](#) patients. Patients receiving [clozapine](#) received a mean dose of



600 milligrams/day as compared with 600 milligrams of [chlorpromazine](#) per day. During the initial 6-week study, 92% [clozapine](#) and 60% of [chlorpromazine](#) patients were evaluated as clinically recovered. At both the 3-year and the 4-year follow-up evaluation, the difference in [clozapine](#) and [chlorpromazine](#) continued. The results of this study must be viewed with caution, however, since both [chlorpromazine](#) and [clozapine](#) were dosed in equal doses and other investigators (Meltzer et al, 1979a) have found that the mean clinical antipsychotic dose of [clozapine](#) was 241 +/- 162 mg/day in contrast with the mean clinical antipsychotic dose of [chlorpromazine](#) of 691 +/- 411 mg/day. In the study by Leon, more equivalent results may have been obtained if equivalent antipsychotic doses had been used (Leon, 1979).

c) [Clozapine](#) was found to be more effective than [chlorpromazine](#) in the treatment of acutely psychotic schizophrenic individuals. Unlike [chlorpromazine](#), no extrapyramidal reactions occurred in those patients taking [clozapine](#). Characteristic clinical side effects of [clozapine](#) included sedation, hypotension, and increased salivation (Shopsin et al, 1979). Similar results have also been reported from investigators in Canada (Guirguis et al, 1977).

#### 4.6.B Haloperidol

##### 4.6.B.1 Hostile behavior

a) [Clozapine](#) reduced hostility in patients with [schizophrenia](#) and was superior to [haloperidol](#) and [risperidone](#) in that regard. One hundred fifty seven patients with a diagnosis of [schizophrenia](#) or [schizoaffective disorder](#) and a history of poor response to drug treatment were randomly assigned to receive [clozapine](#), [olanzapine](#), [risperidone](#), or [haloperidol](#) in cross-titration with the antipsychotic drug used prior to the start of the study. Concomitant mood stabilizers and antidepressants had been phased out earlier. Daily doses of [olanzapine](#), [risperidone](#), and [haloperidol](#) were escalated within the first week to the target doses of 20, 8, and 20 milligrams (mg), respectively. Patients receiving [clozapine](#) were scheduled to achieve the target daily dose of 500 mg on day 24. Doses remained fixed for the remainder of the initial 8-week period. In a second (6-week) period, doses were allowed to vary: 200 to 800 mg for [clozapine](#), 10 to 40 mg for [olanzapine](#), 4 to 16 mg for [risperidone](#), and 10 to 30 mg for [haloperidol](#). Hostility, measured by the hostility item of the Positive and Negative Syndrome Scale (PANSS), improved significantly (in comparison to baseline) in the [clozapine](#) group only ( $p=0.019$ ). This effect was independent of effects on psychotic symptoms (delusional thinking, hallucinations) or on sedation. The effect of [clozapine](#) on hostility was superior to that of [haloperidol](#) ( $p=0.021$ ) or [risperidone](#) ( $p=0.012$ ) but not to that of [olanzapine](#) (Citrome et al, 2001a).

##### 4.6.B.2 Schizophrenia, Refractory

a) [Olanzapine](#) and [risperidone](#) improved neurocognitive deficits more than did [haloperidol](#) or [clozapine](#) in patients with [schizophrenia](#) or [schizoaffective disorder](#) that was refractory to treatment with typical antipsychotics. In a randomized, double-blind study, inpatients were given [clozapine](#) ( $n=24$ ) 200 to 800 milligrams (mg) per day, [olanzapine](#) ( $n=26$ ) 10 to 40 mg/day, [risperidone](#) ( $n=26$ ) 4 to 16 mg/day, or [haloperidol](#) ( $n=25$ ) 10 to 30 mg/day. Dose escalation and fixed-dose treatment (target doses: [olanzapine](#) 20 mg/day, [risperidone](#) 8 mg/day, [haloperidol](#) 20 mg/day, [clozapine](#) 500 mg/day) occurred during the first 8 weeks of the 14-week study; during the last 6 weeks, dosages were adjusted individually (generally increased if response was insufficient, but sometimes reduced because of adverse effects). Improvement over time in global neurocognitive score was seen for [olanzapine](#) and [risperidone](#). In general executive and perceptual organization and in processing speed and attention, improvement was seen with [olanzapine](#). In simple motor function, there was improvement with [clozapine](#). Changes in global neurocognitive performance with [olanzapine](#) and [risperidone](#) were of medium magnitude (approximately 8 to 9 "IQ equivalents") but large enough to be clinically significant. Beneficial changes with [clozapine](#) were modest. Despite cognitive gains, patients still had significant impairments of cognitive ability and social/vocational functioning.

Improvements in neurocognitive deficits were associated with improvements in negative symptoms (Bilder et al, 2002).

**b)** Schizophrenic patients treated with [clozapine](#) were more likely to be rated as improved and less likely to discontinue treatment due to lack of efficacy than a matched group treated with [haloperidol](#). Seventy-one patients between the ages of 20 to 55 years with a diagnosis of schizophrenic or [schizoaffective disorder](#) were enrolled in this 6-month, double-blind, prospective, randomized trial. These outpatients, were documented as poor or partial responders to antipsychotic therapy and had a rating of at least moderate on 1 of 4 Brief Psychiatric Rating Scale (BPRS) items (conceptual disorganization, suspiciousness, hallucinatory behavior, or unusual thought content). The two major outcome measures for this study were time to discontinuation of study medication due to lack of clinical response and 20% improvement in the 4 item BPRS cluster during two consecutive rating periods. The [haloperidol](#) group (n=34) was targeted to receive 10 milligrams (mg)/day, along with 2 mg/day of [benztropine](#), while the [clozapine](#) group was to receive 500 mg/day (n=37). Doses could be adjusted in either group to a range of 4 to 16 mg/day for the [haloperidol](#) group and 200 to 800 mg/day for the [clozapine](#) group depending upon the patient's clinical course. At the end of 29 weeks, 50.5% of the haloperidol-treated group (mean dose 18.9 mg/day) and 11.6% of the [clozapine](#) group (mean dose 523 mg/day) had discontinued treatment due to lack of efficacy (p=0.02). The mean BPRS ratings at the end of the study were 3.2 and 4.2 for the [clozapine](#) and [haloperidol](#) groups respectively (p less than 0.001). There was no difference found between the groups as measured by the Schedule for Assessment of Negative Symptoms (SANS) score using the sum of the 4 global ratings. Haloperidol-treated patients experienced more dry mouth and decreased appetite, while the clozapine-treated group reported more salivation, sweating, and dizziness. Three [haloperidol](#) and 2 clozapine-treated patients dropped-out of the study due to adverse drug effects (Kane et al, 2001).

**c)** [Clozapine](#) exhibited improved efficacy with fewer adverse effects as compared to [haloperidol](#) in a randomized, double-blind, 12-month study conducted at Veterans Affairs medical centers (n=423 with refractory [schizophrenia](#)). Using intention-to-treat analysis, [schizophrenia](#) symptom scores were significantly improved with [clozapine](#) over [haloperidol](#) at 6 weeks (p equals 0.008) and 6 months (p equals 0.001), with no statistical difference in quality of life measures. When crossover cases were excluded, quality of life measures were significantly better in the [clozapine](#) group at 3 months and 1 year (p equals 0.02). [Clozapine](#) also reduced scores for [tardive dyskinesia](#), [akathisia](#) and extrapyramidal syndrome. [Clozapine's](#) higher costs for drug acquisition and laboratory monitoring were offset by decreased inpatient hospital stays (Rosenheck et al, 1997).

**d)** These investigators later evaluated compliance with [clozapine](#) versus [haloperidol](#). The results confirmed that [clozapine](#) established better medication continuation and regimen compliance. Patients taking [clozapine](#) continued taking the study drug for a mean of 35.5 weeks as compared with on 27.2 weeks among [haloperidol](#) patients (p=0.0001). No differences were found between the groups in the proportion of prescribed pills that were returned at any time point. Continuation with medication is greater with [clozapine](#) than [haloperidol](#) and is partly explained by greater symptom improvement and reduced side effects. No differences were discovered in regimen compliance (Rosenheck et al, 2000).

#### 4.6.B.3) Adverse Effects

**a)** The results of one study suggest that patients receiving atypical antipsychotics have a higher incidence of [PANCREATITIS](#) than patients receiving a conventional antipsychotic medication. In a retrospective, pharmacovigilance study, 192 cases of [pancreatitis](#) were identified in patients taking [clozapine](#) (mean dose, 306.7 milligrams (mg)/day), [olanzapine](#) (mean dose, 15 mg/day), [risperidone](#), (mean dose, 4 mg/day) or [haloperidol](#) (mean dose, 8.2 mg/day). Of the identified cases, 40%, 33%, and 16% were related to treatment with the atypical antipsychotic medications [clozapine](#), [olanzapine](#), or [risperidone](#), respectively, as compared with 12% of the cases which were related to the conventional neuroleptic, [haloperidol](#). In most patients, time to onset of [pancreatitis](#) was within 6 months after initiation of treatment (Koller et al, 2003a).

b) No significant difference was found in sexual disturbances occurring in clozapine-treated versus haloperidol-treated patients (Hummer et al, 1999). Inpatients receiving either [clozapine](#) (n=100) or [haloperidol](#) (n=53) were screened. The most common adverse event in both groups was diminished sexual desire occurring in 4 (33.3%) of the haloperidol-treated women, 26 (63.4%) of the haloperidol-treated men, 7 (28%) of the clozapine-treated women, and 43 (57.3%) of the clozapine-treated men. Among women treated, [amenorrhea](#) occurred in 4 (33.3%) of the [haloperidol](#) patients and in 3 (12%) of the [clozapine](#) patients. Larger studies may be needed to show differences.

c) In a prospective study, the incidence of [alanine aminotransferase \(ALT\)](#) elevation to more than twice the upper normal limit was statistically greater with [clozapine](#) (37%, n=167) than with [haloperidol](#) (17%, n=71). Among those receiving [clozapine](#), the rates of elevations in [aspartate aminotransferase \(AST\)](#) and [gamma-glutamyl transpeptidase \(GGT\)](#) to more than twice the upper normal limit were 12% and 15%, respectively. No such increases in [bilirubin](#) or [alkaline phosphatase](#) occurred in clozapine-treated patients. These effects were transient in the majority of patients (disappearing by week 13) with no clinical manifestations reported (Hummer et al, 1997).

#### 4.6.C [Olanzapine](#)

##### 4.6.C.1 Hostile behavior

a) [Clozapine](#) reduced hostility in patients with [schizophrenia](#) and was superior to [haloperidol](#) and [risperidone](#) in that regard. One hundred fifty seven patients with a diagnosis of [schizophrenia](#) or [schizoaffective disorder](#) and a history of poor response to drug treatment were randomly assigned to receive [clozapine](#), [olanzapine](#), [risperidone](#), or [haloperidol](#) in cross-titration with the antipsychotic drug used prior to the start of the study. Concomitant mood stabilizers and antidepressants had been phased out earlier. Daily doses of [olanzapine](#), [risperidone](#), and [haloperidol](#) were escalated within the first week to the target doses of 20, 8, and 20 milligrams (mg), respectively. Patients receiving [clozapine](#) were scheduled to achieve the target daily dose of 500 mg on day 24. Doses remained fixed for the remainder of the initial 8-week period. In a second (6-week) period, doses were allowed to vary: 200 to 800 mg for [clozapine](#), 10 to 40 mg for [olanzapine](#), 4 to 16 mg for [risperidone](#), and 10 to 30 mg for [haloperidol](#). Hostility, measured by the hostility item of the Positive and Negative Syndrome Scale (PANSS), improved significantly (in comparison to baseline) in the [clozapine](#) group only (p=0.019). This effect was independent of effects on psychotic symptoms (delusional thinking, hallucinations) or on sedation. The effect of [clozapine](#) on hostility was superior to that of [haloperidol](#) (p=0.021) or [risperidone](#) (p=0.012) but not to that of [olanzapine](#) (Citrome et al, 2001b).

##### 4.6.C.2 [Schizophrenia](#) - Suicidal intent

a) In the International Suicide Prevention Trial (InterSePT), [clozapine](#) was shown to be more effective than [olanzapine](#) in reducing suicidal behavior in high-risk, adult, patients with [schizophrenia](#) or [schizoaffective disorder](#). Men and women between the ages of 18 to 65 years, at high risk of committing suicide, were recruited to participate in this 2-year, prospective, randomized, international, parallel group, study. The endpoints in this study included significant suicide attempts (including completed suicides) or hospitalization due to imminent suicide risk (type 1 events) or ratings of "much worse" or "very much worse" on the Clinical Global Impression of Suicide Severity (CGI-SS) scale (type 2 events). Of the total sample of 980 patients enrolled in the study, 62% (609) were diagnosed as having [schizophrenia](#) and 38% (371) were diagnosed with [schizoaffective disorder](#). Twenty-seven percent (263) of these patients were considered treatment resistant. The patients were divided into two treatment groups ([clozapine](#) or [olanzapine](#)) and did not differ significantly in terms of age, sex, race, diagnosis, treatment resistance, number of previous suicide attempts, or baseline concomitant medications. Both groups had weekly or biweekly clinical contact. Dropout rates for the two groups were similar with 192 discontinuing treatment with [clozapine](#) and 187 with [olanzapine](#). [Clozapine](#) showed a hazard ratio of 0.76 (95% CI, 0.58-0.97) for

type 1 events ( $p=0.03$ ) and 0.78 (95% CI, 0.61 to 0.99) for type 2 events ( $p=0.04$ ) compared to [olanzapine](#). The most frequently reported adverse events for the [olanzapine](#) group were weight gain, somnolence, dry mouth, and dizziness, while [salivary hypersecretion](#), somnolence, weight gain, and dizziness were the most frequently reported adverse events reported for the [clozapine](#) group. The overall number of adverse events did not differ significantly between the two groups. Decreased white blood cell counts occurred in 5.8% of clozapine-treated patients and in 0.8% of olanzapine-treated patients, but there were no reports of [agranulocytosis](#) or deaths due to [granulocytopenia](#) in either group. There was a total of 8 suicide deaths in the two groups (5 [clozapine](#) and 3 [olanzapine](#)). The mean daily [olanzapine](#) dosage was 16.6 +/- 6.4 mg and the mean daily [clozapine](#) dosage was 274.2 +/- 155.0 mg (Meltzer et al, 2003).

#### 4.6.C.3) Adverse Effects

a) The results of one study suggest that patients receiving atypical antipsychotics have a higher incidence of [PANCREATITIS](#) than patients receiving a conventional antipsychotic medication. In a retrospective, pharmacovigilance study, 192 cases of [pancreatitis](#) were identified in patients taking [clozapine](#) (mean dose, 306.7 milligrams (mg)/day), [olanzapine](#) (mean dose, 15 mg/day), [risperidone](#), (mean dose, 4 mg/day) or [haloperidol](#) (mean dose, 8.2 mg/day). Of the identified cases, 40%, 33%, and 16% were related to treatment with the atypical antipsychotic medications [clozapine](#), [olanzapine](#), or [risperidone](#), respectively, as compared with 12% of the cases which were related to the conventional neuroleptic, [haloperidol](#). In most patients, time to onset of [pancreatitis](#) was within 6 months after initiation of treatment (Koller et al, 2003b).

b) Results of a retrospective analysis showed that [olanzapine](#) treatment was associated with a lower rate of extrapyramidal symptoms (EPS) than [haloperidol](#), but was similar to rates occurring with [risperidone](#) and [clozapine](#) therapy. In a pooled analysis of 23 randomized, controlled clinical trials in 4611 patients with [schizophrenia](#), frequency and severity of EPS associated with [olanzapine](#) therapy (2.5 to 20 milligrams (mg)/day) was compared with that of [haloperidol](#) (1 to 20 mg/day), [risperidone](#) (4 to 12 mg/day), [clozapine](#) (25 to 625 mg/day), and placebo. Dystonic events (ie, [dystonia](#), [oculogyric crisis](#), [opisthotonos](#), [torticollis](#)) occurred in significantly fewer patients during [olanzapine](#) treatment as compared with [haloperidol](#) (0.5% vs 5.6%, respectively;  $p$  less than 0.001) or [risperidone](#) (1% vs 3.2%, respectively;  $p=0.047$ ) treatment, while no significant difference was found between [olanzapine](#)- and [clozapine](#)-treated patients. As compared with [olanzapine](#)-treated patients, a significantly higher percentage of [haloperidol](#)-treated patients experienced parkinsonian events (ie, [akinesia](#), cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, and tremor) (9.3% vs 28.3%, respectively;  $p$  less than 0.001) or [akathisia](#) events (ie, [akathisia](#), hyperkinesia) (6.7% vs 20.4%, respectively;  $p$  less than 0.001) during therapy. However, no significant difference was observed between the [olanzapine](#) group as compared with the placebo, [risperidone](#), or [clozapine](#) groups in regard to the occurrence of parkinsonian or [akathisia](#) events. Overall, EPS occurred in significantly more patients treated with [haloperidol](#) as compared with [olanzapine](#) (44.4% vs 16.2%, respectively;  $p$  less than 0.001) and in fewer patients treated with [clozapine](#) as compared with [olanzapine](#) (2.6% vs 6.8%, respectively;  $p=0.047$ ). The overall rate of EPS was similar between the placebo and [risperidone](#) groups as compared with [olanzapine](#). Significantly fewer patients received anticholinergic medications in the [olanzapine](#) group as compared with the [haloperidol](#) ( $p$  less than 0.001) or [risperidone](#) ( $p=0.018$ ) groups. No difference was found between [olanzapine](#)-treated patients as compared with placebo or [clozapine](#) in regard to percentage of patients given anticholinergic drugs during therapy (Carlson et al, 2003).

c) In an open-label trial ( $n=24$ ), [olanzapine](#)-treated patients had significantly lower levels of serum anticholinergic activity than [clozapine](#)-treated patients. Prior to enrollment, subjects were stabilized on therapeutic doses, averaging 15 milligrams (mg)/day and 444 mg/day for [olanzapine](#) and [clozapine](#), respectively. The mean serum anticholinergic levels were 0.96 and 5.47 picomoles/[atropine](#) equivalents in the [olanzapine](#) and [clozapine](#) groups, respectively ( $p$  less than 0.001). Scores assessing clinical anticholinergic effects were significantly higher for salivation, constipation, micturition disturbances and palpitations/[tachycardia](#) in [clozapine](#) versus [olanzapine](#) recipients ( $p$  less than 0.05). Dry mouth



was more problematic with [olanzapine](#) therapy ( $p$  less than 0.0008). The groups did not differ cognitively with respect to Mini Mental State Exam scores. Although efficacy was not a primary endpoint, the Brief Psychiatric Rating Scale scores favored [clozapine](#) ( $p=0.002$ ), with no statistical difference in Clinical Global Impression Scale, Severity subscale scores. No patients in either group discontinued therapy due to adverse effects (Chengappa et al, 2000).

#### 4.6.D Risperidone

##### 4.6.D.1 Hostile behavior

a) [Clozapine](#) reduced hostility in patients with [schizophrenia](#) and was superior to [haloperidol](#) and [risperidone](#) in that regard. A total of 157 patients with a diagnosis of [schizophrenia](#) or [schizoaffective disorder](#) and a history of poor response to drug treatment were randomly assigned to receive [clozapine](#), [olanzapine](#), [risperidone](#), or [haloperidol](#) in cross-titration with the antipsychotic drug used prior to the start of the study. Concomitant mood stabilizers and antidepressants had been phased out earlier. Daily doses of [olanzapine](#), [risperidone](#), and [haloperidol](#) were escalated within the first week to the target doses of 20, 8, and 20 milligrams (mg), respectively. Patients receiving [clozapine](#) were scheduled to achieve the target daily dose of 500 mg on day 24. Doses remained fixed for the remainder of the initial 8-week period. In a second (6-week) period, doses were allowed to vary: 200 to 800 mg for [clozapine](#), 10 to 40 mg for [olanzapine](#), 4 to 16 mg for [risperidone](#), and 10 to 30 mg for [haloperidol](#). Hostility, measured by the hostility item of the Positive and Negative Syndrome Scale (PANSS), improved significantly (in comparison to baseline) in the [clozapine](#) group only ( $p=0.019$ ). This effect was independent of effects on psychotic symptoms (delusional thinking, hallucinations) or on sedation. The effect of [clozapine](#) on hostility was superior to that of [haloperidol](#) ( $p=0.021$ ) or [risperidone](#) ( $p=0.012$ ) but not to that of [olanzapine](#) (Citrome et al, 2001).

##### 4.6.D.2 Schizophrenia

a) [Clozapine](#) was superior to [risperidone](#) for improving positive and negative symptoms of [schizophrenia](#) in patients with poor previous response to treatment. In a prospective, double-blind study, patients meeting DSM-IV criteria for [schizophrenia](#) and having had poor response to previous treatment underwent a single-blind placebo run-in period when all psychotropic and anticholinergic medications were withdrawn. They were then randomly assigned to treatment with [clozapine](#) ( $n=138$ ) or [risperidone](#) ( $n=135$ ). Starting with daily doses of [clozapine](#) 12.5 milligrams (mg) and [risperidone](#) 1 mg, dosages were titrated over a period of 4 weeks to a minimum of 300 mg/day and 4 mg/day, respectively, and possibly to 600 mg/day and 6 mg/day. Patients unable to tolerate the minimum dose were withdrawn from the study. During the next 8 weeks, doses were adjusted at 2-week intervals within the range of 200 to 900 mg/day for [clozapine](#) and 2 to 15 mg/day for [risperidone](#). For patients who completed the 12-week study ( $n=201$ ), median final daily doses were 600 mg for [clozapine](#) and 9 mg for [risperidone](#). Changes in the Positive and Negative Syndrome Scale of the BPRS (Brief Psychiatric Rating Scale) and in the Clinical Global Impression (CBI) scale were significantly greater in the [clozapine](#) group than in the [risperidone](#) group for the intent-to-treat population (those who received at least one dose of treatment medication and had one post-dose BPRS evaluation) and in the per-protocol population (those who completed the 28-day dose-setting period) ( $p$  less than 0.008 for all comparisons). Eighty-six percent of patients in the [clozapine](#) per-protocol population and 70% in the [risperidone](#) per-protocol population showed 20% or more improvement in the BPRS score (for difference between groups,  $p$  less than 0.01). By the end of the study, 94 (76%) patients in the [clozapine](#) group and 81 (64%) in the [risperidone](#) group no longer met the severity of psychopathology inclusion criteria ( $p$  less than 0.05). Extrapyramidal symptoms occurred significantly less frequently in the [clozapine](#) group than in the [risperidone](#) group (13% vs 28%,  $p=0.008$ ). However, convulsions, dizziness, [sialorrhea](#), [tachycardia](#), and somnolence occurred significantly more frequently among those receiving [clozapine](#). No case of [agranulocytosis](#) was observed during the study. [Granulocytopenia](#) occurred with low incidence in both groups (1% [clozapine](#), 2% [risperidone](#)). Low neutrophil count was significantly more frequent among

risperidone-treated patients (3% vs 11%,  $p$  less than 0.01). Hypotension occurred more frequently among risperidone-treated patients ( $p$  less than 0.01). Weight gain was significantly greater for the [clozapine](#) group (2.4 kilograms vs 0.2 kilograms;  $p$  less than 0.002) (Azorin et al, 2001).

#### 4.6.D.3) Adverse Effects

a) Adverse effects and death were more commonly reported as the reasons for the discontinuation of [clozapine](#) while ineffectiveness was more often reported as the reason for discontinuation of [risperidone](#) (long-acting injection) in a retrospective, phase 3 study ( $n=322$ ). Patients with a diagnosis of [schizophrenia](#), [schizoaffective disorder](#), [bipolar disorder](#) or other [psychotic disorders](#) who received [clozapine](#) ( $n=161$ ), and had mean duration of therapy of 12.3 +/- 18.6 months (range, 0.25 to 100 months; median, 3 months) were matched by age (mean age, 40 +/- 12.6 years; range, 18 to 83 years) and gender at discontinuation to patients who discontinued [risperidone](#) long-acting injection ( $n=161$ ). The [risperidone](#) patients (mean age, 39.9 +/- 13.1 years, range 18 to 83 years) were matched without knowledge of the reason for discontinuation of therapy (mean duration of therapy of 5.9 +/- 8.7 months; range, 0.5 to 46 months; median, 3 months). The reasons for discontinuation differed significantly between [clozapine](#) and [risperidone](#) injection; additionally, death as reason for discontinuation was significantly more common with [clozapine](#) (13%) vs [risperidone](#) injection (1.9%) (Taylor et al, 2009).

#### Reasons for Discontinuation: Clozapine vs Risperidone

Reason	<a href="#">Clozapine</a> ( $n=161$ ) n (%)	<a href="#">Risperidone</a> ( $n=161$ ) n (%)	OR (95% CI)	p value
Patient's decision	77 (47.8)	64 (39.7)	1.41 (0.89 to 2.21)	0.139
Adverse effects	57 (35.4)	32 (19.9)	2.19 (1.31 to 3.67)	0.0023
Ineffectiveness	3 (1.9)	59 (36.6)	0.034 (0.01 to 0.14)	less than 0.0001
Death	21 (13)	3 (1.9)	7 (2.09 to 23.5)	0.0003
Other	3 (1.9)	3 (1.9)	-	-

The cause of death reported in [clozapine](#) patients (mean age, 49.2 +/- 14.5 years, range 30 to 83 years) included: [pneumonia](#) ( $n=5$ ), [lung carcinoma](#) ( $n=3$ ), other [carcinoma](#) ( $n=2$ ), [myocardial infarction](#) ( $n=2$ ), cerebrovascular accident ( $n=2$ ), clozapine overdose ( $n=2$ ), [gastrointestinal hemorrhage](#) ( $n=1$ ), [cardiac arrest](#) ( $n=1$ ), [left ventricular failure](#) ( $n=1$ ), [asphyxia](#) during restraint ( $n=1$ ) and sepsis ( $n=1$ ). There was no incidence of [neutropenia](#) or [agranulocytosis](#) at the time of death in any of the patients. The cause of death in the [risperidone](#) patients included: [myocardial infarction](#) ( $n=1$ ), [left ventricular failure](#) ( $n=1$ ) and sudden unexplained death ( $n=1$ ). The mortality rate for [clozapine](#) patients was 8.5 per 1000 patient-years (95% CI, 5.53 to 13.07) vs 5.3 per 1000 patient-years (95% CI, 1.7 to 16.61) (Taylor et al, 2009).

b) The results of one study suggest that patients receiving atypical antipsychotics have a higher incidence of [pancreatitis](#) than patients receiving a conventional antipsychotic medication. In a retrospective, pharmacovigilance study, 192 cases of [pancreatitis](#) were identified in patients taking [clozapine](#) (mean dose, 306.7 milligrams (mg)/day), [olanzapine](#) (mean dose, 15 mg/day), [risperidone](#), (mean dose, 4 mg/day) or [haloperidol](#) (mean dose, 8.2 mg/day). Of the identified cases, 40%, 33%, and 16% were related to treatment with the atypical antipsychotic medications [clozapine](#), [olanzapine](#), or [risperidone](#), respectively, as compared with 12% of the cases which were related to the conventional neuroleptic, [haloperidol](#). In most patients, time to onset of [pancreatitis](#) was within 6 months after initiation of treatment (Koller et al, 2003).

c) [Clozapine](#) was associated with fewer extrapyramidal side effects (EPS) than was [risperidone](#) (Miller et al, 1998). Outpatients receiving stable doses of [clozapine](#) ( $n=41$ ), [risperidone](#) ( $n=23$ ), or conventional antipsychotics ( $n=42$ ) were screened for EPS. Utilizing the Barnes [Akathisia](#) Scale, [akathisia](#) was noted in 7.3% of [clozapine](#) patients, 13% of [risperidone](#) patients, and 23.8% of conventional antipsychotic



users. From the Simpson-Angus scale, rigidity and cogwheeling were noted in 4.9% and 2.4% of [clozapine](#) patients, 17.4% and 17.4% of [risperidone](#) patients, and 35.7% and 26.2% of conventional antipsychotic users, respectively. However, salivation was noted in 36.6% of [clozapine](#) patients, 8.7% of [risperidone](#) patients, and 4.8% of conventional antipsychotic users.

**d)** Insomnia and extrapyramidal side effects were more common with [risperidone](#), and sedation and weight gain were more common with [clozapine](#) in a single-blind, crossover pilot study of the side effect profiles of the 2 drugs (Daniel et al, 1996). Twenty outpatients with [schizophrenia](#) or [schizoaffective disorder](#) were randomized to each drug for 6 weeks separated by a 1-week tapering-off period before crossover. The mean doses at week 6 were 6.1 milligrams/day (range 1 to 10 mg/d) of [risperidone](#) and 375 milligrams/day (range 75 to 800 mg/d) of [clozapine](#). Three patients dropped out of the study; there was no significant difference in therapeutic effect between the 2 treatment groups. Mean body weight was greater ( $p$  less than 0.005) and sleepiness and lack of alertness were reported more often after the [clozapine](#) treatment phase. Restlessness and insomnia were more frequent complaints after the [risperidone](#) phase. A longer, double-blind study with a large sample of patients is needed to further elucidate the therapeutic differences and side effect profiles of these 2 drugs.

#### 4.6.E Ziprasidone

##### 4.6.E.1 Schizophrenia

**a)** [Ziprasidone](#) was as effective as [clozapine](#) in the treatment of adults with [schizophrenia](#) resistant or intolerant to multiple cycles of antipsychotic therapy, according to an 18-week, randomized, double-blind, flexible-dose, equivalence MOZART trial (Monitoring Oral [Ziprasidone](#) As Rescue Therapy;  $n=147$ ). Patients diagnosed with DSM-IV [schizophrenia](#) and resistant or intolerant to 6 weeks of antipsychotic therapy, with baseline Clinical Global Impression Severity (CGI-S) scale score of at least 4, and a Positive and Negative Syndrome Scale (PANSS) score of at least 80 were included in the study. At baseline patients had a mean total PANSS score was 107 and CGI-S score of 5.2. Following a 1- to 7-day washout period and a 3-day placebo run-in period, patients were randomized to receive either [ziprasidone](#) ( $n=73$ ) or [clozapine](#) ( $n=73$ ). [Ziprasidone](#) therapy was initiated with 80 milligrams (mg)/day divided in 2 doses for 3 days, then flexibly dosed 80 to 160 mg/day. [Clozapine](#) was initiated with 25 mg/day titrated to 300 mg/day over 10 days, maintained for 1 week, then flexibly dosed 250 to 600 mg/day. Concomitant benzodiazepines, anticholinergic drugs, and [propranolol](#) was permitted. Clinical equivalence was defined as 13.5 points on the PANSS total score to yield an effect size of 0.45. The rate of premature discontinuation from the trial was similar in both groups (28 patients in each group (38.4%)) mainly due to adverse events. In an intent-to-treat analysis with last observation carried forward, the PANSS total score change from baseline was  $-25 \pm 22$  (95% CI,  $-30.2$  to  $-19.8$ ) in ziprasidone-treated patients compared with  $-24.5 \pm 22.5$  (95% CI,  $-29.7$  to  $-19.2$ ) in clozapine-treated patients, with no significant difference seen between treatment groups, yielding a baseline to endpoint effect size of 1.41 and 1.38, respectively. There were no significant differences between treatment groups in an analysis of subscale PANSS positive, negative, and general psychopathology, and in CGI-S score improvement. Treatment-emergent adverse events occurred in 71% ( $n=52$ ) of ziprasidone-treated patients and in 79.5% ( $n=58$ ) of clozapine-treated patients. There were significant decreases from baseline in median fasting total cholesterol, LDL-C, and [triglycerides](#) in ziprasidone-treated patients ( $p$  less than 0.05) (Sacchetti et al, 2009).

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