

## DRUGDEX® Evaluations

### CLOZAPINE

#### 0.0 Overview

##### 1) Class

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

##### 2) Dosing Information

###### a) Adult

- 1) Schizoaffective disorder - Suicidal behavior, Recurrent
  - a) initial, 12.5 mg ORALLY 1-2 times a day, then continued with daily dosage increments of 25-50 mg/day, if well-tolerated, to achieve a target dose of 300-450 mg/day (in 2-3 divided doses) by the end of 2 weeks
  - b) maintenance: dosage adjustments should be made no more than 1-2 times per week, in increments not to exceed 100 mg; MAX daily dosage is 900 mg/day
- 2) Schizophrenia, Treatment-resistant
  - a) initial, 12.5 mg ORALLY 1-2 times a day, then continued with daily dosage increments of 25-50 mg/day, if well-tolerated, to achieve a target dose of 300-450 mg/day (in 2-3 divided doses) by the end of 2 weeks
  - b) maintenance: dosage adjustments should be made no more than 1-2 times per week, in increments not to exceed 100 mg; MAX daily dosage is 900 mg/day
- 3) Schizophrenia - Suicidal behavior, Recurrent
  - a) initial, 12.5 mg ORALLY 1-2 times a day, then continued with daily dosage increments of 25-50 mg/day, if well-tolerated, to achieve a target dose of 300-450 mg/day (in 2-3 divided doses) by the end of 2 weeks
  - b) maintenance: dosage adjustments should be made no more than 1-2 times per week, in increments not to exceed 100 mg; MAX daily dosage is 900 mg/day

###### b) Pediatric

- 1) safety and effectiveness in pediatric patients have not been established

##### 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) Death
- f) Drug-induced eosinophilia
- g) Fecal impaction
- h) Gastrointestinal hypomotility
- i) Hepatitis
- j) Hyperglycemia
- k) Ischemic bowel disease
- l) Leukopenia
- m) Myocarditis, 5 cases/100,000 patient years
- n) Neuroleptic malignant syndrome
- o) Neutropenia
- p) Orthostatic hypotension
- q) Pancreatitis
- r) Paralytic ileus
- s) Perforation of intestine
- t) Pericardial effusion
- u) Pulmonary embolism

- v) Respiratory arrest
  - w) Seizure
  - x) Sudden cardiac death
  - y) Syncope
  - z) Tardive dyskinesia
  - aa) Thrombocytopenia
  - ab) White blood cell finding, Decreased
- 5) Clinical Applications
- a) FDA Approved Indications
    - 1) Schizoaffective disorder - Suicidal behavior, Recurrent
    - 2) Schizophrenia, Treatment-resistant
    - 3) 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 (Canada, 1997)
  - 2) Solubility
    - a) Systemic: Very slightly soluble in water (Prod Info Clozapine, 98).

### 1.2 Storage and Stability

- A) Oral route
  - 1) Storage temperatures for clozapine tablets should not exceed 86 degrees F (30 degrees C) (Prod Info Clozaril(R), 2002).
  - 2) Store clozapine oral disintegrating tablets at 25 degrees Celsius (77 degrees Fahrenheit) with excursions permitted to 15 to 30 degrees Celsius (59 to 86 degrees Fahrenheit) (Prod Info Fazaclo(TM), 2003).
- B) 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

Normal Dosage

Dosage in Geriatric Patients

#### 1.3.1 Normal Dosage

Intramuscular route

Oral route

Parkinson's disease - Psychotic disorder

Tardive dyskinesia

**1.3.1.A Intramuscular route**

- 1) Short-term intramuscular administration of clozapine effectively managed 59 treatment-resistant schizophrenic patients whose refusal to take oral medications precipitated an acute exacerbation. Patients had previously received oral clozapine at a mean dose of 307 milligrams/day. The average parenteral dose was 202 milligrams/day for a duration of 3 to 8 days. All patients improved and 90% became compliant with oral clozapine. In addition to the desired sedative effect, parenteral clozapine was associated with constipation (12%), headache (10%), dry mouth (7%) and injection site reactions (5%) (Lokshin et al, 1999).
- 2) In clinical trials, patients have been treated with clozapine intramuscularly in daily doses of up to 600 milligrams/day. The usual range is 150 to 300 milligrams daily (Ayd, 1974c).

**1.3.1.B Oral route**

- 1) The recommended initial dose of clozapine for treatment-resistant schizophrenia and recurrent suicidal behavior is 12.5 milligrams (mg) (one-half 25 mg tablet) once or twice daily (Prod Info Clozaril(R), 2002; Prod Info Fazaclo(TM), 2003). 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.

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

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

Target doses of 300 to 450 milligrams/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.

- 2) If therapy is interrupted for two days or more, clozapine should be reinitiated at a dose of 12.5 milligrams once or twice daily. If well-tolerated, titration to the therapeutic dose may proceed more rapidly than recommended for initial therapy. Patients previously experiencing untoward reactions with initial therapy should be retitrated with caution even following 24 hours off of the drug (Prod Info Clozaril(R), 2002; Prod Info Fazaclo(TM), 2003).

- 3) In a double-blind trial conducted at a state psychiatric hospital (n=50), daily doses of 300 to 600 milligrams were generally superior to 100 milligrams/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 milligrams/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 milligrams/day, n=3 on 600 milligrams/day) of this sample met response criteria. At the 16-week timepoint, the 600 milligrams/day dose was statistically superior to the lower doses (p less than 0.05). After 48 weeks, both 300 milligrams/day and 600 milligrams/day were statistically equivalent, with 100 milligrams/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 milligrams/day) (Simpson et al, 1999).

- 4) 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).

- 5) One author reports that therapeutic doses of clozapine range from 50 to 800 milligrams daily. Most patients appear to respond to doses of 200 to 400 milligrams 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.C Parkinson's disease - Psychotic disorder**

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

**1.3.1.D Tardive dyskinesia**

See Drug Consult reference: TARDIVE DYSKINESIA - DRUG THERAPY

**1.3.1.E IMPORTANT NOTE**

- 1) Clozapine should NOT be dispensed without appropriate white blood cell count monitoring (Prod Info Clozaril(R), 2002).
- 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), 2002).

**1.3.1.F DISCONTINUATION OF TREATMENT**

- 1) 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 Clozaril(R), 2002; Prod Info Fazaclo(TM), 2003).

**1.3.1.G MAXIMUM DOSE**

- 1) 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 Clozaril(R), 2002; Prod Info Fazaclo(TM), 2003).

**1.3.1.H ORAL DISINTEGRATING TABLETS - PATIENT INSTRUCTIONS**

- 1) Oral disintegrating tablets are supplied as blister packs and should not be opened until ready for use. Peel back foil to expose tablet; do NOT push the tablet through the foil. Just prior to use, remove the tablet from the blister unit and immediately place the entire tablet in the mouth; allow the tablet to disintegrate and then swallow with saliva. Water is not needed to take clozapine oral disintegrating tablets (Prod Info Fazaclo(TM), 2003).

**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 Clozaril(R), 2002).
- B) Elderly patients may be particularly susceptible to the anticholinergic effects of Clozaril (clozapine), such as urinary retention and constipation (Prod Info Clozaril(R), 2002).
- 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).
- D) Low-dose initial treatment for geriatric patients is recommended (12.5 milligrams given once on the first day) with subsequent increases not exceeding 25 mg daily (Prod Info Clozaril(R) Australia, 1996).

**1.4 Pediatric Dosage**

Normal Dosage

Dosage in Other Disease States

**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 Clozaril(R), 2002); (Prod Info Clozaril(R) Australia, 1996).
- 2) 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 (Frazier et al, 1994). 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.

**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 norclozapine 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

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

### 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-desmethyloclozapine, 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****1) 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; Fazaclor(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

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Immunologic Effects

Musculoskeletal Effects

Neurologic Effects

Ophthalmic Effects

Otic Effects

Psychiatric Effects

Renal Effects

Respiratory Effects

Other

#### 3.3.1 Cardiovascular Effects

Abnormal ECG

Cardiac complication

Cardiac dysrhythmia

Cardiomyopathy

Edema

Hypertension

Hypotension

Orthostatic hypotension

Phlebitis

Sudden cardiac death

Tachyarrhythmia

### **3.3.1.A Abnormal ECG**

1) Premature ventricular contractions are temporally associated with clozapine and occur with patients at a frequency less than 1%. A minority of patients experience ECG repolarization changes including ST segment depression and flattening of T-waves or inversion of T-waves; clinical significance is unclear. All of these effects normalize after clozapine is discontinued (Prod Info Clozaril(R), 2002).

### **3.3.1.B 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).

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 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.C 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.D 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) A total of 82 reports of myocarditis associated with clozapine use have been received from the USA, Canada, UK, 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), 2002).

3) Twenty-eight cases of myocarditis, including 18 deaths, and 41 cases of cardiomyopathy, including 10 deaths, were reported to the Food and Drug Administration in clozapine recipients over a 10-year period (La Grenade et al, 2001). Additionally, postmarketing evaluation revealed cases of congestive heart failure; causality was complicated because of serious preexisting cardiac disease (Prod Info Clozaril(R), 2002).

4) 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/L) were  $1.28 \pm 0.33$ ,  $1.47 \pm 0.57$ ;  $1.39 \pm 0.29$ ,  $1.70 \pm 0.4$ ;  $1.47 \pm 0.41$ ,  $1.7 \pm 0.48$ ; and  $1.49 \pm 0.3$ ,  $1.8 \pm 0.58$  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).

5) Based on reports to the Food and Drug Administration, those who developed myocarditis and survived were generally treated for a shorter time (median 2 weeks vs 4 weeks) and took a lower daily dose (median 225 mg vs 450 mg) than those who died. However in patients with cardiomyopathy, the median dose (450 mg vs 500 mg) and the duration of therapy (8 months vs 10 months) were similar in those who survived and those who died (La Grenade et al, 2001).

6) 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).

7) 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.E 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.F 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 re-challenge). 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.G 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 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.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, reinstate 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 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.J 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.K 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).

## 3.3.2 Dermatologic Effects

Cellulitis

Dermatological finding

Rash

Sweating symptom

### 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, PHOTSENSITIVITY, 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

Acid-base balance - finding

Body temperature finding

Diabetes mellitus

Diabetic ketoacidosis

Disorder of fluid AND/OR electrolyte

Excessive salivation

Hyperlipidemia

Hyperprolactinemia

Lactic acidosis

Metabolic syndrome

Selenium deficiency

Sweating

Weight gain

**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 ng/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) Literature Reports

a) 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).

### 3.3.4 Gastrointestinal Effects

Abdominal discomfort

Bowel obstruction

Colitis, Necrotizing

Constipation

Diarrhea

Excessive salivation

Fecal impaction

Gastrointestinal hypomotility

Heartburn

Ischemic bowel disease

Nausea

Nausea and vomiting

Pancreatitis

Paralytic ileus

Parotitis

Perforation of intestine

Summary

Swelling of salivary gland

Vomiting

Xerostomia

#### **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. Re-challenge 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 benzotropine 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**

Agranulocytosis

Blood coagulation disorder

Disorder of hematopoietic structure

Drug-induced eosinophilia

Hematology finding

Neutropenia

Thromboembolic disorder

**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/millimeters cubed. In the US 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). The mechanisms of clozapine-induced agranulocytosis have been reviewed (Pirmohamed & Park, 1997a)

**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 milligrams (mg) per 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/milliliter (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 milligrams (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 milligrams/deciliter). 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 micrograms/day of filgrastim administered subcutaneously with the onset of agranulocytosis, increasing by 300 micrograms/day for the first 3 days to a total of 900 micrograms/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 micrograms/kilogram/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) Summary

a) 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 milligrams/day), Klonopin, Cogentin, and Lopid. 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 milligrams daily 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-DESMETHYLCLOZAPINE, the major metabolite of clozapine, is toxic. N-desmethylclozapine 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/cubic millimeter (mm<sup>3</sup>), interrupt therapy until the count falls below 3000 cells/mm<sup>3</sup> (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%

#### 3) LITERATURE REPORTS

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 milligrams/day, respectively. Their eosinophil counts peaked at 1365 and 984 per cubic millimeter, 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/cubic millimeter (mm<sup>3</sup>) and neutropenia was defined as an absolute neutrophil count below 2000 cells/mm<sup>3</sup>. 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 milligrams/day developed eosinophilia with a peak of 1320/microliter on treatment day 26 (Lucht & Rietschel, 1998). Clozapine was discontinued and the eosinophil count decreased to 220/microliter on day 45. Also of note is that neutropenia developed with a low of 1800/microliter on day 32 and IgE increased to 254 IU/deciliter (reference value less than 120 IU/deciliter).

d) A 37-year-old man developed eosinophilia (700 cells/cubic millimeter) 2 weeks after beginning clozapine therapy (Amital et al, 1997). 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.

e) Eosinophilia developed in a 38-year-old schizophrenic patient following 5 weeks of clozapine therapy (eosinophil count of 1500 cells/cubic millimeter). 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 Hematology finding

1) N-desmethylclozapine, the major metabolite of clozapine, is toxic. N-desmethylclozapine is further metabolized to an unstable compound that is toxic to hemopoietic precursors of both myeloid and erythroid lineages. Therapeutic use of clozapine has been associated with neutropenia, agranulocytosis, neutrophilia, and rare eosinophilia. A few recent studies suggest patients of Jewish and Asian origin may be at higher risk for agranulocytosis. Adverse effects that were temporally associated with clozapine and occurred in patients are anemia and leukocytosis. Other effects voluntarily reported by the manufacturer include sepsis, thrombocytopenia, thrombocytosis, pulmonary embolism, deep vein thrombosis, elevated hemoglobin, elevated hematocrit, and increased erythrocyte sedimentation rate and a causal relationships that could not be determined.

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).

### 3.3.5.F Neutropenia

#### 1) Summary

a) In clinical studies, neutropenia occurred in 2.7 to 22% of patients. The peak onset was 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 per cubic millimeter ( $\text{mm}^3$ ) or absolute neutrophil count (ANC) below 1500 per  $\text{mm}^3$ ). 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 per  $\text{mm}^3$ ) 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 milligrams (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/cubic millimeter ( $\text{mm}^3$ ), while the total white blood cell (WBC) count was within a normal range (4100/ $\text{mm}^3$ ). However, the blood sample taken the same afternoon at 2 p.m. showed that the neutrophil count had returned to normal (2200/ $\text{mm}^3$ ) and the total WBC count had risen to 5500/ $\text{mm}^3$ . Blood tests were continued twice a week and whenever the morning neutrophil counts fell between 1200 and 1900/ $\text{mm}^3$  (WBC counts: 4100 to 4700/ $\text{mm}^3$ ), they were between 2200 and 2700/ $\text{mm}^3$  in the afternoon (WBC counts: 5400 to 5800/ $\text{mm}^3$ ). 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 daily. 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 milligrams per day), the patient's WBC count was stable and ranged between 6000 and 10000 cubic millimeters ( $\text{mm}^3$ ). 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 the 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 milligrams/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 milligrams) despite decreased leukocytes (2480 cells/cubic millimeter (mm<sup>3</sup>)), decreased neutrophil granulocytes (800 cells/mm<sup>3</sup>) and an acute febrile respiratory infection. He received G-CSF 300 micrograms with an increase in leukocytes and neutrophils 6 hours later (2680/mm<sup>3</sup>) and 1250/mm<sup>3</sup>, 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 reinstate clozapine therapy despite previous neutropenia after receiving pretreatment with lithium. Clozapine was previously discontinued after a decrease in granulocytes to 1400 cells/cubic millimeter. After failing other antipsychotics, lithium was initiated and increased to 0.8 to 1.1 millimoles/liter. Clozapine was introduced 2 weeks later at 12.5 milligrams (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.G Thromboembolic disorder

#### 1) Summary

**a)** Six cases of PULMONARY EMBOLISM and 6 cases of VENOUS THROMBOSIS were reported during clozapine therapy. The adverse reaction was fatal in 5 cases with the affected patients being 3 women and 9 men aged 25-59 years. Complications that included VENOUS THROMBOEMBOLISM developed within the first 3 months of clozapine therapy in 8 of the patients (Hagg & Soderstrom, 2000). Adverse effects voluntarily reported by the manufacturer are THROMBOCYTOSIS and DEEP VEIN THROMBOSIS; a causal relationship could not be determined (Prod Info Clozaril(R), 2002).

#### 2) LITERATURE REPORTS

**a)** 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 milligrams per 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

Hepatotoxicity

Increased liver enzymes

Liver finding

#### 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

Drug-induced lupus erythematosus, Systemic

Immune hypersensitivity reaction

Immunology finding

Systemic lupus erythematosus

### 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 Lipid. 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<sub>1</sub> and D<sub>2</sub> dopamine receptors, or the blockage of 5<sub>2</sub> serotonergic, alpha, adrenergic, muscarinic, and H<sub>1</sub> histamine receptors (Stoppe et al, 1992).

### 3.3.7.C Immunology 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

Musculoskeletal finding

Pain

Polyserositis

Rhabdomyolysis

Serum creatinine raised

### 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) Summary

- a) 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 creatine 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 creatine 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

Dizziness

Dystonia

EEG finding

Headache

Movement disorder

Myoclonus

Neuroleptic malignant syndrome

Neurological finding

Paralysis

Seizure

Somnolence

Stuttering

#### 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 with 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<sup>3</sup> and his creatine kinase at 1501 units(U)/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<sup>3</sup>. 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 U/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; Battegay 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**

Disorder of ear

Ear and auditory finding

**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**

Delirium

Obsessive-compulsive disorder

Psychiatric sign or symptom

**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 in 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

Interstitial nephritis

Nocturnal enuresis

Urinary incontinence

Urinary retention

Urogenital finding

### **3.3.13.A Interstitial nephritis**

#### **1) Summary**

**a)** Voluntary postmarketing reports from the manufacturer include the adverse effect of acute interstitial nephritis during clozapine therapy, however a causal relationship could not be determined (Prod Info Clozaril(R), 2002). There have also been a few case reports of interstitial nephritis (Fraser and Jibani, 2000)(Elias et al, 1999).

#### **2) LITERATURE REPORTS**

**a)** 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).

**b)** 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) Summary**

**a)** Bladder urgency and/or enuresis occurred in a series of 10 patients during treatment with clozapine (Frankenburg et al, 1996). In another study it occurred in 11 of 25 patients (Lin et al, 1999). The incidence of nocturnal enuresis was at least 0.23% to as high as 41% of patients treated with clozapine (Lin et al, 1999; Steingard, 1994). URINARY URGENCY and URINARY FREQUENCY, occurred in 1% of patients (n=842) with therapeutic use of clozapine (Prod Info Clozaril(R), 2002).

#### **2) LITERATURE REPORTS**

**a)** 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).

**b)** 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).

**c)** 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 Urinary incontinence**

#### **1) Summary**

**a)** In clinical manufacturer trials, incontinence has occurred in 1% of patients (n=842) with therapeutic use of clozapine (Prod Info Clozaril(R), 2002). Two other studies reported incontinence in patients ranging from 29% to 44% (Lin et al, 1999; Fuller et al, 1996).

#### **2) LITERATURE REPORTS**

**a)** In a retrospective review of 61 Chinese inpatients with chronic schizophrenia treated with clozapine for at least 3 months, the incidence of urinary incontinence (UI) 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 UI. The same characteristics were also statistically equivalent between subjects with persistent versus self-limiting UI. Of the 27 patients with UI, 15 (56%) had persistent and 12 (44%) had self-limiting UI; 25 (93%) had nocturnal enuresis with (n=11) or without (n=14) daytime symptoms; 2 (7%) had daytime UI only. Concomitant medications were not associated with UI in this sample (Lin et al, 1999).

**b)** 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.D Urinary retention

#### 1) Summary

**a)** Urinary retention occurred in 1% of patients (n=842) during clozapine therapy. Elderly patients may be particularly susceptible to the anticholinergic effects of clozapine, such as urinary retention (Prod Info Clozaril(R), 2002).

### 3.3.13.E Urogenital finding

#### 1) Summary

**a)** In clinical trials, ABNORMAL EJACULATION occurred in 1% of patients (n=842) with clozapine therapy. Adverse effects temporally associated with clozapine and occurring at a frequency less than 1% include DYSMENORRHEA, IMPOTENCE, DECREASE LIBIDO, INCREASED LIBIDO, BREAST PAIN, VAGINAL ITCHING, and POLYDIPSIA. Voluntary postmarketing reports also noted PRIAPISM, however a causal relationship could not be determined (Prod Info Clozaril(R), 2002).

**2)** In clinical trials, incontinence, urinary urgency/urinary frequency, urinary retention, and abnormal ejaculation have occurred in patients with clozapine therapy. Elderly patients may be particularly susceptible to the anticholinergic effects of Clozaril (clozapine), such as urinary retention. Adverse effects temporally associated with clozapine and occurring less frequently include dysmenorrhea, impotence, decrease libido, increased libido, breast pain, vaginal itching, and polydipsia. Reports also include acute interstitial nephritis and priapism but a causal relationship could not be determined.

### 3.3.15 Respiratory Effects

Lung finding

Pleural effusion

Pulmonary embolism

Respiratory finding

#### 3.3.15.A Lung finding

##### 1) Summary

**a)** 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. In clinical trials, DYSPNEA, NASAL CONGESTION, and THROAT DISCOMFORT occurred in 1% of patients (n=842). Adverse effects temporally associated with clozapine and occurring at a frequency less than 1% include COUGHING, PNEUMONIA, RHINORRHEA, HYPERVENTILATION, WHEEZING, BRONCHITIS, LARYNGITIS, and SNEEZING. Voluntary postmarketing reports include ASPIRATION and PLEURAL EFFUSIONS; a causal relationship could not be determined (Prod Info Clozaril(R), 2002).

#### 3.3.15.B 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 milligrams/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/cubic millimeter, 23.6% eosinophils). Clozapine was discontinued and he improved with antibiotics. The patient was re-challenged 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).

### 3.3.15.C Pulmonary embolism

#### 1) Summary

a) (Hagg et al, 2000f) identified 12 cases of thromboembolism associated with clozapine treatment (mean dose of 277 milligrams per day). Six cases of venous thrombosis and 6 cases of pulmonary embolism were reported; five patients died. No confounding illness was found in any of the patients that would have contributed to thromboembolic disease. One other case of pulmonary embolism was noted and the patient recovered (Maynes, 2000).

#### 2) Incidence: rare

#### 3) LITERATURE REPORTS

a) 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).

### 3.3.15.D Respiratory finding

1) Pulmonary effusion and embolisms have occurred with therapeutic clozapine use. 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. Dyspnea and nasal congestion occurred in patients. Adverse effects temporally associated with clozapine and occurring at a low frequency include coughing, pneumonia, rhinorrhea, hyperventilation, wheezing, bronchitis, laryngitis, aspiration and sneezing.

### 3.3.16 Other

Summary

Dead - sudden death

Death

Extrapyramidal disease

Fever

Malaise

Seizure

Withdrawal sign or symptom

#### 3.3.16.A Summary

##### 1) OTHER EFFECTS

a) Withdrawal and sudden death has been associated with clozapine therapy.

#### 3.3.16.B Dead - sudden death

##### 1) Summary

a) In a retrospective review of inpatient mental health records (1991 to 1997, n=5479) and national death registry data, investigators discovered a higher incidence of sudden death among clozapine users compared to nonusers. Of 561 clozapine recipients, there were 6 sudden deaths (1.07%), 2 suicides (0.35%), and 2 disease-related deaths (0.35%). The 6 sudden deaths occurred in 4 current and 2 former (2 weeks and 5 years posttreatment) users of clozapine, respectively. Of 4918 not exposed to clozapine, there were 14 sudden deaths (0.28%), 5 suicides (0.1%) and 86 disease-related deaths (1.75%). Sudden deaths were significantly more frequent in the clozapine group (p less than 0.01), while disease-related deaths were significantly more common in the non-clozapine group (p less than 0.05). The average age at sudden death was lower in clozapine users (41 versus 51 years, p less than 0.04). However, the validity of attributing a sudden death to clozapine 5 years after its discontinuation is

doubtful. These data should be interpreted with caution because of the small numbers of sudden deaths and lack of autopsies (Modai et al, 2000).

### 3.3.16.C 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 timepoints 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.D Extrapyramidal disease

See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

### 3.3.16.E Fever

#### 1) Summary

a) Fever was associated in 4% to 6% of patients (sometimes along with flu-like symptoms) following therapeutic dosages of clozapine. It (100.4 degrees Fahrenheit (38 degrees Centigrade)) 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); (Blum, 1990).

#### 2) Incidence: 5%

**3.3.16.F Malaise**

## 1) Summary

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

**3.3.16.G Seizure**

See Drug Consult reference: PREVENTION OF CLOZAPINE-INDUCED SEIZURES

**3.3.16.H Withdrawal sign or symptom**

## 1) Summary

- a) Several different kinds of withdrawal symptoms including cholinergic rebound, dystonias, dyskinesias and worsening psychotic symptoms have occurred with clozapine therapy (Tollefson et al, 1999; Delassus-Guenault et al, 1999; Stanilla et al, 1997)

## 2) LITERATURE REPORTS

a) In a double-blind, placebo-controlled study of 106 patients undergoing elective discontinuation of clozapine, the immediate substitution of olanzapine 10 milligrams (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).

b) 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 milligrams (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).

c) 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.

d) Three cases of acute delirium and psychosis occurred upon withdrawal of clozapine. The patients involved were male, ages 38, 46, and 63, whose schizophrenia had been controlled on 250 to 600 milligrams/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 reinstatement 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).

e) A withdrawal syndrome occurred in 9 of 13 patients after sudden discontinuation of long-term clozapine therapy at doses ranging from 50 to 200 milligrams/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 (Zapletalek et al, 1980).

f) 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, 2008) (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) 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 also not demonstrated adverse effects due to clozapine use during gestation in rats and rabbits. Therefore, 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, 2008).

- 5) Literature Reports

a) 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).

b) 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 breast-feeding 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).

c) 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).

d) A case report described an infant born to a mother treated with clozapine 100 mg per day until the last nine 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 one minute and 8 at five 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).

e) There are no adequate and well-controlled studies in pregnant women. In animal studies, there was no evidence of impaired fertility or harm to the fetus when rat and rabbits were exposed to disease approximately 2 to 4 times the human dose (Prod Info CLOZARIL(R) oral tablets, 2008).

#### 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 breast-fed 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 is a result of postnatal exposure to clozapine (Mendhekar, 2007). Animal studies have indicated that clozapine may be excreted in breast milk. Therefore, breast-feeding should be avoided during clozapine treatment (Prod Info CLOZARIL(R) oral tablets, 2008).

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 breast-feeding 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 one minute and 8 at five 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

Drug-Drug Combinations

Drug-Food Combinations

#### 3.5.1 Drug-Drug Combinations

Aprindine

Belladonna  
Belladonna Alkaloids  
Benztropine  
Buspirone  
Carbamazepine  
Cimetidine  
Ciprofloxacin  
Citalopram  
Dehydroepiandrosterone  
Droperidol  
Encainide  
Erythromycin  
Flecainide  
Fluoxetine  
Fluvoxamine  
Fosphenytoin  
Guarana  
Lithium  
Lorazepam  
Lorcainide  
Mate  
Nefazodone  
Nicotine  
Norfloxacin  
Paroxetine  
Perphenazine  
Phenobarbital  
Phenylalanine

Phenytoin

Propafenone

Quinidine

Rifampin

Risperidone

Ritonavir

Sertraline

St John's Wort

Thioridazine

Tramadol

Venlafaxine

Zotepine

#### **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), 2002j).
- 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), 2002n). 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, benzotropine, 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), 2002f). 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), 2002j).
- 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), 2002g; 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), 2002j).

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), 2002m; Centorrino et al, 1994a; Centorrino et al, 1996e; 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, 1996d).

**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), 2002c; Chong et al, 1997a; 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, 1997a; 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, 1997).

**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, 1991a) 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, 1991).

### 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, 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: 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, 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. 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 (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 (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).

### 3.5.1.S 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 adenyl 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.T 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.U Lorcaïnide

- 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), 2002j).
- 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.V 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, 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: 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, 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. 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, 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 (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, 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 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, 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).

**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.W 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 norclozapine 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 norclozapine 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 norclozapine, 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 norclozapine. 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 norclozapine 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 norclozapine, 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 norclozapine 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.X 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), 2002b).
- 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.Y 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.Z 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), 2002l; Centorrino et al, 1996c; 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, 1996b).

### 3.5.1.AA 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), 2002h).

- 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.AB 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, 1991b) 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.AC 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 ( $r_s=0.347$ ,  $p$  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 ( $r_s=0.246$ ,  $p=0.092$ ; 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.AD 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), 2002e). 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: 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, 1991c).

### 3.5.1.AE 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), 2002j).
- 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.AF 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), 2002k).
- 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.AG 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.AH 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.AI 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.AJ 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), 2002d; Chong et al, 1997c; Centorrino et al, 1996a). 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 Zolof(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, 1997b).
  - 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, 1996).

**3.5.1.AK 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.AL 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), 2002h).
- 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.AM 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.AN 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), 2002i). 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.AO 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 x 10<sup>9</sup> cells/L and/or a neutrophil count less than 1.5 x 10<sup>9</sup> 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> )	Recommended Monitoring (*reduced monitoring permitted only if all WBC counts are greater than or equal to 3500 and ANC is greater than or equal to 2000)
Less than 6 months	Less than 1 month	No	Continue 6 months of weekly testing
	Greater		

Less than 6 months	than 1 month	No	Restart 6 months of weekly testing
6 to 12 months	Less than 1 month	No	Weekly testing for 6 weeks, then return to every 2 weeks for 6 months*
6 to 12 months	Greater than 1 month	No	Weekly testing for 6 months, then return to every 2 weeks for 6 months*
Greater than 12 months	Less than 1 month	No	Weekly testing for 6 weeks, then return to every 4 weeks*
Greater than 12 months	Greater than 1 month	No	Weekly testing for 6 months, then every 2 weeks for 6 months, then return to every 4 weeks*

\* 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<sup>3</sup> and an ANC above 2000 cells/mm<sup>3</sup>, 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<sup>3</sup> or greater but less than 3500/mm<sup>3</sup>) and/or mild granulocytopenia (ANC is 1000/mm<sup>3</sup> or greater but less than 1500/mm<sup>3</sup>) develop, monitoring should be twice-weekly until WBC count is greater than 3500/mm<sup>3</sup> and ANC is greater than 2000/mm<sup>3</sup>. At this point, return to previous monitoring (Prod Info CLOZARIL(R) Tablets, 2005).

6) If moderate leukopenia (WBC count is 2000/mm<sup>3</sup> or greater but less than 3000/mm<sup>3</sup>) and/or moderate granulocytopenia (ANC is 1000/mm<sup>3</sup> or greater but less than 1500/mm<sup>3</sup>) develop, therapy should be interrupted. Monitor daily until WBC are greater than 3000/mm<sup>3</sup> and ANC is greater than 1500/mm<sup>3</sup>, then twice-weekly until WBC is greater than 3500/mm<sup>3</sup> and ANC is greater than 2000/mm<sup>3</sup>. Rechallenge may occur when WBC are greater than 3500/mm<sup>3</sup> and ANC is greater than 2000/mm<sup>3</sup>. 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<sup>3</sup> and/or the ANC falls below 1000 cells/mm<sup>3</sup>, 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<sup>3</sup> and the ANC returns to levels above 1500 cells/mm<sup>3</sup>. Twice-weekly WBC counts and ANC should be taken until the total WBC counts return to levels above 3500 cells/mm<sup>3</sup> and ANC return to levels above 2000/mm<sup>3</sup>. After WBC are greater than 3500/mm<sup>3</sup>, 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.

**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, bowel blockage, certain nervous system problems, or certain heart problems.

**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 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 fluvoxamine (Luvox®), paroxetine (Paxil®), cimetidine (Tagamet®), carbamazepine (Tegretol®), ciprofloxacin (Cipro®), erythromycin (Ery-tab®), 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®, Zestril®) or medicine for heart rhythm problems (such as flecainide, encainide, propafenone, Rythmol®, Tambocor®).

Tell your doctor if you are also using other medicine to treat mental illness (such as chlorpromazine, haloperidol, risperidone, thioridazine, Haldol®, Mellaril®, Risperdal®, Thorazine®), medicine to treat anxiety (such as alprazolam, clonazepam, Ativan®, Valium®, Xanax®), medicine for nausea or vomiting (such as prochlorperazine, promethazine, Compazine®, Phenergan®), or medicine to treat depression (such as citalopram, venlafaxine, Celexa®, Effexor®).

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 breastfeeding, or if you ever had neuroleptic malignant syndrome (NMS). Tell your doctor if you have heart disease, liver disease, kidney disease, lung disease, an enlarged prostate, or a problem with your intestines. Tell your doctor if you have glaucoma, if you have ever had a head injury, or if you have a history of seizures.

Tell your doctor if you have diabetes, because this medicine may raise your blood sugar.

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.

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.

Tardive dyskinesia (a movement disorder) may occur and may not go away after you stop using the medicine. 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.

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:

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 or fainting.

Nausea, vomiting, loss of appetite, or pain in your upper stomach.

Pain in your lower leg (calf).

Seizures.

Swelling in your hands, ankles, or feet.

Weak and rapid heartbeat, tiredness, chest pain, fever, 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.

Dry mouth, increased sweating.

Excess saliva or drooling.

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 D<sub>2</sub> blockade and clinical efficacy than was previously thought (Pilowsky et al, 1992).

5) Positron emission tomography (PET) has been used for quantification of D<sub>2</sub> receptor occupancy induced by antipsychotic drugs in the basal ganglia. The classical neuroleptics have their antipsychotic effects mediated by a blockade of D<sub>2</sub> receptors. In clozapine-treated patients, the D<sub>2</sub> 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 led the authors to hypothesize that it is actually the difference in the dopamine D<sub>2</sub> receptor occupancy that accounts for the differences in clinical properties between clozapine and the typical antipsychotic drugs (Trichard et al, 1998).

6) Dopamine D<sub>4</sub> receptors have greater affinity for clozapine than for any other antipsychotic. The D<sub>4</sub> 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 dichotomous (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**

Aggressive behavior

Anorexia nervosa

Bipolar disorder

Borderline personality disorder

Catatonia

Cognitive function finding

Dementia

Depression

Excessive thirst

Extrapyramidal disease

Gilles de la Tourette's syndrome

HIV infection - Psychotic disorder

Movement disorder, Involuntary

Multiple sclerosis - Psychotic disorder

Parkinson's disease

Parkinson's disease - Psychotic disorder

Postpartum psychosis

Schizoaffective disorder, Refractory

Schizoaffective disorder - Suicidal behavior, Recurrent

Schizophrenia, Treatment-resistant

Schizophrenia - Suicidal behavior, Recurrent

Tardive dyskinesia

#### **4.5.A Aggressive behavior**

##### **1) Overview**

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

##### **2) Summary:**

Appears beneficial for the treatment of aggressive behavior

Sedative effects may contribute to the beneficial results

##### **3) Adult:**

- a)** Clozapine was effective in lessening frequency and intensity of aggressive and SELF-DESTRUCTIVE BEHAVIOR in 80% of 42 non-psychotic hospitalized patients. Patients received clozapine 15 to 75 milligrams daily (Balassa et al, 1971).

#### **4.5.B Anorexia nervosa**

See Drug Consult reference: ANOREXIA NERVOSA - DRUG THERAPY

#### **4.5.C Bipolar disorder**

##### **1) Overview**

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence is inconclusive

Recommendation: Adult, Class IIb; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

##### **2) Summary:**

Effective in patients with bipolar or schizoaffective disorder with refractory MANIA in uncontrolled trials

Effective in patients with psychotic bipolar disorder in a small prospective cohort study

**3) Adult:**

**a)** Clozapine was effective and relatively well tolerated in acute and long-term treatment of patients with psychotic bipolar disorder who have not responded to conventional pharmacotherapies. A small cohort prospective study included 34 bipolar disorder patients with psychotic features who were treated with clozapine at flexible doses (25 mg to 600 mg per day) over a 24-month period. All patients showed significant improvement 24 months from intake as assessed by the Brief Psychiatric Rating Scale and the Clinical Global Impressions-Severity of Illness scale (p less than 0.001). Such improvement was significantly greater among patients with bipolar disorder than with schizophrenia (p less than 0.05). For patients with bipolar disorder with psychotic features who are resistant to or intolerant of usual treatment options, clozapine may be an effective alternative (Ciapparelli et al, 2000).

**b)** Clozapine was more effective in a group of schizophrenic patients with bipolar features (n=41) than those without bipolar features (n=19) (Cassano et al, 1997). In an open, follow-up study, both groups received clozapine 75 to 600 milligrams (mg) and other drugs necessary for the relief of their symptoms. The average dose after 1 year for the bipolar group was 261 mg versus 298 mg for the group without bipolar features. After 12 months of treatment, according to the Brief Psychiatric Rating Scale scores, patients with bipolar features tended to respond significantly better (p less than 0.001 versus baseline) than those without bipolar features (p less than 0.05 versus baseline).

**c)** An open-label trial demonstrated the effectiveness of add-on clozapine for up to 1 year in treatment-resistant patients with a history of mania. Subjects had diagnoses of schizoaffective disorder, bipolar type (n=12) or bipolar I disorder (n=26) and were randomized to add-on clozapine or optimization of standard therapy for 1 year. The average daily dose of clozapine differed by diagnosis: 623 milligrams (mg)/day for schizoaffective and 234 mg/day for bipolar I (p=0.008). The dropout rates due to intolerance were 16% for clozapine and 47% for standard therapy (who were then crossed over to clozapine). Five of six psychiatric rating scales showed significantly greater improvement with add-on clozapine versus standard therapy alone. The Brief Psychiatric Rating scale score improved at least 30% from baseline to 6 months in 82% and 57% of clozapine recipients and the comparator group, respectively. Clozapine's additive efficacy permitted significant decreases in the concurrent medication regimen. Individuals without psychotic features benefited from clozapine to a similar degree as those with psychotic features. As evaluated via somatic complaint questionnaire, the incidence and severity of adverse effects did not differ between groups. Lack of blinding may have introduced bias into the study; further research is warranted (Suppes et al, 1999).

**d)** Clozapine has been shown to be an effective therapy for treatment of mania in resistant bipolar disorder patients (N=10) and schizoaffective disorder patients (N=15). In a prospective, open trial of clozapine, patients who had either a poor response or were intolerant of lithium, failed at least 2 neuroleptics, and failed either valproate or carbamazepine were treated with clozapine. Marked improvement (defined as a 50% improvement in score) was noted in 72% of the patients on the Young Mania Rating Scale and 32% exhibited marked improvement on the Brief Psychiatric Rating Scale (Calabrese et al, 1996).

**e)** In a non-controlled study, clozapine was used in the treatment of 17 bipolar disorder patients who had either failed or were intolerant to trials of lithium, valproate, carbamazepine, or neuroleptics. The study suggests that clozapine monotherapy is an effective mood stabilizer that reduces the number of affective episodes and rehospitalizations in patients with severe refractory bipolar illness. A controlled study is needed (Zarate et al, 1995).

**f)** Another author reported marked improvement in seven patients treated with clozapine for bipolar disorder, characterized by dysphonic mania with psychotic features and chronic disability refractory to standard treatments and anticonvulsants. During the subsequent follow up (3 to 5 years) most of the patients sustained gains in psychosocial function, and 6 of the 7 patients remaining on clozapine required no further hospitalization (Suppes et al, 1992).

**4) Pediatric:**

**a)** A 15-year-old male adolescent with severe treatment refractory bipolar disorder with psychotic features experienced a dramatic improvement in mood and psychotic symptoms when clozapine 300 milligrams (mg) per day was added to lithium 1350 mg per day. He had previously been treated with combinations of lithium, carbamazepine, and typical neuroleptics. Ten days after starting clozapine in combination with lithium, clinical improvement in restlessness, insomnia, and speech became apparent. Three weeks after beginning clozapine, Brief Psychiatric Rating Scale decreased from 74 to 37, Children Global Assessment Scale changed from 25 to 72, and Clinical Global Impression Severity of Illness subscale decreased from 7 to 3. Side effects included mild sedation and an increase in body weight. The patient continued to do well after nine months of therapy with lithium and clozapine 200 mg daily (Masi & Milone, 1998).

**4.5.D Borderline personality disorder****1) Overview**

FDA Approval: Adult, no; Pediatric, no  
Efficacy: Adult, Evidence is inconclusive  
Recommendation: Adult, Class IIb  
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

**2) Summary:**

Lead to improvements in symptomatology in a small sample of patients with borderline personality disorder

**3) Adult:**

**a)** Clozapine treatment greatly reduced the need for hospitalization in 7 patients with borderline personality

disorder (BPD), whether or not they had comorbid psychosis. Retrospective analysis of the records of patients who had been hospitalized for BPD and treated with clozapine revealed that, for the 7 patients who were initially discharged on clozapine treatment (average dose 334 milligrams/day; range 175 to 550 milligrams/day), state hospital use was reduced from an average of 110 days per year to 6.3 days per year (Brickman et al, 2002).

**b)** Preliminary data from a case series (n=7) of severe borderline personality disorder suggest that clozapine (mean dose: 421 milligrams/day) may decrease self- mutilation and aggressive behavior. The subjects were Caucasian females (mean age: 37 years) at state psychiatric facilities who were refractory to various combinations of psychotropic medications. Investigators reviewed patients' medical records to compare outcomes during 1 year before versus 1 year after the index date of clozapine initiation. Average Global Assessment of Functioning scores improved 48%; hospital privileges increased 60%; concurrent anxiolytic and antipsychotic medication use decreased 67% and 89%, respectively; and injuries to staff and peers dropped 93%. Both the number and duration of seclusion and restraint incidents (as proxy measures for self-mutilation) were reduced by 91% to 98% (Chengappa et al, 1999).

**c)** In a 4-month, open-label trial, low-dose clozapine improved symptomatology in patients (n=12) with severe borderline personality disorder (BPD) (Benedetti et al, 1998). BPD patients with severe psychotic-like symptoms who had failed a previous therapeutic program received clozapine starting at 12.5 milligrams (mg) and titrated to the lowest effective dose. Clozapine doses ranged from 25 to 100 mg/day (mean 43.8 mg/day). Since no available rating scale is specifically structured to assess changes in symptomatology of BPD patients, outcomes were difficult to measure. Utilizing the 5 items from the Brief Psychiatric Rating Scale relating to psychotic-like symptoms (items 4, 8, 11, 12, 15), 6 of 12 patients showed a 50% reduction in score after 1 month and 8 of 12 patients showed a 50% reduction after 4 months.

#### 4.5.E Catatonia

##### 1) Overview

FDA Approval: Adult, no; Pediatric, no  
Efficacy: Adult, Evidence is inconclusive  
Recommendation: Adult, Class IIb  
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

##### 2) Summary:

Effective in 1 case report

##### 3) Adult:

**a)** A 56-year-old woman with organic catatonia following frontal lobe injury responded to clozapine therapy (Rommel et al, 1998). Her catatonia manifested as restlessness, and rhythmic repetitive movements of her arms with rocking motion of her trunk. She did not respond to phenothiazines or haloperidol decanoate. Clozapine 350 milligrams made her symptoms slowly resolve. After 2 months, clozapine was withdrawn and symptoms reappeared 2 days later. Clozapine was successfully restarted and then gradually withdrawn after 1 year without relapse.

#### 4.5.F Cognitive function finding

##### 1) Overview

FDA Approval: Adult, no; Pediatric, no  
Efficacy: Adult, Evidence is inconclusive  
Recommendation: Adult, Class IIb  
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

##### 2) Summary:

May improve cognitive function in schizophrenic patients

##### 3) Adult:

**a)** Data from 12 published trials suggest that clozapine may improve some aspects of cognitive functioning in schizophrenia. The author of a review article reported positive results with clozapine for the following parameters: verbal fluency (6 of 7 studies); attention/ psychomotor speed (7 of 10 studies); verbal learning and memory (5 of 8 studies). The latter component is important in terms of employment potential. Mixed or equivocal results were noted for executive functioning, verbal working memory, and visual learning and memory. Two trials showed no cognitive improvements with clozapine (McGurk, 1999).

**b)** One study reported improved cognitive function, especially attention and verbal fluency in both treatment-resistant and non-treatment-resistant schizophrenia after clozapine therapy, for at least six weeks, with major improvement noted at six months. The data also suggest that clozapine treatment was superior to typical neuroleptics in improving cognitive function in schizophrenia (Lee et al, 1994).

#### 4.5.G Dementia

See Drug Consult reference: BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

#### 4.5.H Depression

##### 1) Overview

FDA Approval: Adult, no; Pediatric, no  
Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Conflicting data regarding the efficacy of clozapine in patients with depression (Ayd, 1974; Nahunek et al, 1973)

3) Adult:

a) A case of recurrent psychotic depression, unresponsive to multiple drug therapies and electroconvulsive therapy, responded to clozapine treatment (Dassa et al, 1993).

b) A 45-year-old woman with psychotic depression responded to a trial of clozapine instituted because of concomitant parkinsonian syndrome. The patient was resistant to conventional therapy (Parsa et al, 1991).

#### 4.5.I Excessive thirst

1) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

May be of value in reducing the severity of psychogenic polydipsia in patients with chronic schizophrenia

Unknown mechanism of action (Lee et al, 1991)

3) Adult:

a) Patients with polydipsia-hyponatremia syndrome improved after switching to clozapine therapy from their previous conventional neuroleptic agent (Canuso & Goldman, 1999). In an open study, 10 patients with polydipsia and hyponatremia (plasma sodium less than 125 milliequivalents/liter (mEq/L) were switched to clozapine therapy at 300, 600, and 900 milligrams (mg). Two patients were unable to tolerate the clozapine 900-mg dose. However, plasma osmolality normalized with clozapine 300 mg/day and the 2 higher doses were found to have no further effect. Plasma osmolality rose an average of 15.2 milliosmoles/kilogram above the patients' mean values. No fluid restrictions were required during the 18 weeks of clozapine therapy.

#### 4.5.J Extrapyrimal disease

1) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

May ameliorate classic neuroleptic-induced extrapyramidal syndrome consisting of concurrent chronic akathisia, parkinsonism, TARDIVE DYSKINESIA and dystonia.

3) Adult:

a) Drug-induced LARYNGEAL DYSTONIA resolved after clozapine was substituted for other drugs being used to treat schizophrenia in a 26-year-old woman. The woman presented in a florid psychotic state and with acute laryngeal dysfunction, including dysphonia and dysphagia. She showed no other extrapyramidal side effects. Her current medications (thioridazine, haloperidol, and zuclopentixol) were tapered and discontinued. She was given 2 other regimens (chlorpromazine and biperiden; promethazine, gabapentin, and biperiden), which were discontinued because of persistence of dysphonia and psychosis. Six days after admission she had an episode of food asphyxiation. Clozapine was prescribed, with the dose increased to 550 milligrams/day over 3 weeks. Improvement of laryngeal dysfunction was evident in the first week. Vocalization problems eventually resolved. There was also improvement of her psychotic state. The authors attributed the improvement in dystonia to a direct action of clozapine as an antidystonic agent (Lanzaro et al, 2001).

b) Clozapine successfully managed severe, disabling neuroleptic-induced blepharospasm, a rare form of tardive dystonia, in a case series (n=4). With slow titration to doses ranging from 100 to 200 milligrams (mg)/day, clozapine completely suppressed the symptoms of blepharospasm within 3 to 4 months with no psychotic exacerbations. In one instance, discontinuation of clozapine "unmasked" blepharospasm, which disappeared again with the reinstitution of clozapine. Clozapine continued to control blepharospasm for up to 5 years of follow-up (Levin & Reddy, 2000).

c) In an 18-week open, prospective trial, clozapine demonstrated efficacy in the treatment of all 3 co-existing aspects of neuroleptic-induced extrapyramidal syndrome in 20 patients with refractory schizophrenia. By the end of the study, clozapine (average dose 209 milligrams/day) significantly improved akathisia, parkinsonism and tardive dyskinesia by 78%, 69% and 74%, respectively, as assessed by standard rating scales (p less than 0.0001). Subjects also experienced statistical improvement in scores for psychosis, depression and anxiety (Spivak et al, 1997a).

d) Cases of disabling tardive dystonia and psychosis not responding well to antipsychotics, but

progressively improving with clozapine treatment were presented (Bassitt & Neto, 1998a; Raja et al, 1996a; Friedman, 1994a).

**e)** Case studies have shown that low doses of clozapine (mean dose 26.4 milligrams at bedtime) were found effective for the relief of nocturnal akathisia in nine patients with Parkinson's disease (Linazasoro et al, 1993). Three patients also experienced a marked improvement in resting tremor and five patients experienced a resolution of the confused state accompanying the akathisia.

**f)** Tardive dyskinesia response to clozapine was variable in 37 patients treated over a 4-year period. It was thought that those with the dystonic subtype may be effectively treated with clozapine (Lieberman et al, 1989). A review of 8 published studies reported similar findings (Lieberman et al, 1991).

#### 4.5.K Gilles de la Tourette's syndrome

##### 1) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

##### 2) Summary:

Effective in 1 case report of TICS

##### 3) Adult:

**a)** A 30-year-old man with acute paranoid syndrome and a long history of tics achieved total remission of his tics with clozapine therapy (Schmider, 1998). He was considered to have a nongenetic form of tics with multiple simple motor tics of the limbs and face, and simple and complex vocal tics. Clozapine was increased to 350 milligrams/day with a stable remission reported 1 month later.

#### 4.5.L HIV infection - Psychotic disorder

##### 1) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

##### 2) Summary:

Pilot data suggest possible benefit with clozapine

##### 3) Adult:

**a)** Clozapine was efficacious in relieving both psychotic and neuroleptic-induced parkinsonian symptoms in an open-label pilot study of 6 patients with acquired immunodeficiency syndrome. After a one-week neuroleptic washout, subjects received clozapine 12.5 milligrams (mg)/day with upward titration. Psychotic symptoms decreased significantly from baseline to month 3 of treatment at a mean dose of 27 mg/day, as evidenced by changes in average Brief Psychiatric Rating Scale scores (54 to 24 points, p less than 0.001) and Clinical Global Impression scores (2 to 8 points, p less than 0.001). The mean Unified Parkinson's Disease Rating scale also improved significantly over the same time period (14.5 to 3.4 points, p less than 0.001). The only adverse effect was leukopenia necessitating clozapine discontinuation and colony stimulating factor support (n=1) (Lera & Zirulnik, 1999).

#### 4.5.M Movement disorder, Involuntary

##### 1) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

##### 2) Summary:

May reduce involuntary movements in patients with Huntington's disease or Parkinson's disease  
Also effective in 1 case of paroxysmal hemidystonia, 4 cases of generalized dystonia and 1 case of Meige syndrome, although adverse effects were often treatment-limiting

##### 3) Adult:

**a)** A case series of generalized dystonia (n=4) and Meige syndrome (n=1) refractory to multiple prior medications revealed beneficial effects with clozapine. The patients ranged in age from 23 to 65 years with illness durations of 2 to 20 years. The Burke-Fahn-Marsden Evaluation Scale for Dystonia showed average 32% and 38% improvements on movement score and disability score, respectively. Patients' visual analog scale ratings of subjective feelings of normalcy increased from a mean of 10% to 37% on clozapine. Three of five patients reported some degree of pain relief with clozapine. Efficacy was not found to be dose-related. Despite gradual dose titration, clozapine-induced adverse effects were problematic, necessitating dose reductions in all patients and discontinuation in one patient (Karp et al, 1999).

**b)** In a small number of patients (n=18) with Huntington's disease or Parkinson's disease, clozapine reduced or suppressed involuntary movements. Doses received were between 12.5 and 500 milligrams/day. Patients with Huntington's disease experienced improvement in 3 to 5 weeks; patients with Parkinson's

experienced improvement in 1 to 2 days (Bonuccelli et al, 1994; Bennett et al, 1994; Friedman & Lannon, 1990; Caine et al, 1979). Patients with Gilles de la Tourette's syndrome and atypical persistent DYSKINESIAS failed to improve.

**c)** In an open-label study of 10 patients with idiopathic Parkinson's disease and LEVODOPA-INDUCED DYSKINESIAS, clozapine in a mean daily dose of 30 milligrams (mg) significantly reduced dyskinesias as rated by the Abnormal Involuntary Movements Scale (AIMS). Patients had a mean duration of Parkinson's symptoms of 11 years, a Hoehn & Yahr score of three, and had taken levodopa for 10 years. Improvement in the AIMS began 1 week after initiation of therapy and continued for 4 months of observation. Beginning in the third week of clozapine therapy, significant improvements in AIMS score was seen at 30, 60, 90, 120, and 150 minutes following levodopa dose, when compared to baseline conditions (p less than 0.05). Six patients experienced optimal response to clozapine (decrease in AIMS score by more than 60%). No significant differences were noted over the four months in the United Parkinson's Disease Rating Scale III. One patient experienced orthostatic hypotension and was taken off clozapine and four other patients experienced sedation and were not titrated above a clozapine 25-mg dose. No patients experienced neutropenia (Pierelli et al, 1998).

**d)** A 54-year-old woman with delayed-onset PAROXYSMAL HEMIDYSTONIA improved with clozapine therapy (Maurer et al, 1998). She also had fixed dystonia of the foot in combination with symptomatic epilepsy and secondary generalized seizures. Her paroxysmal involuntary movements had begun at the age of 15 years and occurred intermittently every other day for less than 1 minute. She was wheelchair-bound and treated with anticonvulsants. There was no response to tiapride or levodopa. After clozapine 75 milligrams (mg) was initiated, there were no paroxysmal movements for the next 10 days. Clozapine had no effect on the fixed dystonia. She was maintained on clozapine 125 mg daily.

**e)** Clozapine effectively reduced mixed tremor (both resting and postural) associated with Parkinson's disease in a prospective trial (n=17). A single 12.5 milligram (mg) clozapine dose resulted in moderate to marked tremor improvement in 88% of subjects. Chronic use over 15.5 months at an average dose of 45 mg/day revealed sustained efficacy without adverse effects. Initial sedation disappeared with continued use of clozapine. The authors recommend a trial of clozapine for the treatment of mixed tremor in Parkinson's disease before resorting to neurosurgery (Bonuccelli et al, 1997).

**f)** Clozapine was administered in increasing doses of 25, 50, and 150 milligrams/day for three weeks to a group of five patients with abnormal involuntary movements of Huntington's chorea (Bonuccelli et al, 1994). They reported reduction of chorea, with moderate to marked reduction of abnormal involuntary movements and improvement of activities of daily living. No significant side effects were noted. In another case report, gradual and modest improvement in depression and psychotic symptoms were noted but there was no effect on abnormal movements (Sajatovic et al, 1991).

**g)** The effect of clozapine on resting tremor in five parkinsonian patients who previously failed to respond to standard parkinsonian drugs was studied. One patient had dramatic improvement of severe resting tremors and four others had significant improvement. The clozapine dose ranged between 12.5 to 25 milligrams daily. The tremor controlling effects of clozapine were observed within 1 to 2 days. The most common adverse effects were weight gain and sedation. One patient had worsening of his shuffling gait (Friedman & Lannon, 1990). Another author reported that the addition of clozapine therapy (100 to 200 milligrams/day) to six patients with advanced Parkinson's disease suppressed the L-DOPA-induced dyskinesias without altering relief of Parkinsonism. (Bennett et al, 1994).

#### 4.5.N Multiple sclerosis - Psychotic disorder

##### 1) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

##### 2) Summary:

Effective in treating psychosis associated with multiple sclerosis in 1 case

##### 3) Adult:

**a)** The successful use of clozapine to treat psychosis (paranoid delusions, thought disorder, and deterioration of self-care) in a 43-year-old woman with multiple sclerosis (MS) was described (Chong & Ko, 1997). Similar to other MS patients, this woman had a poor response to typical neuroleptics and easily developed extrapyramidal symptoms. Over 1 year on clozapine 125 milligrams/day, she improved her Brief Psychiatric Rating Scale score from 71 to 34. However, she did have 3 attacks of weakness in her lower limbs that lasted 1 to 2 days each time.

#### 4.5.O Parkinson's disease

See Drug Consult reference: PARKINSON'S DISEASE - DRUG OVERVIEW

#### 4.5.P Parkinson's disease - Psychotic disorder

##### 1) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Clozapine therapy has been effective in treating psychosis associated with Parkinson's disease  
Clozapine did not worsen Parkinson's symptoms

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) (Trosch et al, 1998a). 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.

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).

e) An 81-year-old man with zoophilia, intermittent hypersexuality, and impulsivity due to his dopaminergic medication for Parkinson's disease benefited from clozapine therapy (Fernandex & Durso, 1998). He was receiving carbidopa/levodopa with pergolide with good control of his parkinsonian symptoms when the hypersexuality began. Clozapine 12.5 milligrams was begun and titrated up to 50 mg with no recurrence of the hypersexuality or impulsivity and a decrease in hallucinations.

f) In an open-label study, it was concluded that clozapine can improve hallucinations and psychosis without compromising motor function in patients with advanced Parkinson's disease (PD). Eleven patients with PD complicated by psychosis received clozapine long term (Kahn et al, 1991).

g) Mixed results on the efficacy and side effects of clozapine were reported in five parkinsonian patients with levodopa-induced hallucinations (Pfeiffer et al, 1990a).

#### 4.5.Q Postpartum psychosis

1) Overview

FDA Approval: Adult, no; Pediatric, no  
Efficacy: Adult, Evidence is inconclusive  
Recommendation: Adult, Class IIb  
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Postpartum psychosis has been successfully treated in one case report

3) Adult:

a) Postpartum psychosis was managed successfully in a lactating 28-year-old patient with mastitis. The psychosis was treated initially with zuclopenthixol 600 milligram (mg) that produced severe extrapyramidal

side effects, and the mastitis was treated with bromocriptine 7.5 mg. Bromocriptine was discontinued and zuclopenthixol was gradually replaced with clozapine at a final dose of 200 milligrams. Both the psychosis and mastitis resolved within a few days. Because clozapine does not cause long-term increases in serum prolactin, the authors recommend it as the drug of choice in postpartum psychosis in lactating patients with mastitis (Kornhuber & Weller, 1991). However, breast-feeding during clozapine treatment is not recommended by the manufacturer; clozapine has been detected in breast milk in animal studies (Prod Info Clozaril(R) Australia, 1996).

#### 4.5.R Schizoaffective disorder, Refractory

##### 1) Overview

FDA Approval: Adult, no; Pediatric, no  
Efficacy: Adult, Evidence is inconclusive  
Recommendation: Adult, Class IIb  
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

##### 2) Summary:

Combination therapy with lithium and clozapine was beneficial for patients with schizoaffective disorder but not for schizophrenic patients  
Effective in patients with schizoaffective disorder in a small, prospective cohort study

##### 3) Adult:

**a)** The addition of lithium to maintenance clozapine therapy was beneficial for patients with treatment-resistant schizoaffective disorder but not for schizophrenic patients. In a randomized, placebo-controlled, double-crossover study, hospitalized patients with treatment-resistant schizoaffective disorder (n=10) or schizophrenia (n=10) and on a stable clozapine regimen (range, 100 to 800 milligrams (mg)/day) received alternating augmentation therapy with lithium (initial, 300 mg every 12 hours; target plasma level, 0.5 mmol/L) or placebo for four 4-week phases. At the end of the first crossover, lithium treatment was associated with significantly better improvements on the Clinical Global Improvement (CGI) scale and the Positive and Negative Symptom Scale (PANSS) total score in schizoaffective patients (p less than or equal to 0.01 and p less than or equal to 0.02, respectively). The PANSS Negative score was significantly more improved with lithium therapy in the schizoaffective patients at the end of both crossover periods (p less than or equal to 0.01). Significant improvements in CGI and PANSS scores were not found with clozapine and lithium combination therapy in patients with schizophrenia, however, two (20%) of the patients in this group developed transient neurological impairments, typical of lithium toxicity, during the first week of lithium administration. Overall, safety data showed significant increases in absolute neutrophil counts and total white blood cell counts with each phase of lithium treatment. Commonly reported adverse effects included hypersalivation, sedation, tremor, and polyuria (Small et al, 2003).

**b)** Clozapine was effective and relatively well tolerated in acute and long-term treatment of patients with schizoaffective disorder who have not responded to conventional pharmacotherapies. A small cohort prospective study included 26 schizoaffective disorder patients who were treated with clozapine at flexible doses (25 mg to 600 mg per day) over a 24-month period. All patients showed significant improvement 24 months from intake as assessed by the Brief Psychiatric Rating Scale and the Clinical Global Impressions-Severity of Illness scale (p less than 0.001). Such improvement was significantly greater among patients with schizoaffective disorder than with schizophrenia (p less than 0.05). For patients with schizoaffective disorder who are resistant to or intolerant of usual treatment options, clozapine is an effective alternative (Ciapparelli et al, 2000).

#### 4.5.S Schizoaffective disorder - Suicidal behavior, Recurrent

FDA Labeled Indication

##### 1) Overview

FDA Approval: Adult, yes; Pediatric, no  
Efficacy: Adult, Evidence favors efficacy  
Recommendation: Adult, Class IIa  
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

##### 2) Summary:

Shown to be effective in decreasing the number of suicide attempts in patients with schizophrenia and schizoaffective disorder at high risk for suicide

##### 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=.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 20mg daily) on suicidal rates of patients with schizophrenia (Meltzer et al, 2000).

#### 4.5.T Schizophrenia, Treatment-resistant

FDA Labeled Indication

##### 1) Overview

FDA Approval: Adult, yes; **Pediatric, no**

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIa

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

##### 2) Summary:

Indicated for the management of severely ill schizophrenic patients who fail to respond adequately to standard antipsychotic drug treatment

##### 3) Adult:

###### a) GENERAL INFORMATION

**1)** Clozapine was effective and relatively well tolerated in acute and long-term treatment of patients with refractory schizophrenia who have not responded to conventional pharmacotherapies. A small cohort prospective study included 31 refractory schizophrenia patients who were treated with clozapine at flexible doses (25 mg to 600 mg per day) over a 24-month period. All patients showed significant improvement 24 months from intake as assessed by the Brief Psychiatric Rating Scale and the Clinical Global Impressions-Severity of Illness scale (p less than 0.001). For patients with refractory schizophrenia who are resistant to or intolerant of usual treatment options, clozapine is an effective alternative (Ciapparelli et al, 2000).

**2)** 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).

**3)** A meta-analysis of 30 randomized trials comparing clozapine to conventional neuroleptics determined that clozapine was generally superior in terms of clinical outcome (rating scale scores) and relapse rates in short-term treatment of hospitalized adults. Adverse effects such as blood dyscrasias, hypersalivation, fever and sedation were generally more frequent with clozapine, while extrapyramidal symptoms and dry mouth were more common with traditional agents. The authors noted that more long-term, community-based studies are needed with evaluation of global and social functioning, ability to work, patient satisfaction and family burden. More controlled data are also required to assess clozapine therapy in special patient populations (ie, children, adolescents, various comorbidities) (Wahlbeck et al, 1999).

**4)** Combination therapies of clozapine and fluoxetine, and clozapine, risperidone, and paroxetine have been used successfully in refractory schizophrenia (Patel et al, 1997; Cassidy & 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).

5) 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 an open-label 12-week study of treatment-refractory schizophrenic patients, clozapine (n=21) and risperidone (n=14) significantly improved psychopathology as rated by the Positive and Negative Syndrome Scale (PANSS), p less than 0.003. Patients were included if they met DSM-IV criteria for schizophrenia, had poor response to two prior neuroleptic treatments, had a minimum baseline Brief Psychiatric Rating Scale score of 46, and persistently poor functioning for at least 2 years. Patients had a mean age of 39 years and a mean duration of illness of 18 years. Improvements in the Clinical Global Impressions scale were seen with both treatments (p less than 0.011). Neurocognitive measures did not improve greatly over the 12-week treatment period. Patients receiving risperidone (mean dose 9 milligrams per day) experienced improvements within the first 2 weeks of therapy and remained stable over the treatment period; however, patients receiving clozapine (mean dose 363 milligrams per day) continued to improve over the 12-week treatment period. Extrapyramidal symptoms improved significantly in the clozapine group (p less than 0.01), but not the risperidone group. Tardive dyskinesia symptoms did not change significantly with either group (Lindenmayer et al, 1998).

3) 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).

4) 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.

5) 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).

**c) COMBINATION THERAPY**

1) The addition of lithium to maintenance clozapine therapy was beneficial for patients with treatment-

resistant schizoaffective disorder but not for schizophrenic patients. In a randomized, placebo-controlled, double-crossover study, hospitalized patients with treatment-resistant schizoaffective disorder (n=10) or schizophrenia (n=10) and on a stable clozapine regimen (range, 100 to 800 milligrams (mg)/day) received alternating augmentation therapy with lithium (initial, 300 mg every 12 hours; target plasma level, 0.5 mmol/L) or placebo for four 4-week phases. At the end of the first crossover, lithium treatment was associated with significantly better improvements on the Clinical Global Improvement (CGI) scale and the Positive and Negative Symptom Scale (PANSS) total score in schizoaffective patients (p less than or equal to 0.01 and p less than or equal to 0.02, respectively). The PANSS Negative score was significantly more improved with lithium therapy in the schizoaffective patients at the end of both crossover periods (p less than or equal to 0.01). Significant improvements in CGI and PANSS scores were not found with clozapine and lithium combination therapy in patients with schizophrenia, however, two (20%) of the patients in this group developed transient neurological impairments, typical of lithium toxicity, during the first week of lithium administration. Overall, safety data showed significant increases in absolute neutrophil counts and total white blood cell counts with each phase of lithium treatment. Commonly reported adverse effects included hypersalivation, sedation, tremor, and polyuria (Small et al, 2003).

2) Treatment-resistant schizophrenic patients refusing to give blood or swallow tablets benefited from combined electroconvulsive therapy (ECT) and clozapine (James & Gray, 1999). Six patients received ECT (2 treatments) before beginning clozapine therapy on day 6. Clozapine was then titrated to 300 mg daily by the end of ECT (10 more treatments) at week 6. At the end of the ECT, all patients consented voluntarily to weekly blood testing. Scores on the Brief Psychiatric Rating Scale had increased by 32%. Improvement persisted for 4 to 8 weeks post-ECT. After 6 months, all patients were still receiving clozapine with 3 freely compliant, 2 compliant with difficulty, and 1 threatening to refuse medication.

3) Two SEVERELY PSYCHOTIC patients, both of whom had a diagnosis of schizoaffective disorder, were successfully treated with electroconvulsive therapy (ECT) which facilitated clozapine administration and clinical stability (Green et al, 1994). The authors concluded that ECT may be useful in patients whose behavior is so disruptive that they cannot or will not take oral medication, and in cases where rapid control of behavior is necessary for the safety of themselves and others. In the two reported cases, following pretreatment with ECT, both patients have been successfully maintained on clozapine therapy for up to three years. Similar cases have been reported (Poyurovsky & Weizman, 1996).

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).

**4.5.U Schizophrenia - Suicidal behavior, Recurrent**

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; Pediatric, no  
Efficacy: Adult, Evidence favors efficacy  
Recommendation: Adult, Class IIa  
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Shown to be effective in decreasing the number of suicide attempts in patients with schizophrenia and schizoaffective disorder at high risk for suicide

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=.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 20mg daily) on suicidal rates of patients with schizophrenia (Meltzer et al, 2000).

#### 4.5.V Tardive dyskinesia

See Drug Consult reference: TARDIVE DYSKINESIA - DRUG THERAPY

### 4.6 Comparative Efficacy / Evaluation With Other Therapies

Chlorpromazine

Haloperidol

Olanzapine

Risperidone

#### 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

Hostile behavior

Schizophrenia, Refractory

##### 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, 2001).

#### 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 bupropion, 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 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, 2003).

**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

Bipolar disorder

Drug-induced psychosis

Hostile behavior

Schizophrenia

Schizophrenia - Suicidal intent

##### 4.6.C.1 Bipolar disorder

**a)** In a retrospective study of 50 consecutive patients treated for bipolar disorder with atypical antipsychotic medications, clozapine (n=5), olanzapine (n=20), and risperidone (n=25), along with standard mood stabilizers, showed similar efficacy. Overall, 68% of patients showed improvement of at least 1 point in their Clinical Global Impressions assessment over the 12-week study. Mean dosages were 210 milligrams (mg) per day for clozapine, 11.7 mg/day for olanzapine, and 1.7 mg day for risperidone. The only serious adverse event to occur during the study was a seizure in a patient taking clozapine. Extrapyramidal symptoms (EPS) were reported in 12 of 42 subjects (28.6%). Parkinsonism occurred in 4 of 25 patients taking risperidone, 1 of 20 taking olanzapine, and 1 of 5 taking clozapine. Weight gain was more extreme in patients taking clozapine and olanzapine than in those taking risperidone. Weight gain, which was greater than reported in other studies, may have been affected by concurrent mood enhancing medications (Guille et al, 2000).

##### 4.6.C.2 Drug-induced psychosis

**a)** In a small (n=18), open study, clozapine and olanzapine were both effective in reducing symptoms of dopaminergic drug-induced psychosis in patients with Parkinson's disease. However, olanzapine and not clozapine caused worsening of Parkinsonian symptoms. The starting dose of clozapine was 6.25 to 25 milligrams (mg) per day and was increased at weekly intervals as necessary to optimize clinical status. The final mean dose of clozapine at the end of the 8-week study was 16.9 mg/day (range: 6.25 to 37.5 mg/day). Olanzapine was started at 2.5 to 5 mg/day. The final mean dose of olanzapine for the 6 patients completing the study was 4.7 mg/day (range: 2.5 to 10 mg/day). Three patients dropped out of the study after receiving the starting dose of olanzapine (2.5 mg for 2 patients, 5 mg for 1 patient) because of worsening of parkinsonism. All patients in the clozapine group completed the study, despite side effects of somnolence, falls, orthostatic hypotension, and syncope. Neuropsychiatric symptoms markedly improved with both medications (72% and 65% reduction in Neuropsychiatric Inventory global scores for clozapine and olanzapine, respectively). Parkinsonian motor scores (raw scores) improved by 20% in the clozapine group and worsened by 25% in the olanzapine group. It is possible that the differences observed were due to non-equivalence of the doses and that the dosage of olanzapine was excessive (Gimenez-Roldan & Mateo D Navarro, 2001).

##### 4.6.C.3 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.C.4 Schizophrenia

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, 2002a).

#### 4.6.C.5 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 ( $p=.03$ ) 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, 2003).

#### 4.6.C.6 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) 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

Bipolar disorder

Hostile behavior

Parkinson's disease - Psychotic disorder

Schizophrenia

##### 4.6.D.1 Bipolar disorder

**a)** In a retrospective study of 50 consecutive patients treated for bipolar disorder with atypical antipsychotic medications, clozapine ( $n=5$ ), olanzapine ( $n=20$ ), and risperidone ( $n=25$ ), along with standard mood stabilizers, showed similar efficacy. Overall, 68% of patients showed improvement of at least 1 point in their Clinical Global Impressions assessment over the 12-week study. Mean dosages were 210 milligrams (mg) per day for clozapine, 11.7 mg/day for olanzapine, and 1.7 mg/day for risperidone. The only serious adverse event to occur during the study was a seizure in a patient taking clozapine. Extrapyramidal symptoms (EPS) were reported in 12 of 42 subjects (28.6%). Parkinsonism occurred in 4 of 25 patients taking risperidone, 1 of 20 taking olanzapine, and 1 of 5 taking clozapine. Weight gain was more extreme in patients taking clozapine and olanzapine than in those taking risperidone. Weight gain, which was greater than reported in other studies, may have been affected by concurrent mood enhancing medications (Guille et al, 2000a).

##### 4.6.D.2 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.D.3 Parkinson's disease - Psychotic disorder

a) In subjects with Parkinson's Disease (PD), risperidone may be considered as an alternative to clozapine however, risperidone may worsen extrapyramidal symptoms more than clozapine and therefore must be used with caution. A small ( $n=10$ ) double-blind trial compared the efficacy and safety of risperidone and clozapine for the treatment of psychosis in patients with PD. Five patients were randomized to receive clozapine and five patients received risperidone. Clozapine was started at 12.5 mg at bedtime and risperidone was started at 0.5 mg per day and both were titrated to symptomatic improvement was achieved or intolerable side effects emerged. Each subject received drug for 3 months and was assessed prior to initiation of treatment and after 2, 4, 8, and 12 weeks of treatment. Assessment was based on scores from the Brief Psychiatric Rating Scale and the Unified Parkinson's Disease Rating Scale. Mean improvement in the Brief Psychiatric Rating Scale psychosis score was similar in the clozapine and the risperidone groups ( $p=0.23$ ). Although the mean motor Unified Parkinson's Disease Rating Scale scores worsened in the risperidone group and improved in the clozapine group, this difference did not reach statistical significance. Risperidone may be a reasonable alternative to clozapine in the treatment of psychosis in patients with PD however, it must be used with caution since it may worsen extrapyramidal side effects (Ellis et al, 2000).

#### 4.6.D.4 Schizophrenia

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, 2002b).

b) 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 (CGI) 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).

**c)** In the treatment of refractory schizophrenia, giving a risperidone trial before clozapine was more beneficial given its better side effect profile. A retrospective review study compared the relative efficacy profiles of clozapine and risperidone in a group of the most refractory, chronically institutionalized patients. The specific goal was to identify superiority (or lack thereof) of either agent on global clinical outcome as well as on specific symptom domains, including positive symptoms, negative symptoms, and aggressive behavior, compared with a baseline of conventional antipsychotic treatment in a total of 24 patients. Information obtained from systematic retrospective chart review was blindly rated by 2 psychiatrists using the 7-point Clinical Global Impressions Improvement (CGI-I) scale on overall clinical state and along specific symptom domains as above. The mean dose was 520 +/- 94 mg daily for clozapine and 7.5 +/- 2.2 mg daily for risperidone. Fourteen patients (58%) were classified as responders to clozapine, while 6 (25%) responded to risperidone. On specific symptom domains, response rates to clozapine were 38% (9/24) on positive symptoms, 29% (7/24) on negative symptoms, and 71% (12/17) on aggressive behavior. For risperidone, response rates were 17% (4/24) on positive symptoms, 8% (2/24) on negative symptoms, and 41% (7/17) on aggressive behavior. The results of this study would support the utility of first giving a risperidone trial in patients with treatment-refractory schizophrenia because of its better side effect profile compared with clozapine (Sharif et al, 2000).

**d)** Risperidone and clozapine had similar antipsychotic effects in 59 patients with paranoid schizophrenia. In a double-blind randomized study, patients were divided in three groups receiving either 4 milligrams risperidone, 8 milligrams risperidone, or 400 milligrams clozapine daily for 28 days. The antipsychotic effect was highly significant for both risperidone and clozapine. Patients on 4 milligrams of risperidone better tolerated therapy than those patients receiving clozapine. Withdrawals from clozapine treatment were mostly due to side effects, whereas withdrawals from risperidone treatment occurred from lack of therapeutic response (Heinrich et al, 1994).

**e)** Similar effectiveness of risperidone and clozapine was also observed in an 8-week, double-blind trial that allowed dose adjustment based on response in 86 patients with treatment-resistant chronic schizophrenia. The mean effective dose was 6.4 milligrams (mg) for risperidone and 291 mg for clozapine. The larger proportion of patients with clinical improvement after 7 and 14 days' treatment with risperidone suggested earlier onset of effect compared to clozapine treatment (Bondolfi et al, 1998)

**f)** In a prospective, open-label, 12-week trial, risperidone was found to be a poor substitute for clozapine in the treatment of chronic refractory schizophrenia. Six patients with schizophrenia and 4 with schizoaffective disorder were switched from a mean clozapine dose of 565 milligrams(mg)/day to a mean dose of risperidone 8 mg/day at 12 weeks. No subjects improved after being switched. Overall, patients who were switched from clozapine tended to worsen when taking risperidone. Statistically significant increases over baseline in the mean total of the Positive and Negative Syndrome Scale occurred at 9 and 12 weeks (P less than 0.05). The Brief Psychiatric Rating Scale scores also increased significantly over baseline at weeks 6, 9, and 12 (P less than 0.05). Five subjects failed to complete the entire 12 weeks. Of the 5 patients that completed the 12 weeks, the Clinical Global Impressions Scale indicated that 2 patients were unchanged, one was minimally worse, and 2 were much worse. The authors concluded that this study does not support replacing clozapine with risperidone for patients with treatment-resistant schizophrenia (Still et al, 1996).

#### 4.6.D.5 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 (yr); range, 18 to 83 yr) and gender at discontinuation to patients who discontinued risperidone long-acting injection (n=161). The risperidone patients (mean age, 39.9 +/- 13.1 yr , range 18 to 83 yr) 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	Clozapine (n=161) n (%)	Risperidone (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)	-	-
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The cause of death reported in clozapine patients (mean age, 49.2 +/- 14.5 yr, range 30 to 83 yr) 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, 2003b).

**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.

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**DRUGDEX® Evaluations****METHYLPHENIDATE****0.0 Overview****1) Class**

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

Amphetamine Related  
Central Nervous System Agent  
CNS Stimulant

**2) Dosing Information****a) Methylphenidate****1) Pediatric**

- a)** safety and effectiveness not established in pediatric patients under 6 years of age (Prod Info DAYTRANA

**1) Attention deficit hyperactivity disorder**

- a)** apply TOPICALLY 2 hours before needed effect and remove 9 hours after application; week-1, 1 (2); week-3, 20 mg (25 cm(2)); week-4, 30 mg (37.5 cm(2)); titrate dose to effect (Prod Info DAYTR

**b) Methylphenidate Hydrochloride****1) Adult**

- a)** individualize dosage according to need and response of patient (Prod Info CONCERTA(R) extended-rele:

**1) Attention deficit hyperactivity disorder**

- a)** immediate-release (IR), 10 to 60 mg/day ORALLY divided 2 to 3 times daily, preferably 30 to 45

- b)** extended-release (Concerta(R)), (age up to 65 yr), no prior methylphenidate therapy, initial, 18 mg adjust dosage at weekly intervals in 18 mg increments; MAX 72 mg/day (Prod Info CONCERTA(R) e

- c)** extended-release (Concerta(R)), (age up to 65 yr) conversion from prior methylphenidate therap; to 15 mg/day), 18 mg ORALLY in morning; (prior therapy of 20 to 30 mg/day); 36 mg in morning; (pr morning; (prior therapy of 40 to 60 mg/day), 72 mg in morning (Prod Info CONCERTA(R) extended-

- d)** extended-release (Metadate(R) CD), 20 mg ORALLY once daily in the morning; may adjust dose; MAX 60 mg/day

- e)** extended-release (Ritalin LA(R), no prior methylphenidate therapy), 20 mg ORALLY once daily in intervals in 10 mg increments; MAX 60 mg/day

- f)** extended-release (Ritalin LA(R), prior methylphenidate therapy), once daily (taken in the morning total daily oral dose of prior methylphenidate therapy; may adjust dosage at weekly intervals in 10 mg

**2) Fatigue**

- a)** immediate release, 7.5 mg ORALLY twice daily, titrate up to MAX 60 mg/day

**3) Narcolepsy**

- a)** immediate release, 10- to 60 mg/day ORALLY divided 2 to 3 times daily, preferably 30 to 45 min

**2) Pediatric**

- a)** safety and effectiveness not established in pediatric patients under 6 years of age (Prod Info CONCERTA

- b)** individualize dosage according to need and response of patient (Prod Info CONCERTA(R) extended-rele:

**1) Attention deficit hyperactivity disorder**

- a)** immediate-release, (age 6 yr and older) 5 mg ORALLY twice daily (before breakfast and lunch); intervals; MAX 60 mg/day

- b)** extended-release (Concerta(R)), (age 6 to 12 yr) no prior methylphenidate therapy, initial, 18 mg dosage at weekly intervals in 18 mg increments; MAX 54 mg/day (Prod Info CONCERTA(R) extend

- c)** extended-release (Concerta(R)), (age 13 to 17 yr) no prior methylphenidate therapy, initial, 18 mg dosage at weekly intervals in 18 mg increments; MAX 72 mg/day or 2 mg/kg/day (Prod Info CONCE

- d)** extended-release (Concerta(R)), (age 6 to 17 yr) conversion from prior methylphenidate therapy 15 mg/day), 18 mg ORALLY in morning; (prior therapy of 20 to 30 mg/day), 36 mg in morning; (prior (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

- e)** extended-release (Concerta(R)), (age 13 to 17 yr) conversion from prior methylphenidate therap; 60 mg/day), 72 mg ORALLY in the morning (Prod Info CONCERTA(R) extended-release oral tablets

- f)** extended-release (Metadate(R) CD), (age 6 y and older) 20 mg ORALLY once daily in the mornin mg increments; MAX 60 mg/day

- g)** extended-release (Ritalin LA(R), (no prior methylphenidate therapy), 20 mg ORALLY once daily intervals in 10 mg increments; MAX 60 mg/day

- h)** extended-release (Ritalin LA(R), (prior methylphenidate therapy), once daily (taken in the mornin total daily oral dose of prior methylphenidate therapy; may adjust dosage at weekly intervals in 10 mg

**2) Narcolepsy**

- a)** (age 6 y and older) immediate-release, 5 mg ORALLY twice daily (before breakfast and lunch); d intervals; MAX 60 mg/day

**3) Contraindications****a) Methylphenidate**

- 1)** marked agitation, anxiety, and tension; may aggravate symptoms (Prod Info DAYTRANA(TM) transdermal sys

- 2)** glaucoma (Prod Info DAYTRANA(TM) transdermal system, 2006)

- 3) hypersensitivity to methylphenidate or other components of the product (Prod Info DAYTRANA(TM) transderm
- 4) monoamine oxidase inhibitors, such as isocarboxazid, phenelzine, selegiline, tranylcypromine, within 14 days (Prod Info DAYTRANA(TM) transdermal system, 2006)
- 5) tics, motor (Prod Info DAYTRANA(TM) transdermal system, 2006)
- 6) Tourette's syndrome, family history or diagnosis (Prod Info DAYTRANA(TM) transdermal system, 2006)
- b) Methylphenidate Hydrochloride
  - 1) angina pectoris; may increase blood pressure or heart rate (Prod Info METADATE CD(TM) extended release (TM) extended release oral capsules, 2008)
  - 2) cardiac arrhythmias; may increase blood pressure or heart rate (Prod Info METADATE CD(TM) extended release oral capsules, 2008)
  - 3) fructose intolerance, glucose-galactose malabsorption, or sucrase-isomaltase insufficiency; contains sucrose (TM) extended release oral capsules, 2008)
  - 4) glaucoma (Prod Info METADATE CD(TM) extended release oral capsules, 2008; Prod Info RITALIN(R) oral tablets, 2006)
  - 5) halogenated anesthetics; risk of sudden blood pressure increase during surgery, do not take on day of surgery (TM) extended release oral capsules, 2008)
  - 6) heart failure; may increase blood pressure or heart rate (Prod Info METADATE CD(TM) extended release oral capsules, 2008)
  - 7) hypersensitivity to methylphenidate or other components of the product (Prod Info METADATE CD(TM) extended release oral capsules, 2008; Prod Info RITALIN(R) oral tablets, RITALIN-SR(R) sustained-release oral tablets, 2006)
  - 8) hypertension, severe; may increase blood pressure (Prod Info METADATE CD(TM) extended release oral capsules, 2008)
  - 9) hyperthyroidism or thyrotoxicosis; may increase blood pressure or heart rate (Prod Info METADATE CD(TM) extended release oral capsules, 2008)
  - 10) marked agitation, anxiety, and tension; may aggravate symptoms (Prod Info METADATE CD(TM) extended release oral capsules, 2008; Prod Info RITALIN(R) oral tablets, RITALIN-SR(R) sustained-release oral tablets, 2006)
  - 11) monoamine oxidase inhibitors, such as isocarboxazid, phenelzine, selegiline, tranylcypromine, within 14 days (Prod Info METADATE CD(TM) extended release oral capsules, 2008; Prod Info RITALIN(R) oral tablets, 2006)
  - 12) myocardial infarction, recent; may increase blood pressure or heart rate (Prod Info METADATE CD(TM) extended release oral capsules, 2008)
  - 13) tics, motor (Prod Info METADATE CD(TM) extended release oral capsules, 2008; Prod Info RITALIN(R) oral tablets, 2006)
  - 14) Tourette's syndrome, family history or diagnosis (Prod Info METADATE CD(TM) extended release oral capsules, 2008; Prod Info RITALIN-SR(R) sustained-release oral tablets, 2006)
- 4) Serious Adverse Effects
  - a) Methylphenidate
    - 1) Contact dermatitis
    - 2) Decreased body growth
    - 3) Drug dependence
    - 4) Lowered convulsive threshold
    - 5) Mania
    - 6) Psychotic disorder
    - 7) Tic
  - b) Methylphenidate Hydrochloride
    - 1) Aggressive behavior
    - 2) Cerebrovascular accident
    - 3) Dead - sudden death
    - 4) Decreased body growth
    - 5) Drug dependence
    - 6) Gastrointestinal obstruction
    - 7) Mania
    - 8) Myocardial infarction
    - 9) Psychotic disorder
    - 10) Seizure
    - 11) Visual disturbance
- 5) Clinical Applications
  - a) Methylphenidate
    - 1) FDA Approved Indications
      - a) Attention deficit hyperactivity disorder
  - b) Methylphenidate Hydrochloride
    - 1) FDA Approved Indications
      - a) Attention deficit hyperactivity disorder
      - b) Narcolepsy
    - 2) Non-FDA Approved Indications
      - a) Fatigue

## 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 Information)
- B) Synonyms
  - Methylphenidate
  - Methylphenidate HCl
  - Methylphenidate Hydrochloride
  - Methylphenidylacetate
- C) Physicochemical Properties
  - 1) Molecular Weight
    - a) 269.77 (Fleeger, 1994)

### 1.2 Storage and Stability

- A) Methylphenidate
  - 1) Preparation
    - a) Topical application route
      - 1) APPLICATION
        - a) Apply the patch to a clean, dry area of the hip area 2 hours before an effect is needed. Avoid walking. When applying the patch the next morning, place on the opposite hip at a new site if possible (Product Information, 2006).
        - b) Apply patch immediately after opening the pouch and removing the protective liner. Do not use force to press firmly in place with palm of the hand for approximately 30 seconds. Make sure there is good contact around the edges. Once the patch has been properly placed, bathing, swimming, or showering will not cause a patch to fall off, a new patch may be applied at a different site, but the total recommended duration of use should not exceed 7 days. Do not expose the patch application site to direct external heat sources, such as heating pads, electric blankets, or wearing the patch. Temperature-dependent increases in methylphenidate exposure of greater than 50% have been reported with the DAYTRANA(TM) transdermal system, 2006).
      - 2) DISPOSAL OF PATCH
        - a) After patch removal, fold patch so the patch adheres to itself. The folded patch may be flushed down the toilet in a lidded container. If the patient discontinues the prescription, each unused patch should be removed from the pouch, folded onto itself, and flushed down the toilet or disposed of in an appropriate lidded container (Product Information, 2006).
- B) Methylphenidate Hydrochloride
  - 1) Preparation
    - a) Oral route
      - 1) For extended-release tablets, the dose should be given once daily in the morning, with or without food, and must not be chewed, divided, or crushed (Product Information CONCERTA(R) extended-release oral tablets, 2004).
      - 2) For extended-release capsules, the dose should be given once daily in the morning. Capsules may be taken with or without food over a spoonful of applesauce; the applesauce should not be warm, and the drug/applesauce mixture should be taken immediately (Product Information RITALIN LA(R) oral extended-release capsule, 2004). Capsule contents of Ritalin(R) LA should not be taken with food (Product Information RITALIN LA(R) oral extended-release capsule, 2004).
- C) Transdermal route
  - 1) Patch, Extended Release
    - a) Store at 25 degrees Celsius (77 degrees Fahrenheit); excursions permitted between 15 and 30 degrees Celsius. Store patches unpouched. Use within 2 months after opening tray (Product Information DAYTRANA(TM) transdermal system, 2006).

### 1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Other Disease States

**1.3.1 Normal Dosage****1.3.1.A Methylphenidate Hydrochloride****1.3.1.A.1 Oral route**

Attention deficit hyperactivity disorder

Cancer; Adjunct

Dementia

Depression, Monotherapy

Narcolepsy

Shivering, Postanesthesia; Treatment and Prophylaxis

Syncope

Traumatic brain injury

**1.3.1.A.1.a Attention deficit hyperactivity disorder****1) Extended-Release**

**a)** The recommended starting dose of Concerta(R) extended-release tablet for new patients is morning. Dosage may be adjusted weekly in 18 mg increments to a maximum of 72 mg per day methylphenidate regimens may follow the dosage conversion recommendation below (Prod Inf 2008):

Previous Methylphenidate Daily Dose	Recommended Concerta Dose
5 mg twice or 3 times daily	18 mg in the mor
10 mg twice or 3 times daily	36 mg in the mor
15 mg twice or 3 times daily	54 mg in the mor
20 mg twice or 3 times daily	72 mg in the mor

**b)** Pharmacologic treatment of attention deficit hyperactivity disorder may be needed for extent indicate how long the patient should be treated. The physician should periodically reevaluate th off medication to assess the patient's functioning without pharmacotherapy. Improvement may l temporarily or permanently discontinued. The dosage should be reduced or discontinued if parz adverse events occur. If improvement is not observed after appropriate dosage adjustments ov drug should occur (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

**c)** For methylphenidate extended release capsules (Metadate(R) CD), the starting dose is 20 n breakfast. Doses may be increased by 20 mg at weekly intervals to a MAXIMUM dose of 60 mc dosages above 60 mg are not recommended (Prod Info Metadate(R) CD, 2002).

**2) Immediate-Release**

**a)** Recommended dosage is from 10 to 60 milligrams daily. Average dose is 20 to 30 milligram times daily preferably 30 to 45 minutes before meals (Prod Info RITALIN(R) oral tablet, RITALIN

**b)** Methylphenidate in doses of 10 to 90 milligrams orally daily was reported more effective tha disorder, residual type, in adults in a double-blind crossover trial (Wender et al, 1985).

**1.3.1.A.1.b Cancer; Adjunct**

**1)** The combination of oral methylphenidate 15 milligrams (mg) daily (10 mg at breakfast and 5 mg to enhance the analgesic efficacy of the narcotic agents and decrease sedation in patients with chrc et al, 1987a).

**1.3.1.A.1.c Dementia**

**1)** Some of the negative symptoms associated with vascular dementia and dementia of Alzheimer's milligrams/day in an open-label, non-blinded preliminary study. Results were similar among the 12 A (Galynker et al, 1997a).

**1.3.1.A.1.d Depression, Monotherapy**

- 1) Methylphenidate 5 to 40 milligrams per day appears to be safe and effective for the treatment of lacking contraindications for use (Frye, 1997a; Emptage & Semla, 1996a).
- 2) Methylphenidate 10 to 20 milligrams per day produced a positive response in 7 of 8 post-liver tra symptoms (Plutchik et al, 1998a).
- 3) Acute stroke patients (n=21) receiving methylphenidate 30 milligrams per day demonstrated gre activities of daily living, and motor function than patients receiving placebo in a prospective, random (Grade et al, 1998a).
- 4) A report of the efficacy of methylphenidate in the treatment of depression in cancer patients has Methylphenidate was given in doses of 10 milligrams orally three times daily initially, with subsequer period of 2 to 3 days; increases to a maximum of 80 milligrams daily were permitted by week 2 of tre marked improvement, with 13 showing moderate improvement; maximum improvement was genera

#### 1.3.1.A.1.e Narcolepsy

- 1) Recommended dosage is from 10 to 60 milligrams daily. Average dose is 20 to 30 milligrams dai SR(R) oral tablet, 2004).
- 2) Doses should be administered 2 to 3 times daily preferably 30 to 45 minutes before meals (Prod tablet, 2004).

#### 1.3.1.A.1.f Shivering, Postanesthesia; Treatment and Prophylaxis

- 1) Methylphenidate 20 mg suppressed postoperative shivering in 17 of 42 post-anesthetic patients received halothane anesthesia (Imray & White, 1968).

#### 1.3.1.A.1.g Syncope

- 1) Six of 7 patients with recurrent NEUROCARDIOGENIC SYNCOPE became clinically asymptoma milligrams 3 times daily for 7 months. The patients were previously unresponsive to or poorly tolerar

#### 1.3.1.A.1.h Traumatic brain injury

- 1) Methylphenidate 0.25 milligrams/kilogram twice daily improved speed of mental processing in pa injury, but orienting to distractions, sustained attention, and motor speed were unaffected (Whyte et

### 1.3.2 Dosage in Renal Failure

#### A) Methylphenidate Hydrochloride

- 1) Due to minimal excretion as unchanged drug (Faraj et al, 1974a; Prod Info RITALIN LA(R) oral extended-methylphenidate are unlikely to be altered significantly in renal impairment, suggesting no need for dose adju

### 1.3.3 Dosage in Hepatic Insufficiency

#### A) Methylphenidate Hydrochloride

- 1) As methylphenidate is metabolized primarily to ritalinic acid (essentially inactive) via non-microsomal este are unlikely to be altered significantly in liver disease (Prod Info RITALIN LA(R) oral extended-release capsul adjustment. However, adequate studies in this setting are lacking.

### 1.3.6 Dosage in Other Disease States

#### A) Methylphenidate Hydrochloride

##### 1) GLAUCOMA

- a) Use of methylphenidate in patients with glaucoma is contraindicated (Prod Info RITALIN(R) oral table has been suggested that when used cautiously in conjunction with glaucoma medications and regular of pressure measurements, methylphenidate may be safe in patients with well-controlled, open-angle glauc

## 1.4 Pediatric Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Other Disease States

### 1.4.1 Normal Dosage

Methylphenidate

Methylphenidate Hydrochloride

**1.4.1.A Methylphenidate****1.4.1.A.1 Transdermal route****1.4.1.A.1.a Attention deficit hyperactivity disorder**

1) The recommended dose titration schedule for children 6 to 12 years of age for the treatment of a the table below (Prod Info DAYTRANA(TM) transdermal system, 2006):

	Upward Titration, if Response is Not Maximiz	
	Week 1	Week 2
Patch size	12.5 cm(2)	18.75 cm(2)
Nominal Delivered Dose *	10 mg/9 hrs	15 mg/9 hrs
Delivery rate *	1.1 mg/hr	1.6 mg/hr

Key: \* = nominal in vivo delivery rate in pediatric subjects aged 6 to 12 when applied to the hip, centimeters squared mg = milligrams, hrs = hours

Individualize titration, final dosage, and wear time for each patient according to the needs and r before desired effect and remove patch 9 hours after application. The patch may be removed e is preferred or late day side effects occur. The dose titration schedule applies to methylphenida children (Prod Info DAYTRANA(TM) transdermal system, 2006).

2) Although the design of a double-blind, placebo-controlled, randomized trial did not allow for eval not appear to be improved efficacy with a dose increase from 20 mg over 9 hours to 30 mg over 9 h system, 2006).

2) Safety and effectiveness not established in pediatric patients under 6 years of age (Prod Info DAYTRANA

**1.4.1.B Methylphenidate Hydrochloride****1.4.1.B.1 Oral route****1.4.1.B.1.a Attention deficit hyperactivity disorder**

1) Extended Release

a) For Ritalin(R) LA extended-release capsules, the starting dose recommended by the manuf: gradual upward titration based on efficacy and tolerability; weekly 10-mg increments to a maxim RITALIN LA(R) oral extended-release capsule, 2004). When a lower initial dose is desired, low may given; following titration to 10 mg twice daily of the immediate-release formulation, patients Ritalin(R) LA dose guidelines are for these latter patients, and those currently receiving immedi: methylphenidate who are to be switched to Ritalin(R) LA (Prod Info RITALIN LA(R) oral extend

1) Patients currently receiving methylphenidate 10 mg twice daily or 20-mg methylphenida daily

2) Patients currently receiving methylphenidate 15 mg twice daily should be given Ritalin(F

3) Patients currently receiving methylphenidate 20 mg twice daily or 40-mg methylphenida daily

4) Patients currently receiving methylphenidate 30 mg twice daily or 60-mg methylphenida daily

The recommended starting dose of Concerta(R) extended-release tablet for new patients a day in the morning. Dosage may be adjusted weekly in 18 mg increments to a maximum of and to a maximum of 72 mg per day (not to exceed 2 mg/kg/day) in adolescents 13 to 17 y thrice daily regimens of methylphenidate may follow the dosage conversion recommendati release oral tablets, 2008):

Previous Methylphenidate Daily Dose	Recommended Concerta(R) Starting Dose
5 mg twice or 3 times daily	18 mg in the morning
10 mg twice or 3 times daily	36 mg in the morning
15 mg twice or 3 times daily	54 mg in the morning
20 mg twice or 3 times daily	72 mg in the morning (age 13 to 17 years only)

Initial conversion dosage should not exceed 54 milligrams (mg) daily in children 6 to 12 yea 17 years of age. Following conversion, doses may be adjusted if needed up to the maximu generally occur at weekly intervals (Prod Info CONCERTA(R) extended-release oral table: Pharmacologic treatment of attention deficit hyperactivity disorder may be needed for exter that indicate how long the patient should be treated. The physician should periodically reev with trials off medication to assess the patient's functioning without pharmacotherapy. Impr either temporarily or permanently discontinued. The dosage should be reduced or discontir other adverse events occur. If improvement is not observed after appropriate dosage adjus of the drug should occur (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

b) CHILDREN 6 YEARS & OLDER: For methylphenidate extended release capsules (Metadat once daily in the morning before breakfast. Doses may be increased by 20 mg at weekly interv

once daily in the morning. Daily dosages above 60 mg are not recommended. Metadate CD ext whole or the content of the capsule may be sprinkled onto a tablespoonful of applesauce and the capsule or its content (Prod Info Metadate(R) CD, 2002).

**c)** Average total daily dose was 34.3 mg/day for EXTENDED-RELEASE METHYLPHENIDATE mg/day for IMMEDIATE-RELEASE METHYLPHENIDATE (n=94) among children 6 to 12 years comparing the efficacy of the 2 formulations of the drug. Immediate-release (given 3 times daily methylphenidate had comparable efficacy, and both were significantly superior to placebo (p less

**2) Immediate Release**

**a)** In children over 6 years of age, usual dose is 5 milligrams twice daily increased at weekly intervals to administer 5 milligrams before breakfast and lunch (Prod Info RITALIN(R) oral tablet, RITALIN

**b)** The maximum recommended dose is 60 milligrams. Drug should be discontinued if there is (Prod Info RITALIN(R) oral tablet, RITALIN-SR(R) oral tablet, 2004).

**c)** According to the results of one triple-blind, placebo controlled, crossover study involving 251 (ADHD), three times a day dosing produces the most reliable improvements in the treatment of on weight, ranged from 5 to 20 milligrams (mean dose = 8.8 milligrams; 0.30 milligram/kilogram dosing schedule was associated with a greater improvement in behavioral measures compared were no significant differences between the two dosing schedules in the incidence of adverse e

**d)** In 11 hyperkinetic children aged 7 to 12, 0.3 milligram/kilogram/day markedly improved impu milligram/kilogram/day produced results similar to placebo in a double blind study (Brown & Sle to be no more efficacious and more toxic than lower (0.3 milligram/kilogram/day) doses (Holliste

**e)** Isolated studies have raised the possibility that a small group of children may develop some al, 1980; Eichlseder, 1985; Winsberg et al, 1974). Other non-controlled studies have observed : medications in children with attention deficit disorders (Riddle & Rapoport, 1976; Charles et al, determined whether some hyperactive children who initially respond to methylphenidate develo is probably a rare occurrence. In patients who become less responsive to methylphenidate ther dosing or noncompliance should also be considered.

**f)** Methylphenidate 0.3 milligram/kilogram twice daily at 8 am and 12 noon for 14 days improve children (n=14) with acquired attention disorder secondary to brain injury in a double-blind, plac 1998).

**1.4.2 Dosage in Renal Failure**

**A) Methylphenidate**

**1)** Transdermal methylphenidate has not been studied in patients with renal insufficiency (Prod Info DAYTR/

**B) Methylphenidate Hydrochloride**

**1)** Due to minimal excretion as unchanged drug (Faraj et al, 1974a; Prod Info RITALIN LA(R) oral extended-methylphenidate are unlikely to be altered significantly in renal impairment, suggesting no need for dose adju

**1.4.3 Dosage in Hepatic Insufficiency**

**A) Methylphenidate**

**1)** Transdermal methylphenidate has not been studied in patients with hepatic insufficiency (Prod Info DAYT

**B) Methylphenidate Hydrochloride**

**1)** As methylphenidate is metabolized primarily to ritalinic acid (essentially inactive) via non-microsomal este are unlikely to be altered significantly in liver disease (Prod Info RITALIN LA(R) oral extended-release capsul adjustment. However, adequate studies in this setting are lacking.

**1.4.5 Dosage in Other Disease States**

**A) Methylphenidate Hydrochloride**

**1) EPILEPSY**

**a)** Use of methylphenidate (0.3 milligram/kilogram once daily) appears to be safe and effective to treat a children with epilepsy who are seizure free, while receiving antiepileptic drugs, before starting methylphe for those children still having seizures while receiving antiepileptic drugs (Gross-Tsur et al, 1997a).

**2) TOURETTE'S SYNDROME**

**a)** In a 2-year non-blinded, prospective, follow-up study of 32 children (aged 6.1 to 11.9 years) receiving from a previous trial (mean 16.5 milligrams (mg), range 5 to 40 mg), long-term methylphenidate therapy with attention deficit hyperactivity disorder (ADHD) and chronic multiple tic disorder or Tourette's syndror not worsen tics in patients with ADHD and Tourette's syndrome, the possibility of individual exacerbation 1999a).

**2.0 Pharmacokinetics**

Onset and Duration

Drug Concentration Levels

ADME

**2.1 Onset and Duration****A) Onset****1) Initial Response**

- a) ATTENTION-DEFICIT/HYPERACTIVITY DISORDER, ORAL:** within 2 weeks (Prod Info Ritalin(R) LA, 2006)  
**1) Represents time to significant improvement in symptoms scores in children treated with 10 to 40 mg**

**2.2 Drug Concentration Levels****A) Peak Concentration****1) TRANSDERMAL:** 39 ng/mL (Prod Info DAYTRANA(TM) transdermal system, 2006).

**a) The mean peak d-methylphenidate plasma concentration was 39 ng/mL (0 to 114 ng/mL) in pediatric children wearing times of transdermal methylphenidate. These mean peak concentrations varied inversely by age ranging from 18 to 53 ng/mL (18 to 83 ng/mL) in 6 year olds (Prod Info DAYTRANA(TM) transdermal system, 2006).**

**b) The mean peak d-methylphenidate concentrations were 1.9 times higher for transdermal methylphenidate over a period of 7.5 to 10.5 hours, when Tmax usually occurs. These higher concentrations were consistent with 3 and 4 days of multiple dosing the Cmaxs were higher with chronic dosing of transdermal methylphenidate. Similar Cmaxs were produced similar Cmaxs as single doses of the once daily oral methylphenidate (Prod Info DAYTRANA(TM) transdermal system, 2006).**

**2) ORAL (Ritalin and Ritalin-SR at 0.3 mg/kg):** Children-10.8 ng/mL(Gillis & editor, 2000); Adults-7.8 nanograms per mL (Prod Info Concerta™, 2000a).

**a) Ritalin and Ritalin-SR brands of methylphenidate- Following administration of 0.3 mg of methylphenidate per kg body weight, the mean peak plasma concentration was 10.8 ng/mL (Gillis & editor, 2000); Adults-7.8 nanograms per mL (Gillis & editor, 2000)**

**b) Peak plasma concentrations showed marked variability between subjects (Gillis & editor, 2000).**

**c) Concerta brand of methylphenidate-Following administration of 18 mg of methylphenidate: 3.7 nanograms per mL (Gillis & editor, 2000)**

**d) Metadate(R) CD brand of methylphenidate-Following administration of 20 mg of Metadate(R) CD: an early peak plasma concentration of 10.9 ng/mL due to the immediate release component, and a later maximum concentration of 10.9 nanograms per mL in children (Prod Info Metadate CD(R), 2001).**

**e) The peak plasma concentration was increased by 30% when Metadate(R) CD 40 mg was administered for 4 weeks (Prod Info Metadate CD(R), 2001).**

**f) Dose-proportionality was demonstrated in peak plasma concentrations and area under the concentration-time curve for methylphenidate.**

**B) Time to Peak Concentration****1) ORAL:** 1 to 3 hours (Dayton et al, 1970); 6 to 8 hours (extended- release tablets or capsules) (Prod Info Concerta™, 2000a).

**a) In 35 healthy adults, the PEAK PLASMA CONCENTRATION of methylphenidate after a single dose of OF immediate-release 5 mg every 4 hours, and a single dose of slow-release 20 mg was 3.75 ng/mL, 4.17 ng/mL, and 6.7 hours, 6.5 hours, and 3.7 hours, respectively (Modi et al, 2000).**

**b) The peak plasma concentration of a SINGLE and MULTIPLE doses of methylphenidate OROS(R) formulation was 6.7 hours, 6.5 hours, and 3.7 hours, respectively and the time to peak concentration was 7.4 hours and 6.6 hours, respectively in 32 healthy adult subjects (Modi et al, 2000).**

**c) Following 20 to 100 milligrams (mg) doses of methylphenidate, plasma levels of 0.02 mg/liter (L) were reported to range from 1 to 3 hours after a single oral dose (Dayton et al, 1970).**

**d) Plasma levels varied from 7.7 to 22.5 nanograms/milliliter (ng/mL) in 4 children with attention deficit disorder (Hungund et al, 1979).**

**e) Following a single oral dose of methylphenidate extended-release capsules (Ritalin(R) LA) in children or adolescents, the first peak plasma level (mean) occurred in 2 hours (10.8 ng/mL) and the second peak occurred at approximately 4 hours apart, with the second peak usually somewhat higher than the first. Compared to immediate-release capsules, a lower second peak level, higher interpeak minimum level, and less peak/trough fluctuations were observed (Prod Info Ritalin(R) LA, 2002a).**

**f) With a 20-mg dose of Ritalin(R) LA in children, the first peak plasma level (mean) occurred in 2 hours (10.8 ng/mL) in an unpublished study; the mean interpeak minimum plasma level was 6 ng/mL (4.5 hours) (Prod Info Ritalin(R) LA, 2002a).**

**2) TRANSDERMAL:** average lag time was 3.1 hours (Prod Info DAYTRANA(TM) transdermal system, 2006)

**a) The average lag time (time to any d-methylphenidate is detectable in the circulation) was 3.1 hours (range 2.5 to 3.5 hours) (Prod Info DAYTRANA(TM) transdermal system, 2006).**

**C) Area Under the Curve****1) ORAL (20 mg, long acting):** 45.8 ng x h/mL (Modi et al, 2000)

**a) With a single 20-mg dose of Ritalin(R) LA, the mean AUC(0-infinity) in adult was 45.8 ng x h/mL and in children was 32.9 ng x h/mL (Modi et al, 2000).**

**b) The AUC of methylphenidate is 2 times higher when heat is applied to transdermal methylphenidate after when the patch is applied to inflamed skin (Prod Info DAYTRANA(TM) transdermal system, 2006).**

**c) In 35 healthy adults, the AUC of methylphenidate after a single dose of OROS(R) formulation 18 mg, 3 mg, and a single dose of slow-release 20 mg was 42 ng x h/mL, 38 ng x h/mL, and 47 ng x h/mL, respectively (Modi et al, 2000).**

**d) The AUC of a single and multiple doses of methylphenidate OROS(R) formulation 18 mg was 32.9 ng x h/mL in healthy adults (Modi et al, 2000).**

**2.3 ADME**

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

### 2.3.1 Absorption

- A) Bioavailability
  - 1) ORAL: 10 to 52% (immediate-release, children) (Prod Info Ritalin(R) LA, 2002a).
- B) Effects of Food
  - 1) None (Prod Info DAYTRANA(TM) transdermal system, 2006; Prod Info Concerta(TM), 2001).
    - a) Food does not affect the pharmacokinetics or the pharmacodynamics of extended-release oral methylphenidate (Prod Info DAYTRANA(TM) transdermal system, 2006; Prod Info Concerta(TM), 2001).
    - b) Cmax and AUC of methylphenidate after a single dose in 26 healthy adults were unaffected by taking compared to taking the whole capsule (Prod Info Metadate(R) CD, 2002a).
- C) DOSAGE FORM ABSORPTION
  - 1) Extended-release Capsules
    - a) Ritalin(R) LA extended-release capsules have a bimodal release profile, using the SODAS(R) (Spher dose is in immediate-release beads, with the remainder in enteric-coated, delayed-release beads (enabl 2002b). Single daily doses of Ritalin(R) LA extended-release capsules 20, 30, and 40 milligrams (mg) pr twice-daily administration of immediate release Ritalin(R) tablets 10, 15, or 20 mg, respectively (Prod Inf
  - 2) Extended-release Tablets
    - a) Concerta(R) extended-release tablet uses osmotic pressure to deliver methylphenidate at a constant tri-layer core surrounded by a semipermeable membrane with an immediate-release overcoat, which dis (such as the gastrointestinal tract) providing the initial dose. As water permeates through a laser-drilled c through the orifice by the osmotic pressure created by the polymer excipients in the core. The membrane rate at which water enters the tablet core. The tablet must be swallowed whole with the aid of liquids, an Info Concerta(TM), 2001).
  - 3) Sustained-release Tablets
    - a) Ritalin SR(R) tablets are formulated with a wax matrix core in which the medication is placed into cha in half would disrupt the medication channels in the tablet core and thereby alter the sustained release c Ritalin SR(R) tablets in half is not recommended (Pers Comm, 1987).

### 2.3.2 Distribution

- A) Distribution Sites
  - 1) Protein Binding
    - a) 10% to 33% (Prod Info RITALIN LA(R) oral extended-release capsule, 2004; Hungund et al, 1979).
- B) Distribution Kinetics
  - 1) Volume of Distribution
    - a) 1.1 to 6 liters/kilogram (L/kg) (Prod Info Ritalin(R) LA, 2002a; Hungund et al, 1979).
    - 1) Vd in children (Hungund et al, 1979).

### 2.3.3 Metabolism

- A) Metabolism Sites and Kinetics
  - 1) TISSUES, extensive (Prod Info Ritalin(R) LA, 2002a; Faraj et al, 1974).
    - a) Methylphenidate is rapidly and extensively metabolized by nonmicrosomal hydrolytic esterases in live (Prod Info Ritalin(R) LA, 2002a).
- B) Metabolites
  - 1) Ritalinic acid (essentially inactive) (Prod Info DAYTRANA(TM) transdermal system, 2006)(Foraj et al, 197-LA, 2002a; Dayton et al, 1970).
    - a) Ritalinic acid (alpha-phenyl-piperidine acetic acid) possess minimal-to-no pharmacologic activity (Pro 2006; Prod Info Ritalin(R) LA, 2002a). Clinical efficacy is mainly due to the parent compound.
    - b) Compared to oral administration on a mg/kg basis, transdermal methylphenidate results in higher exp pass effect. Minimal to no l-methylphenidate is systemically available after oral administration. In contras high as d-methylphenidate after transdermal methylphenidate administration (Prod Info DAYTRANA(TM),
  - 2) Hydroxymethylphenidate and hydroxyritalinic acid (only small amounts of each in plasma) (Prod Info Rital
    - a) 6-oxo-alpha-phenyl-2-piperidine acetic acid (Foraj et al, 1974)(Bartlett & Egger, 1972; Dayton et al, 1!

### 2.3.4 Excretion

- A) Kidney
  - 1) Renal Excretion (%)
    - a) Immediate release: 78% to 97%, less than 1% unchanged (Prod Info RITALIN LA(R) oral extended-re Faraj et al, 1974; Dayton et al, 1970); sustained release, children: 67% (Prod Info RITALIN(R) oral tablet release, adults: 86% (Prod Info RITALIN(R) oral tablet, RITALIN-SR(R) oral tablet, 2004).
    - 1) About 90% of radiolabeled methylphenidate was recovered in the urine after oral dosing. Ritalinic

dose (Prod Info Concerta(TM), 2001).

- B) Feces
  - 1) Immediate-release: 1% to 3% (Prod Info RITALIN LA(R) oral extended-release capsule, 2004)
- C) Other
  - 1) PLASMA CLEARANCE, 3.1 to 8.5 L/kg/hr in children (Shader et al, 1999; Hungund et al, 1979).

### 2.3.5 Elimination Half-life

- A) Parent Compound
  - 1) (Oral) 2 to 7 hours (average, 3 hours) (Shader et al, 1999; Faraj et al, 1974); (Intravenous) 1 to 2 hours (F
    - a) In children aged 6 to 12 years, the mean elimination half-life for transdermal methylphenidate applied removal of the patch and 1.4 to 2.9 hours for d-methylphenidate and l-methylphenidate, respectively (Pr 2006).
    - b) In 36 healthy adults, the plasma half-life of methylphenidate after a single dose of methylphenidate O immediate-release 5 mg every 4 hours, and a single dose of slow-release 20 mg was 3.5 hours, 3.0 hou
    - c) The elimination half-life of a single dose and multiple doses (once a day on day 3 through day 6) of r was 3.9 hours (Modi et al, 2000).
- B) Metabolites
  - 1) Ritalinic acid, 3 to 4 hours (Prod Info Ritalin(R) LA, 2002a).

## 3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

### 3.0.A Black Box WARNING

- 1) Methylphenidate
  - a) Transdermal (Patch, Extended Release)
    - 1) Methylphenidate patch should be given cautiously to patients with a history of drug dependence or alcohol tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episod Careful supervision is required during withdrawal from abusive use, since severe depression may occur. With unmask symptoms of the underlying disorder that may require follow-up (Prod Info DAYTRANA(TM) transder
  - 2) Methylphenidate Hydrochloride
    - a) Oral (Tablet; Tablet, Extended Release; Tablet, Chewable; Capsule, Extended Release; Solution)
      - 1) Methylphenidate hydrochloride should be given cautiously to emotionally unstable patients, such as those alcoholism, because such patients may increase dosage on their own initiative.
      - 2) Chronically abusive use can lead to marked tolerance and psychic dependence with varying degrees of alcohol occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal, since severe overactivity can be unmasked. Long term follow-up may be required because of the patient's basic personalit tablet, RITALIN-SR(R) oral sustained-release tablet, 2004; Prod Info METHYLIN(R) oral solution, 2004; Prod Prod Info RITALIN LA(R) oral extended-release capsule, 2004).

### 3.1 Contraindications

- A) Methylphenidate
  - 1) marked agitation, anxiety, and tension; may aggravate symptoms (Prod Info DAYTRANA(TM) transdermal sys
  - 2) glaucoma (Prod Info DAYTRANA(TM) transdermal system, 2006)
  - 3) hypersensitivity to methylphenidate or other components of the product (Prod Info DAYTRANA(TM) transderm
  - 4) monoamine oxidase inhibitors, such as isocarboxazid, phenelzine, selegiline, tranylcypromine, within 14 days (Prod Info DAYTRANA(TM) transdermal system, 2006)
  - 5) tics, motor (Prod Info DAYTRANA(TM) transdermal system, 2006)
  - 6) Tourette's syndrome, family history or diagnosis (Prod Info DAYTRANA(TM) transdermal system, 2006)
- B) Methylphenidate Hydrochloride
  - 1) angina pectoris; may increase blood pressure or heart rate (Prod Info METADATE CD(TM) extended release ( (TM) extended release oral capsules, 2008)
  - 2) cardiac arrhythmias; may increase blood pressure or heart rate (Prod Info METADATE CD(TM) extended rele: CD(TM) extended release oral capsules, 2008)
  - 3) fructose intolerance, glucose-galactose malabsorption, or sucrase-isomaltase insufficiency; contains sucrose ( (TM) extended release oral capsules, 2008)
  - 4) glaucoma (Prod Info METADATE CD(TM) extended release oral capsules, 2008; Prod Info RITALIN(R) oral ta

tablets, 2006)

5) halogenated anesthetics; risk of sudden blood pressure increase during surgery, do not take on day of surgery (TM) extended release oral capsules, 2008)

6) heart failure; may increase blood pressure or heart rate (Prod Info METADATE CD(TM) extended release oral

7) hypersensitivity to methylphenidate or other components of the product (Prod Info METADATE CD(TM) exten RITALIN(R) oral tablets, RITALIN-SR(R) sustained-release oral tablets, 2006)

8) hypertension, severe; may increase blood pressure (Prod Info METADATE CD(TM) extended release oral cap extended release oral capsules, 2008)

9) hyperthyroidism or thyrotoxicosis; may increase blood pressure or heart rate (Prod Info METADATE CD(TM) e METADATE CD(TM) extended release oral capsules, 2008)

10) marked agitation, anxiety, and tension; may aggravate symptoms (Prod Info METADATE CD(TM) extended r (R) oral tablets, RITALIN-SR(R) sustained-release oral tablets, 2006)

11) monoamine oxidase inhibitors, such as isocarboxazid, phenelzine, selegiline, tranylcypromine, within 14 days crisis (Prod Info METADATE CD(TM) extended release oral capsules, 2008; Prod Info RITALIN(R) oral tablets, R 2006)

12) myocardial infarction, recent; may increase blood pressure or heart rate (Prod Info METADATE CD(TM) exte METADATE CD(TM) extended release oral capsules, 2008)

13) tics, motor (Prod Info METADATE CD(TM) extended release oral capsules, 2008; Prod Info RITALIN(R) oral tablets, 2006)

14) Tourette's syndrome, family history or diagnosis (Prod Info METADATE CD(TM) extended release oral capsu RITALIN-SR(R) sustained-release oral tablets, 2006)

### 3.2 Precautions

#### A) Methylphenidate

1) history of drug dependence or alcoholism; abuse potential (Prod Info DAYTRANA(TM) transdermal system, 2C

2) cardiac abnormalities, structural; sudden death has been reported with CNS stimulant treatment (Prod Info DA

3) contact sensitization; may lead to future systemic sensitization or other systemic reactions when methylphenid DAYTRANA(TM) transdermal system, 2006)

4) depression, severe; should not be used to treat (Prod Info DAYTRANA(TM) transdermal system, 2006)

5) EEG abnormalities; may lower convulsive threshold (Prod Info DAYTRANA(TM) transdermal system, 2006)

6) external heat source exposure; increase release of drug from patch (Prod Info DAYTRANA(TM) transdermal s

7) fatigue states, normal; should not be used to prevent or treat (Prod Info DAYTRANA(TM) transdermal system,

8) psychosis; may exacerbate symptoms of behavior disturbance and thought disorder (Prod Info DAYTRANA(TI

9) seizures, history of; may lower convulsive threshold (Prod Info DAYTRANA(TM) transdermal system, 2006)

10) underlying medical conditions that may be compromised by increases in blood pressure or heart rate such as myocardial infarction, or hyperthyroidism (Prod Info DAYTRANA(TM) transdermal system, 2006)

#### B) Methylphenidate Hydrochloride

1) history of drug dependence or alcoholism; abuse potential (Prod Info RITALIN(R) oral tablets, RITALIN-SR(R)

2) bipolar disorder; risk of induction of a mixed/manic episode (Prod Info METADATE CD(TM) extended release i

3) cardiac abnormalities, structural or other heart problems; sudden death has been reported with CNS stimulant RITALIN-SR(R) sustained-release oral tablets, 2006)

4) depression, severe; should not be used to treat (Prod Info RITALIN(R) oral tablets, RITALIN-SR(R) sustai

5) EEG abnormalities; may lower convulsive threshold (Prod Info RITALIN(R) oral tablets, RITALIN-SR(R) sustai

6) fatigue states, normal; should not be used to prevent or treat (Prod Info RITALIN(R) oral tablets, RITALIN-SR(

7) psychosis; may exacerbate symptoms of behavior disturbance and thought disorder (Prod Info RITALIN(R) or tablets, 2006)

8) seizures, history of; may lower convulsive threshold (Prod Info RITALIN(R) oral tablets, RITALIN-SR(R) sustai

9) underlying medical conditions that may be compromised by increases in blood pressure or heart rate such as myocardial infarction, or hyperthyroidism (Prod Info RITALIN(R) oral tablets, RITALIN-SR(R) sustained-release or

### 3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Immunologic Effects

Musculoskeletal Effects

Neurologic Effects

Ophthalmic Effects

Psychiatric Effects

Renal Effects

Reproductive Effects

Respiratory Effects

Other

### **3.3.1 Cardiovascular Effects**

Methylphenidate

Methylphenidate Hydrochloride

#### **3.3.1.A Methylphenidate**

Increased blood pressure

Increased heart rate

##### **3.3.1.A.1 Increased blood pressure**

a) Modest increases in systolic and diastolic blood pressure have been reported in studies. Use methylphenidate cautiously in patients with underlying medical conditions (such as preexisting hypertension, heart failure, recent myocardial infarction, or hyperthyroidism) who may be susceptible to increases in blood pressure (Prod Info DAYTRANA(TM) transdermal system, 2006).

##### **3.3.1.A.2 Increased heart rate**

a) Modest increases in heart rate have been reported in studies. Use methylphenidate cautiously in patients with underlying medical conditions (such as preexisting hypertension, heart failure, recent myocardial infarction, or hyperthyroidism) who may be susceptible to increases in heart rate (Prod Info DAYTRANA(TM) transdermal system, 2006).

#### **3.3.1.B Methylphenidate Hydrochloride**

Angina

Bradycardia

Cardiorespiratory arrest

Cerebral vasculitis

Death - sudden death

Hypertension

Myocardial infarction

Premature beats

Raynaud's phenomenon

Supraventricular tachycardia

Tachyarrhythmia

Ventricular premature beats

### 3.3.1.B.1 Angina

a) Angina pectoris was reported during postmarketing experience with methylphenidate hydrochloride extended-release oral tablets, 2008).

### 3.3.1.B.2 Bradyarrhythmia

a) Bradycardia was reported during postmarketing experience with methylphenidate hydrochloride extended-release oral tablets, 2008).

### 3.3.1.B.3 Cardiorespiratory arrest

a) Adults

1) A 19-year-old male suffered full cardiopulmonary arrest after inhaling crushed methylphenidate tablets, resulting in brain damage and subsequently developed fever, tachycardia, and elevated CK-MB concentrations. Echocardiogram revealed hypokinesia with low ejection fraction, consistent with a congestive cardiomyopathy or global myocardial dysfunction. Cardiac lesions that were similar to catecholamine cardiomyopathy without the contraction band necrosis (principal metabolite of methylphenidate) were 2 to 3 times the therapeutic concentrations upon admission. Methylphenidate may be fatal (Massello & Carpenter, 1999).

### 3.3.1.B.4 Cerebral vasculitis

a) Children

1) A case of cerebral vasculitis was reported in an 8-year-old boy who was taking methylphenidate hydrochloride extended-release oral tablets for behavioral problems. A year and a half after he started the methylphenidate treatment, he suddenly developed severe headaches of increasing intensity over a 4-month period. At the third episode, the paresthesias resulted in ataxia, dysmetria in the left upper limb. Cerebral angiogram revealed bilateral complete occlusion of the posterior cerebral arteries, indicating localized vasculitis. After discontinuing the methylphenidate treatment, he was free of symptoms.

### 3.3.1.B.5 Dead - sudden death

a) Incidence: rare

b) Adults

1) Sudden death, stroke, and myocardial infarction have occurred in adults taking usual doses of stimulant drugs. The incidence of sudden death in adults is unknown, however, adults have a greater likelihood than children of having serious structural heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults treated with stimulant drugs. Perform a thorough history to determine if there is a family history of sudden death or ventricular arrhythmia and a physical examination to assess the existence of cardiac disease prior to prescribing these drugs to patients (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

c) Children and Adolescents - With Preexisting Cardiac Risk

1) Taking usual doses of stimulant drugs may cause sudden death in children and adolescents with preexisting cardiac problems. Children or adolescents with known serious cardiac problems should not be treated with stimulant drugs. Determine if there is a family history of sudden death or ventricular arrhythmia and a physical examination to assess the existence of cardiac disease prior to prescribing these drugs to patients (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

d) Children and Adolescents - Healthy

1) A retrospective, case-controlled study examines the association between stimulant medication, and sudden death in healthy children and adolescents. In a collection of data from state vital statistics and death certificates, deaths of sudden death in children and adolescents between the ages of 7 to 19 years were matched and compared to deaths of passengers in motor vehicle accidents. The study determined that 1.8% (n=10) of youths who use stimulant medication compared with only 0.4% (n=2) of youths in the motor vehicle accident group (p=0.02). Limitations to this study included the time lag between the youths stimulant medication use and the information regarding clinical diagnoses, inconsistent postmortem inquiry, and the exclusion of deaths of unknown cause. The study stated that this finding should be considered when evaluating the overall risk and benefit of stimulant medication (Gould et al, 2009). Given the limitations of this study, the U.S. Food and Drug Administration is unable to determine if there is an association between stimulant medication and sudden death (US Food and Drug Administration, 2009).

### 3.3.1.B.6 Hypertension

a) Incidence: less than 1% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Hypertension occurred in less than 1% of patients on methylphenidate hydrochloride extended-release oral tablets (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

c) Modest increases in average blood pressure (about 2 to 4 mmHg) have been caused by the use of stimulant medication. Medical conditions that place patients at risk when blood pressure increases

heart failure, recent myocardial infarction, or ventricular arrhythmia (Prod Info CONCERTA(R) extended-

**d) Adults**

1) During a placebo-controlled, 7-week dose-titration study (n=401), adults taking methylphenidate mg/day) had mean changes from baseline in standing blood pressure that ranged from 0.1 to 2.2 mmHg compared with 1.1 mmHg and -1.8 mmHg, respectively, for placebo treated patients. At the end of controlled, 5-week fixed-dose study (n=226), adults taking methylphenidate hydrochloride extended-release oral tablets, 2008).

2) Since methylphenidate is not used as frequently in adults, there is little literature regarding the effect on hypertensive adults. Methylphenidate has been shown to increase blood pressure in patients who are hypertensive (Flemenbaum, 1972a).

**e) Children**

1) Compared to placebo, systolic and diastolic blood pressure increased approximately 1 to 4 mmHg times a day methylphenidate. In a randomized, placebo-controlled trial of 177 adolescent subjects, mean systolic and diastolic blood pressures for subjects taking methylphenidate hydrochloride (1.4 mg/kg) were 1.1 mmHg systolic and 0.7 mmHg diastolic above baseline blood pressures for subjects taking methylphenidate hydrochloride (1.4 mg/kg) compared to 0.7 mmHg systolic and 1.4 mmHg diastolic for patients receiving the placebo (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

**3.3.1.B.7 Myocardial infarction**

**a) Adults**

1) Myocardial infarction, sudden deaths, and stroke have occurred in adults taking usual doses of methylphenidate. The incidence of these cases is unknown, however, adults have a greater likelihood than children of having serious structural heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults treated with stimulant drugs. Perform a thorough history to determine if there is a family history of sudden cardiac death. Perform a physical exam to assess the existence of cardiac disease prior to prescribing these drugs to patients (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

**3.3.1.B.8 Premature beats**

a) Extrasystoles were reported during postmarketing experience with methylphenidate hydrochloride extended-release oral tablets, 2008).

**3.3.1.B.9 Raynaud's phenomenon**

a) Raynaud's phenomenon was reported during postmarketing experience with methylphenidate hydrochloride extended-release oral tablets, 2008).

**3.3.1.B.10 Supraventricular tachycardia**

a) Supraventricular tachycardia was reported during postmarketing experience with methylphenidate hydrochloride extended-release oral tablets, 2008).

**3.3.1.B.11 Tachyarrhythmia**

**a) Summary**

1) Compared to placebo, resting pulses increased approximately 2 to 6 beats per minute (bpm) during day methylphenidate. In a randomized, placebo-controlled trial of 177 adolescent subjects, mean heart rate for subjects taking methylphenidate hydrochloride extended-release (up to 72 mg/day (1.4 mg/kg) for patients receiving the placebo. During a placebo-controlled, 7-week dose-titration study (n=401), extended-release (36 to 108 mg/day) experienced dose-dependent mean increases of 3.9 to 9.8 bpm with 2.7 bpm in the placebo group. In a second placebo-controlled, 5-week fixed-dose study (n=226) extended-release (18, 36, and 72 mg/day) experienced mean changes from baseline in resting pulse rate of 3.9 to 9.8 bpm in the placebo group. Monitor patients for larger changes in heart rate. Medical conditions that include those with preexisting hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

b) Incidence: 4.8% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

**c) Adults**

1) Tachycardia occurred in 4.8% of adult patients on methylphenidate hydrochloride extended-release oral tablets (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

**3.3.1.B.12 Ventricular premature beats**

a) Ventricular extrasystoles were reported during postmarketing experience with methylphenidate hydrochloride extended-release oral tablets, 2008).

**3.3.2 Dermatologic Effects**

Methylphenidate

Methylphenidate Hydrochloride

### 3.3.2.A Methylphenidate

Contact dermatitis

Erythema

#### 3.3.2.A.1 Contact dermatitis

a) Although, no cases of contact sensitization has occurred when transdermal methylphenidate is used than 9 hours and alternating application sites on the hip); contact sensitization may occur. However, con in clinical effectiveness studies. Contact sensitization is characterized by erythema with intense local rea significantly improve within 2 days or spreads beyond the patch site. Diagnosis should be confirmed by a not indicative of contact sensitization. Once a patient is sensitized to transdermal methylphenidate, admi sensitization or other systemic reactions. Systemic reactions include flare-up of previous dermatitis or of eruptions in previously unaffected skin; headache; fever; malaise; arthralgia; diarrhea; or vomiting. Patie transdermal methylphenidate might not be able to take methylphenidate in any form (Prod Info DAYTRA 1) A study designed to provoke skin sensitization demonstrated transdermal methylphenidate to be were exposed continuously for 3 weeks, followed by a 2 week rest period, and the challenge/rechall irritating than both the placebo control and the saline control. At least 18 (13.5%) of subjects (n=133 methylphenidate based on the results of the challenge and/or rechallenge phases of the study (Proc 2006).

#### 3.3.2.A.2 Erythema

a) Erythema of no or minimal discomfort is a common adverse effect with the use of transdermal methyl efficacy studies, the majority of subjects experienced minimal to definite erythema. In general, the erythe therapy or discontinuation from treatment. If erythema is accompanied by intense local reaction (edema, improve within 2 days or spreads beyond the patch site, then contact sensitization should be suspected. papules do not resolve or significantly reduce within 24 hours after patch removal (Prod Info DAYTRANA

### 3.3.2.B Methylphenidate Hydrochloride

Alopecia

Erythema

Erythroderma

Generalized hyperhidrosis

Rash

#### 3.3.2.B.1 Alopecia

a) Alopecia has been reported in postmarketing experience with methylphenidate hydrochloride extended release oral tablets, 2008).

#### 3.3.2.B.2 Erythema

a) Erythema has been reported in postmarketing experience with methylphenidate hydrochloride extended release oral tablets, 2008).

#### 3.3.2.B.3 Erythroderma

a) A case of a 73-year-old white female treated with 10 milligrams (mg) twice daily of methylphenidate has been reported (Weil, 1968). Two days after initiating therapy, the patient developed an itching RASH fever. Discontinuation of the drug and treatment with antihistamines and prednisone resulted in resolution. Upon reinstitution of the methylphenidate, the dermatitis reappeared and was again abolished upon discontinu

#### 3.3.2.B.4 Generalized hyperhidrosis

a) Incidence: 5.1% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Hyperhidrosis has occurred in 5.1% of adult patients on methylphenidate hydrochloride extended release oral tablets, 2008). In 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

#### 3.3.2.B.5 Rash

- a) Incidence: less than 1% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)
- b) Rash and rash-macular have occurred in less than 1% of patients on methylphenidate hydrochloride (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

### 3.3.3 Endocrine/Metabolic Effects

Methylphenidate

Methylphenidate Hydrochloride

#### 3.3.3.A Methylphenidate

Decreased body growth

Weight decreased

##### 3.3.3.A.1 Decreased body growth

a) It is unknown if chronic use of stimulants, including methylphenidate, in children may cause suppress transdermal system, 2006). However, multiple studies identified growth suppression with oral methylphenidate (Satterfield et al, 1979; Croche et al, 1979; Satterfield et al, 1979; Oettinger et al, 1977; McNutt et al, 1977; Gross, 1976; Millichap, 1975; Safer et al, 1975; Safer & Allen, 1975; Safer et al, 1972; Eisenberg, 1972; Satterfield et al, 1972).

1) Long-term treatment with oral methylphenidate, especially with doses greater than 20 milligrams of growth in some hyperactive children; however, the growth retarding effects appear transient, and reduced with prolonged therapy in most children. The duration of growth suppression and the doses weight deficits after the first year of treatment may be offset by growth spurts in the second year of treatment. The effects of stimulants on growth is complicated since methods of measuring growth have had a follow-up period ranging from 1 to 16 years have generally failed to demonstrate a significant effect with CNS stimulants (Mattes & Gittelman, 1983; Hollister, 1980; Croche et al, 1979; Satterfield et al, 1979; Gross, 1976; McNutt et al, 1976; Gross, 1976; Millichap & Millichap, 1975; Safer et al, 1975; Safer & Allen, 1975; Safer et al, 1972). Investigators supporting the observation that methylphenidate can induce some growth suppression result from some disorder in growth hormone secretion. However, data evaluating this hypothesis have been limited (Barter & Kammer, 1978; Brown, 1977; Brown & Williams, 1976). It has also been suggested that the temporary deficit in height gain that occurs is related to ADHD-associated delayed maturation which is associated with dysregulation of several neurotransmitter systems that may alter neuroendocrine function (Safer et al, 1998).

2) In 1 study, use of methylphenidate was shown to slightly diminish the response to growth hormone deficiency (IGHD), but not those with idiopathic short stature (ISS). Methylphenidate therapy had a small magnitude of the effect was small and the magnitude of the difference in the change in height between methylphenidate and children with IGHD not treated with methylphenidate decreased with time (Racine et al, 1973).

3) One study compared the growth of 63 hyperactive children, 29 received dextroamphetamine (mean 20 mg/day) and 14 received no medication. Height measurements were taken 1 year from student health records. Long-term administration of dextroamphetamine and methylphenidate resulted in inhibition of growth when compared to the control group; however, when the mean percentile loss was calculated, the magnitude of the difference in the change in height between methylphenidate and children with IGHD not treated with methylphenidate decreased with time (Racine et al, 1973). A follow-up study demonstrated that the CNS stimulant during the summer months (Safer et al, 1975).

4) One study involving 72 hyperactive children found a statistically significant decrease in height after 1 year (1.03 centimeters (cm)), but the initial first year height deficits were made up the second year by a gain in height. This suggested the development of tolerance to growth suppression with prolonged treatment (Satterfield et al, 1979). In this study of 60 children, 34 milligrams (mg/day), no significant decrease in height was noticed during the first year and during 5.1 years), the height was statistically greater than the predicted norms.

##### 3.3.3.A.2 Weight decreased

a) Incidence: 9% (Prod Info DAYTRANA(TM) transdermal system, 2006)

b) A decreased weight occurred in 9% of patients on transdermal methylphenidate compared with 0% on placebo (n=183) (Prod Info DAYTRANA(TM) transdermal system, 2006).

#### 3.3.3.B Methylphenidate Hydrochloride

##### 3.3.3.B.1 Decreased body growth

a) Children

1) Studies of children ages 7 to 10 years who were randomized to either methylphenidate or non-methylphenidate

frame, and children ages 10 to 13 years in naturalistic subgroups of newly treated and non-medicated children indicate that children who are treated 7 days per week throughout the year experience slowing growth in height and 2.7 kg less growth in weight over 3 years) without growth rebound during this 3-year treatment with stimulants (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

**2)** Long-term treatment with methylphenidate, especially with doses greater than 20 milligrams (mg) in some hyperactive children; however, the growth retarding effects appear transient, and are reduced with prolonged therapy in most children. The duration of growth suppression and the magnitude of weight deficits after the first year of treatment may be offset by growth spurts in the second year of treatment pertaining to the effects of stimulants on growth is complicated since methods of measuring growth in children have had a follow-up period ranging from 1 to 16 years have generally failed to demonstrate a significant effect with CNS stimulants (Mattes & Gittelman, 1983; Hollister, 1980; Croche et al, 1979; Satterfield et al, 1976; Gross, 1976; McNutt et al, 1976; Gross, 1976; Millichap & Millichap, 1975; Safer et al, 1975; Safer & Allen, 1972). Investigators supporting the observation that methylphenidate can induce some growth suppression result from some disorder in growth hormone secretion. However, data evaluating this hypothesis have been inconclusive (Safer et al, 1979; Barter & Kammer, 1978; Brown, 1977; Brown & Williams, 1976). It has also been suggested that in children with ADHD, the temporary deficit in height gain that occurs is related to ADHD-associated delayed maturation which is associated with dysregulation of several neurotransmitter systems that may alter neuroendocrine function (Safer et al, 1998).

**3)** In 1 study, use of methylphenidate was shown to slightly diminish the response to growth hormone deficiency (IGHD), but not those with idiopathic short stature (ISS). Methylphenidate therapy had a small magnitude of the effect was small and the magnitude of the difference in the change in height between methylphenidate and children with IGHD not treated with methylphenidate decreased with time (Racine et al, 1998).

**4)** One study compared the growth of 63 hyperactive children, 29 received dextroamphetamine (mean 20 mg/day) and 14 received no medication. Height measurements were taken 1 to 5 years from student health records. Long-term administration of dextroamphetamine and methylphenidate resulted in inhibition of growth when compared to the control group; however, when the mean percentile loss was calculated, the mean loss was 1.5 and 1 cm/year, respectively. Growth suppression was only minimal, 1.5 and 1 cm/year, respectively. Growth suppression was only minimal, 1.5 and 1 cm/year, respectively. A follow-up study demonstrated that the CNS stimulant during the summer months (Safer et al, 1975).

**5)** One study involving 72 hyperactive children found a statistically significant decrease in height after 1 year (1.03 centimeters (cm)), but the initial first year height deficits were made up the second year by a growth spurt. This suggested the development of tolerance to growth suppression with prolonged treatment (Satterfield et al, 1976). In this study of 60 children (mean age 7.5 years, 34 milligrams (mg)/day), no significant decrease in height was noticed during the first year and after 5.1 years, the height was statistically greater than the predicted norms.

### 3.3.4 Gastrointestinal Effects

Methylphenidate

Methylphenidate Hydrochloride

#### 3.3.4.A Methylphenidate

Decrease in appetite

Loss of appetite

Nausea

Vomiting

##### 3.3.4.A.1 Decrease in appetite

**a)** Incidence: 26% (Prod Info DAYTRANA(TM) transdermal system, 2006)

**b)** Decreased appetite occurred in 26% of patients on transdermal methylphenidate compared with 5% in placebo group (n=183) (Prod Info DAYTRANA(TM) transdermal system, 2006).

##### 3.3.4.A.2 Loss of appetite

**a)** Incidence: 5% (Prod Info DAYTRANA(TM) transdermal system, 2006)

**b)** Anorexia occurred in 5% of patients on transdermal methylphenidate compared with 1% of placebo group (Prod Info DAYTRANA(TM) transdermal system, 2006). During an open-label study (n=191) of 40-month treatment with 40 mg/day, anorexia occurred in 46% of subjects leading to a 4% discontinuation rate (Prod Info DAYTRANA(TM) transdermal system, 2006).

2006).

#### 3.3.4.A.3 Nausea

a) Incidence: 12% (Prod Info DAYTRANA(TM) transdermal system, 2006)

b) Nausea occurred in 12% of patients on transdermal methylphenidate compared with 2% of placebo (Prod Info DAYTRANA(TM) transdermal system, 2006).

#### 3.3.4.A.4 Vomiting

a) Incidence: 10% (Prod Info DAYTRANA(TM) transdermal system, 2006)

b) Vomiting occurred in 10% of patients on transdermal methylphenidate compared with 5% of placebo (Prod Info DAYTRANA(TM) transdermal system, 2006).

### 3.3.4.B Methylphenidate Hydrochloride

Constipation

Decrease in appetite

Gastrointestinal obstruction

Indigestion

Loss of appetite

Nausea

Stomach ache

Upper abdominal pain

Vomiting

Xerostomia

#### 3.3.4.B.1 Constipation

a) Incidence: 1.4% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Constipation has been reported in 1.4% of adult patients on methylphenidate hydrochloride extended-release oral tablets compared with 0.6% of patients on placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

#### 3.3.4.B.2 Decrease in appetite

a) Incidence: 25.3% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Decreased appetite has been reported in 25.3% of adult patients on methylphenidate hydrochloride extended-release oral tablets compared with 6.6% of patients on placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

c) In a direct, double-blind, crossover comparison of adverse effect profiles, both dextroamphetamine 0.3 mg/kg and methylphenidate 0.3 mg/kg twice daily were well-tolerated in 125 children with attention deficit disorder (ADHD). Children reported more frequently during drug therapy than at baseline were appetite suppression (both drugs) and mean severity of adverse effects was significantly higher in the dextroamphetamine group. However, only 1 child discontinued therapy because of adverse effects (Efron et al, 1997).

#### 3.3.4.B.3 Gastrointestinal obstruction

a) Rare cases of obstructive symptoms have been reported in patients with known gastrointestinal narrowing. The ingestion of drugs in nondeformable controlled-release formulations. This drug should only be used in whole (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

#### 3.3.4.B.4 Indigestion

a) Incidence: 2.2% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Indigestion has been reported in 2.2% of adult patients on methylphenidate hydrochloride extended-release oral tablets compared with 0.6% of patients on placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

**3.3.4.B.5 Loss of appetite**

- a) Incidence: 1.7% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)
- b) Anorexia has been reported in 1.7% of adult patients on methylphenidate hydrochloride extended-release oral tablets, in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

**3.3.4.B.6 Nausea**

- a) Incidence: 12.8% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)
- b) Adults
  - 1) Nausea has been reported in 12.8% of adult patients on methylphenidate hydrochloride extended-release oral tablets, in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

**3.3.4.B.7 Stomach ache**

- a) Incidence: less than 1% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)
- b) Stomach discomfort occurred in less than 1% of patients on methylphenidate hydrochloride extended-release oral tablets, in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

**3.3.4.B.8 Upper abdominal pain**

- a) Incidence: 5.9% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)
- b) Children
  - 1) Upper abdominal pain has been reported in 5.9% of children and adolescent patients on methylphenidate hydrochloride extended-release oral tablets, compared with 3.8% of patients on placebo (n=318), in 4 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

**3.3.4.B.9 Vomiting**

- a) Incidence: 1.7%, adults; 2.8%, children (Prod Info CONCERTA(R) extended-release oral tablets, 2008)
- b) Adults
  - 1) Vomiting has been reported in 1.7% of adult patients on methylphenidate hydrochloride extended-release oral tablets, in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).
- c) Children
  - 1) Vomiting has been reported in 2.8% of children and adolescent patients on methylphenidate hydrochloride extended-release oral tablets, compared with 1.6% of patients on placebo (n=318), in 4 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

**3.3.4.B.10 Xerostomia**

- a) Incidence: 14% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)
- b) Adults
  - 1) Dry mouth has been reported in 14% of adult patients on methylphenidate hydrochloride extended-release oral tablets, in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

**3.3.5 Hematologic Effects****3.3.5.A Methylphenidate Hydrochloride**

Eosinophil count raised

Leukopenia

Pancytopenia

Thrombocytopenia

Thrombocytopenic purpura

**3.3.5.A.1 Eosinophil count raised**

- a) Methylphenidate abuse by the intravenous route can cause an eosinophilia (Hayashi et al, 1980). Ab: 30,338.

**3.3.5.A.2 Leukopenia**

- a) Incidence: less than 1% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)
- b) Leukopenia occurred in less than 1% of patients on methylphenidate hydrochloride extended-release oral tablets, in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008). Leukopenia was also reported during open-label studies. Periodically monitor CBC, differential, and platelets (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

**3.3.5.A.3 Pancytopenia**

a) Pancytopenia was reported during postmarketing experience with methylphenidate hydrochloride extended-release oral tablets, 2008).

**3.3.5.A.4 Thrombocytopenia**

a) Thrombocytopenia was reported during postmarketing experience with methylphenidate hydrochlorid extended-release oral tablets, 2008).

**1) Children**

a) Thrombocytopenia was reported in a 10-year-old boy who received methylphenidate for atte had been treated with methylphenidate for 10 months when a routine blood count revealed thro within 2 weeks of drug discontinuation (Kuperman et al, 2003).

**3.3.5.A.5 Thrombocytopenic purpura**

a) Thrombocytopenic purpura was reported during postmarketing experience with methylphenidate hydr CONCERTA(R) extended-release oral tablets, 2008).

**3.3.6 Hepatic Effects****3.3.6.A Methylphenidate Hydrochloride**

Autoimmune hepatitis

Hepatotoxicity

**3.3.6.A.1 Autoimmune hepatitis**

a) Autoimmune hepatitis occurred in a 57-year-old, asymptomatic Caucasian male 1 month following ini a history of orthotopic liver transplantation secondary to chronic hepatitis C infection 4 years prior, was fc chemistries during a routine scheduled follow-up. Baseline liver chemistries had been stable in the montl AST, ALT, and total bilirubin were 572 units/L, 338 units/L, and 2.7 mg/dL, respectively. Medications take venlafaxine, omeprazole, hydrochlorothiazide, fosinopril, and a multivitamin. Long-acting methylphenidat presentation for impaired concentration and depressive symptoms. The patient denied alcohol abuse an and did not have any fever, chills, abdominal pain, or urine discoloration. Physical examination revealed hepatosplenomegaly evident. No change in mental status or asterixis was found on neurological examin: anti-smooth muscle antibody (1:40) and antinuclear antibody (1:80), with a nucleolar pattern, and an elev normal at baseline. A liver biopsy showed severe lobular and periportal necroinflammatory infiltrate with eosinophils, but lacking endothelialitis and bile duct damage. Subsequently, methylphenidate therapy wa normalize. Besides methylphenidate, other prior medications were continued and prednisone 10 mg/day chemistries returned to patient's approximate baseline values over the next few months, and a liver biop: improvement. Later, the patient was started on combination amphetamine/dextroamphetamine with no fu 2007).

**3.3.6.A.2 Hepatotoxicity**

a) Liver dysfunction is a rare side effect of methylphenidate. Intravenous abuse of methylphenidate was marked elevations in bilirubin, SGOT and SGPT in a 19-year-old black woman. Hepatic biopsy revealed cells and eosinophils. Focal collections of mononuclear cells with Kupffer cell hyperplasia was observed rechallenge with 20 milligrams (mg) intravenously (IV) methylphenidate (Ritalin(R)) twice daily for 2 days hepatotoxicity (Mehta et al, 1984). These data suggest the hepatotoxic potential of the drug when given

**3.3.7 Immunologic Effects****3.3.7.A Methylphenidate Hydrochloride**

Anaphylaxis

Angioedema

Auricular dilatation

Bullous eruption

Generalized exfoliative dermatitis

Generalized pruritus

Immune hypersensitivity reaction

Nasopharyngitis

### 3.3.7.A.1 Anaphylaxis

a) Hypersensitivity reactions such as anaphylactic reactions have been reported in postmarketing experience with extended-release (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

### 3.3.7.A.2 Angioedema

a) Hypersensitivity reactions such as angioedema has been reported in postmarketing experience with extended-release (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

### 3.3.7.A.3 Auricular dilatation

a) Hypersensitivity reactions such as auricular swelling has been reported in postmarketing experience with extended-release (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

### 3.3.7.A.4 Bullous eruption

a) Hypersensitivity reactions such as bullous conditions have been reported in postmarketing experience with extended-release (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

### 3.3.7.A.5 Generalized exfoliative dermatitis

a) Hypersensitivity reactions such as exfoliative conditions have been reported in postmarketing experience with extended-release (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

### 3.3.7.A.6 Generalized pruritus

a) Hypersensitivity reactions such as pruritus have been reported in postmarketing experience with extended-release (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

### 3.3.7.A.7 Immune hypersensitivity reaction

a) Hypersensitivity reactions to methylphenidate are rare in occurrence. However, 2 cases have been reported in the other case erythema multiforme was described (Rothschild, 1972); (Weil, 1968).

### 3.3.7.A.8 Nasopharyngitis

a) Incidence: 2.8% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Children

1) Nasopharyngitis has occurred in 2.8% of child and adolescent patients (n=321) on methylphenidate compared with 2.2% of patients on placebo (n=318), in 4 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

## 3.3.8 Musculoskeletal Effects

Methylphenidate

Methylphenidate Hydrochloride

### 3.3.8.A Methylphenidate

#### 3.3.8.A.1 Bone finding

a) Oral methylphenidate did not significantly affect BONE MINERAL DENSITY and BONE TURNOVER from 3 to 10 years), who were treated with a mean dose of methylphenidate 10 milligrams for an average duration of 54 months. Inclusion criteria for BONE MINERALIZATION), urinary deoxypyridinoline excretion (an indicator of BONE RESORPTION significantly different from boys of the control group (n=9). All the children in the treatment group were within the normal range (Lahat et al, 2000).

b) In a retrospective cohort study of 42 male and female children (between 7 and 16 years old), dental radiographs were taken at a mean dose of 30 milligrams (mg) of oral methylphenidate (MH) for a mean duration of 54 months. Inclusion criteria for MH for a minimum of 2 years at the time of panoramic radiograph. The gender- and age-matched control had not ingested any long-term medication. An oral, written, and radiographic review of gender- and age-matched control outcome of the study was the dental age difference score, which was defined as dental age score for MH minus dental age score for control. The mean dental age score for MH subjects was approximately 6 months behind matched control subjects compared, MH and control subjects were similar (p =0.27). Multiple regression demonstrated that length of drug use were considered (Batterson et al, 2005).

### 3.3.8.B Methylphenidate Hydrochloride

Arthralgia

Bone finding

Muscle rigidity

Muscle twitch

Myalgia

#### 3.3.8.B.1 Arthralgia

a) Arthralgia has been reported in postmarketing experience with methylphenidate extended-release (PI tablets, 2008).

#### 3.3.8.B.2 Bone finding

a) Children

1) Methylphenidate did not significantly affect bone mineral density and bone turnover in children. In a study of 13 children (7-13 years), who were treated with a mean dose of methylphenidate 10 milligrams for an average of 13 months (ADHD), their bone mineral density (as measured by using dual photon absorptiometry), serum bone mineralization, urinary deoxypyridinoline excretion (an indicator of bone resorption), and serum osteocalcin were different from boys of the control group (n=9). All the children in the treatment group were within the normal range (Lahat et al, 2000).

2) In a retrospective cohort study of 42 male and female children (between 7 and 16 years old), the average dose of 30 milligrams (mg) of methylphenidate (MH) for a mean duration of 54 months. The mean dose of MH was 1.5 mg/kg/day for a minimum of 2 years at the time of panoramic radiograph. The gender- and age- groups were healthy and had not ingested any long-term medication. An oral, written, and radiographic review was conducted. The main outcome of the study was the dental age difference score, which was defined as the difference between the dental age score for control subjects and the dental age score for MH subjects. The mean dental age score for MH subjects was approximately 6 months when the median differences were compared, MH and control subjects were similar (p =0.27). Multiple comparisons were made when gender, age, or length of drug use were considered (Batterson et al, 2005).

#### 3.3.8.B.3 Muscle rigidity

a) Incidence: 1.9% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Muscle tightness has occurred in 1.9% of adult patients on methylphenidate hydrochloride extended-release oral tablets, in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

#### 3.3.8.B.4 Muscle twitch

a) Muscle twitching has been reported in postmarketing experience with methylphenidate extended-release oral tablets, 2008).

#### 3.3.8.B.5 Myalgia

a) Myalgia has been reported in postmarketing experience with methylphenidate extended-release (PI tablets, 2008).

### 3.3.9 Neurologic Effects

Methylphenidate

Methylphenidate Hydrochloride

#### 3.3.9.A Methylphenidate

Headache

Insomnia

Lowered convulsive threshold

Tic

#### 3.3.9.A.1 Headache

a) During an open-label study (n=191) of 40-month duration with transdermal methylphenidate worn for subjects (Prod Info DAYTRANA(TM) transdermal system, 2006)

#### 3.3.9.A.2 Insomnia

a) Incidence: 13% (Prod Info DAYTRANA(TM) transdermal system, 2006)

b) Insomnia occurred in 13% of patients on transdermal methylphenidate compared with 5% of placebo (Prod Info DAYTRANA(TM) transdermal system, 2006). During an open-label study (n=191) of 40-month worn for 12 hours daily, insomnia occurred in 30% of subjects leading to a 4% discontinuation rate (Prod 2006).

#### 3.3.9.A.3 Lowered convulsive threshold

a) There is some clinical evidence that methylphenidate may lower convulsive threshold in patients with prior electroencephalogram (EEG) abnormalities in the absence of a history of seizures, and, very rarely prior EEG evidence of seizures. Discontinue methylphenidate if seizures develop (Prod Info DAYTRANA

1) Children with attention deficit hyperactive disorder (ADHD) who have normal electroencephalogram they receive stimulant therapy for ADHD (methylphenidate, dextroamphetamine, or combination am (R)). However, children with epileptiform EEGs may have considerable risk for eventual seizure, although be attributable to use of the stimulant. These conclusions were based on a study of 234 children with ADHD. All had EEGs prior to parental choosing of stimulant treatment or foregoing stimulant treatment. Children (15.4%) demonstrated epileptiform abnormalities compared with 198 with normal EEGs. Of treatment for ADHD. Three of the 30 who received stimulant therapy experienced seizures (p less than 0.05). One 10-year-old male, and a 6-year-old male. The girl was treated uneventfully with methylphenidate for 12 months. The methylphenidate experienced a 4-minute generalized tonic-clonic seizure. Her EEG had revealed a focal epileptiform abnormality. In two boys, the first experienced a 2-minute generalized tonic clonic seizure with focal onset 3 years after an episode at 10 months after initiation of methylphenidate; he was heard to fall and was unresponsive. The EEGs of both boys had shown rolandic spikes, a focal epileptiform abnormality. One child who had begun beginning methylphenidate (Hemmer et al, 2001).

#### 3.3.9.A.4 Tic

a) Incidence: 7% (Prod Info DAYTRANA(TM) transdermal system, 2006)

b) Tic occurred in 7% of patients on transdermal methylphenidate compared with 0% of placebo treated. Transdermal methylphenidate is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome (Prod Info DAYTRANA(TM) transdermal system, 2006).

1) The incidence of TICS emergence was 7.8% in children treated with stimulant medication (methylphenidate) for attention deficit hyperactivity disorder, based on a retrospective chart review (n=555). These children were free of tics and without a history of tics according to the practice of the settings in which they were treated. The incidence of tics was 8.3% of subjects treated with methylphenidate, 6.3% treated with dextroamphetamine, and 7.7% treated with placebo. Mean age of subjects was 11 years. A significant correlation was found between the development of tics. As the authors noted, these children may have developed tics, regardless of treatment (Nolan et al, 2001).

2) Although stimulant therapy was suspected to exacerbate tics, long-term methylphenidate treatment was effective in children with attention-deficit hyperactivity disorder (ADHD) and chronic multiple tic disorder. In a blinded, prospective, follow-up study, 32 children (age ranging from 6.1 and 11.9 years) received methylphenidate in a previous trial (mean 16.5 milligrams (mg), range=5 to 40 mg). The children were evaluated in a similar study for their on-task, fidgeting, worksheet behaviors, and vocal and motor tic frequency. In almost every measure, methylphenidate was superior to placebo (p ranging from less than 0.001 to 0.03). There was no difference in tic condition between baseline and placebo, whereas children spent significantly less time in tic condition on methylphenidate medication conditions than placebo (p less than 0.001). There was no significant difference between methylphenidate and placebo in growth table values. Systolic blood pressure and heart rate were significantly increased (p=0.02 and p=0.03) but clinically insignificant. Although this study showed methylphenidate did not worsen tics in patients with ADHD, the possibility of individual exacerbation of tic cannot be ruled out (Gadow et al, 1999). In another study, abrupt withdrawal of methylphenidate and dextroamphetamine in long-term therapy DID increase tic frequency (Nolan et al, 1999).

3) Tourette's syndrome may be exacerbated or precipitated by the use of stimulant medications for children. Early signs of Tourette's syndrome or tics are difficult to distinguish from hyperactive and conduct disorder and therefore mistakenly be treated with stimulant medications (dextroamphetamine, methylphenidate, or amphetamine). The severe motor and phonic tics requiring discontinuation of the stimulants and possible institution of antipsychotic medication in children with Tourette's syndrome. In children with Tourette's syndrome, clinical evaluation for Tics and Tourette's Syndrome in the child with Tourette's syndrome. In children with no symptoms of Tourette's syndrome but with a familial history of Tourette's syndrome, use of stimulants is contraindicated in children with Tourette's Syndrome. If tics occur during stimulant medication, stimulant medication should be discontinued (Lowe et al, 1982).

4) Numerous case reports have demonstrated tics either starting or worsening after methylphenidate treatment. There is no correlation between stimulant dosages (high or low) or duration of treatment, and tic development.

days, months, even years. Many of the patients who developed tics years later were within the age 1 so it is unknown if disease onset was independent of stimulant use. The highest risk for tic exacerbations are treated with stimulant medication early in life and/or for a long duration. Investigators have noted that discontinuing the stimulant decreased tic severity but did not necessarily completely resolve the tics (1985; Lowe et al, 1982); (Balhman, 1981)(Mitchell & Matthews, 1980; Bremness & Surend, 1979; Peck 1974); (Myerhoff & Synder, 1973).

5) One group of investigators evaluated 1500 children who received methylphenidate in the treatment of attention deficit hyperactivity disorder. The authors found that the incidence of tics developed following the drug administration. The types of tics described included eyelid, facial muscle, head, jaw, neck, limb and trunk tics. The relationship to dose or duration of therapy and that in most patients discontinuing the drug resulted in resolution of tics. In contrast, another study (Erenberg et al, 1985) found that stimulant medications aggravated existing tics.

### 3.3.9.B Methylphenidate Hydrochloride

Akathisia

Central nervous system finding

Cerebrovascular accident

Chorea

Confusion

Dizziness

Dyskinesia

Gilles de la Tourette's syndrome

Headache

Insomnia

Lethargy

Paresthesia

Seizure

Sleep disorder

Somnolence

Tension-type headache

Tremor

Vertigo

#### 3.3.9.B.1 Akathisia

##### a) Adults

1) Symptoms of akathisia occurred in a 46-year-old Caucasian female following initiation of methylphenidate for attention deficit hyperactivity disorder. She had a history of recurrent major depressive disorder, alcohol dependence in full sustained remission, nicotine dependence, and multiple pulmonary eosinophilic granulomas, was prescribed oral methylphenidate 10 mg twice daily. She was also additionally receiving a complex regimen of medications, which included quetiapine. Although she was on a low dose of methylphenidate, she continued treatment. By the fifth day, she was restless, pacing, and felt like she was on clonazepam and diazepam (part of her regular regimen of medications) did not resolve the symptoms. She began experiencing tremors in her left arm. She presented to the emergency room where she was admitted.

led to a prompt relief of symptoms. She was advised to discontinue methylphenidate and following benzotropine, her symptoms did not recur. It was proposed that the addition of methylphenidate may symptoms, a potential side effect of quetiapine (Almeida et al, 2006).

### 3.3.9.B.2 Central nervous system finding

a) Following administration of usual therapeutic doses in the treatment of minimal brain dysfunction/hyp have been reported with the use of methylphenidate. Symptoms have included restlessness, behavior di hallucinations, slurred speech, ataxia, vertigo, and uncontrollable facial and tongue movements (Lucas & the drug usually results in subsiding of these reactions within a few days.

### 3.3.9.B.3 Cerebrovascular accident

#### a) Adults

1) Stroke, sudden death, and myocardial infarction have occurred in adults taking usual doses of st cases is unknown, however, adults have a greater likelihood than children of having serious structur serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adu treated with stimulant drugs (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

### 3.3.9.B.4 Chorea

#### a) Children

1) A case of chorea induced by methylphenidate in a 5-year-old boy receiving the drug for hyperact 1978). The choreic disorder disappeared 2 months after methylphenidate was discontinued.

### 3.3.9.B.5 Confusion

a) Incidence: 1.2% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

#### b) Adults

1) Confusional state has occurred in 1.2% of adult patients on methylphenidate hydrochloride exter patients on placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

### 3.3.9.B.6 Dizziness

a) Incidence: 6.7%, adults; 1.9%, children (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

#### b) Adults

1) Dizziness occurred in 6.7% of adult patients on methylphenidate hydrochloride compared with 5. placebo-controlled clinical trials (n=627) (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

#### c) Children

1) Dizziness occurred in 1.9% of children and adolescent patients on methylphenidate hydrochlorid of patients on placebo (n=318), in 4 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

### 3.3.9.B.7 Dyskinesia

a) Dyskinesia was reported during postmarketing experience with methylphenidate hydrochloride extenc extended-release oral tablets, 2008).

### 3.3.9.B.8 Gilles de la Tourette's syndrome

a) Incidence: 1 to 9% (Prod Info CONCERTA(R) extended-release oral tablets, 2008; Varley et al, 2001)

#### b) Children

1) The cumulative incidence of onset of new tics was 9% in children after 27 months of treatment w release in a long-term uncontrolled study (n=432) . The cumulative incidence of onset of new tics w: methylphenidate hydrochloride extended-release for up to 9 months, in a uncontrolled study (n=682 oral tablets, 2008).

2) The incidence of tics emergence was 7.8% in children treated with stimulant medication (methylp attention deficit hyperactivity disorder, based on a retrospective chart review (n=555). These stimula they were free of tics and without a history of tics according to the practice of the settings in which th of subjects treated with methylphenidate, 6.3% treated with dextroamphetamine, and 7.7% treated v dose or duration of stimulant therapy. Mean age of subjects was 11 years. A significant correlation c of tics. As the authors noted, these children may have developed tics, regardless of treatment with th

3) Although stimulant therapy was suspected to exacerbate tics, long-term methylphenidate treatme effective in children with attention-deficit hyperactivity disorder (ADHD) and chronic multiple tic disor blinded, prospective, follow-up study, 32 children (age ranging from 6.1 and 11.9 years) received mi previous trial (mean 16.5 milligrams (mg), range=5 to 40 mg). The children were evaluated in a simu their on-task, fidgeting, worksheet behaviors, and vocal and motor tic frequency. In almost every me than placebo (p ranging from less than 0.001 to 0.03). There was no difference in tic condition betwe behaviors were not significantly different between baseline and placebo, whereas children spent sig medication conditions than placebo (p less than 0.001). There was no significant difference between growth table values. Systolic blood pressure and heart rate were significantly increased (p=0.02 and clinically insignificant. Although this study showed methylphenidate did not worsen tics in patients w possibility of individual exacerbation of tic cannot be ruled out (Gadow et al, 1999). In another study syndrome, abrupt withdrawal of methylphenidate and dextroamphetamine in long-term therapy DID frequency (Nolan et al, 1999).

4) One group of investigators evaluated 1500 children who received methylphenidate in the treatme

incidence of tics following the drugs administration. The authors found that the incidence of tics dev  
The types of tics described included eyelid, facial muscle, head, jaw, neck, limb and trunk tics. The r  
relation to dose or duration of therapy and that in most patients discontinuing the drug resulted in re  
contrast, another study (Erenberg et al, 1985) found that stimulant medications aggravated existing  
5) Tourette's syndrome may be exacerbated or precipitated by the use of stimulant medications for  
children. Early signs of Tourette's syndrome or tics are difficult to distinguish from hyperactive and a  
therefore mistakenly be treated with stimulant medications (dextroamphetamine, methylphenidate, p  
the severe motor and phonic tics requiring discontinuation of the stimulants and possible institution o  
having an attention deficit disorder, clinical evaluation for Tics and Tourette's Syndrome in the child  
stimulant medication. In children with no symptoms of Tourette's syndrome but with a familial history  
use of stimulants is contraindicated in children with Tourette's Syndrome. If tics occur during stimula  
discontinued (Lowe et al, 1982).

c) Numerous case reports have demonstrated tics either starting or worsening after methylphenidate, pe  
correlation between stimulant dosages (high or low) or duration of treatment, and tic development. Tics h  
even years. Many of the patients who developed tics years later were within the age range where tics fre  
disease onset was independent of stimulant use. The highest risk for tic exacerbation appears to be in si  
stimulant medication early in life and/or for a long duration. Investigators have noted that in those patient  
stimulant decreased tic severity but did not necessarily completely resolve the condition (Price et al, 198  
(Balhman, 1981)(Mitchell & Matthews, 1980; Bremness & Surerd, 1979; Pollack et al, 1977; Denckla et al  
1973).

#### 3.3.9.B.9 Headache

a) Incidence: 22.2%, adults (Prod Info CONCERTA(R) extended-release oral tablets, 2008); greater tha

b) Adults

1) Headache occurred in 22.2% of adult patients on methylphenidate hydrochloride extended-relea  
placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) exte

c) Children

1) In unpublished study data provided by the manufacturer involving children 6 to 12 years of age tr  
(R) LA) for up to 4 weeks, insomnia and headache reportedly occurred in greater than 5% of patient

#### 3.3.9.B.10 Insomnia

a) Incidence: 4.3% to 12.3%, adults; (Prod Info CONCERTA(R) extended-release oral tablets, 2008)2.8  
release oral tablets, 2008)

b) Adults

1) Insomnia has occurred in 12.3% of adult patients on methylphenidate hydrochloride extended-re  
on placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) ex

2) Initial insomnia has occurred in 4.3% of adult patients on methylphenidate hydrochloride extende  
patients on placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERT

c) Children

1) Insomnia has occurred in 2.8% of child and adolescent patients extended-release (n=321) comp  
in 4 double-blind, placebo-controlled clinical trials(Prod Info CONCERTA(R) extended-release oral t

#### 3.3.9.B.11 Lethargy

a) Incidence: less than 1% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Lethargy occurred in less than 1% of patients on methylphenidate hydrochloride extended-releas  
trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

#### 3.3.9.B.12 Paresthesia

a) Incidence: 1.2% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Paresthesia occurred in 1.2% of adult patients on methylphenidate hydrochloride extended-relea  
patients, in 2 double-blind, placebo-controlled clinical trials (n=627) (Prod Info CONCERTA(R) exte

#### 3.3.9.B.13 Seizure

a) For patients with a prior history of seizures, prior EEG abnormalities without seizures, and patients wi  
evidence of seizures, stimulants may lower the convulsive threshold. Discontinue methylphenidate hydr  
Info CONCERTA(R) extended-release oral tablets, 2008).

b) Convulsions and grand mal convulsions were reported during postmarketing experience (Prod Info C  
2008).

c) Children

1) Children with attention deficit hyperactive disorder (ADHD) who have normal electroencephalogr  
they receive stimulant therapy for ADHD (methylphenidate, dextroamphetamine, or combination am  
(R)). However, children with epileptiform EEGs may have considerable risk for eventual seizure, alth  
be attributable to use of the stimulant. These conclusions were based on a study of 234 children wit  
ADHD. All had EEGs prior to parental choosing of stimulant treatment or foregoing stimulant treatm  
children (15.4%) demonstrated epileptiform abnormalities compared with 198 with normal EEGs. Of  
treatment for ADHD. Three of the 30 who received stimulant therapy experienced seizures (p less th

year-old male, and a 6-year-old male. The girl was treated uneventfully with methylphenidate for 12 months. The boy who experienced a 4-minute generalized tonic-clonic seizure. Her EEG had revealed a first experienced a 2-minute generalized tonic clonic seizure with focal onset 3 years after starting episode at 10 months after initiation of methylphenidate; he was heard to fall and was unresponsive of both boys had shown rolandic spikes, a focal epileptiform abnormality. One child who had a normal EEG had a methylphenidate (Hemmer et al, 2001).

2) Use of methylphenidate appears to be safe and effective to treat attention deficit hyperactivity disorder in children who are seizure free, while receiving antiepileptic drugs, before starting methylphenidate therapy. However, children who have had seizures while receiving antiepileptic drugs (Gross-Tsur et al, 1997).

#### 3.3.9.B.14 Sleep disorder

a) Incidence: less than 1% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Sleep disorders have occurred in less than 1% of patients on methylphenidate hydrochloride extended-release oral tablets (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

#### 3.3.9.B.15 Somnolence

a) Incidence: less than 1% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Somnolence occurred in less than 1% of patients on methylphenidate hydrochloride extended-release oral tablets (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

#### 3.3.9.B.16 Tension-type headache

a) Incidence: 1.2% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Tension headache occurred in 1.2% of adult patients on methylphenidate hydrochloride extended-release oral tablets, in 2 double-blind, placebo-controlled clinical trials (n=627) (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

#### 3.3.9.B.17 Tremor

a) Incidence: 2.7% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Tremor occurred in 2.7% of adult patients on methylphenidate hydrochloride extended-release oral tablets, in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

#### 3.3.9.B.18 Vertigo

a) Incidence: 1.7% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Vertigo has occurred in 1.7% of adult patients on methylphenidate hydrochloride extended-release oral tablets, in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

### 3.3.10 Ophthalmic Effects

Methylphenidate

Methylphenidate Hydrochloride

#### 3.3.10.A Methylphenidate

Blurred vision

Disorder of accommodation

Visual disturbance

##### 3.3.10.A.1 Blurred vision

a) Blurring of vision has been reported (Prod Info DAYTRANA(TM) transdermal system, 2006).

##### 3.3.10.A.2 Disorder of accommodation

a) Difficulties with accommodation have been reported (Prod Info DAYTRANA(TM) transdermal system, 2006).

##### 3.3.10.A.3 Visual disturbance

a) Incidence: rare (Prod Info DAYTRANA(TM) transdermal system, 2006)

b) Rarely, symptoms of visual disturbances have been experienced (Prod Info DAYTRANA(TM) transdermal system, 2006).

### 3.3.10.B Methylphenidate Hydrochloride

Diplopia

Dry eye

Glaucoma

Mydriasis

Retinopathy

Visual disturbance

#### 3.3.10.B.1 Diplopia

a) Diplopia was reported during postmarketing experience with methylphenidate hydrochloride extended-release oral tablets, 2008).

#### 3.3.10.B.2 Dry eye

a) Incidence: less than 1% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Dry eyes have occurred in less than 1% of patients on methylphenidate hydrochloride extended-release oral tablets (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

#### 3.3.10.B.3 Glaucoma

a) Use of methylphenidate in patients with glaucoma is contraindicated (Prod Info Ritalin (R), 2001a). However, methylphenidate may be used cautiously in conjunction with glaucoma medications and regular ophthalmologic monitoring, particularly in patients with well-controlled, open-angle glaucoma (Bartlik & Harmon, 1999).

#### 3.3.10.B.4 Mydriasis

a) Mydriasis was reported during postmarketing experience with methylphenidate hydrochloride extended-release oral tablets, 2008).

#### 3.3.10.B.5 Retinopathy

a) Intravenous abuse of methylphenidate can result in the development of retinopathy which is believed to be caused by cornstarch, filtering materials, and other contaminants acting as microemboli (Tse, 1980; Kresca, 1979).

#### 3.3.10.B.6 Visual disturbance

a) Incidence: 1.7% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Blurred vision has occurred in 1.7% of adult patients on methylphenidate hydrochloride extended-release oral tablets on placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

c) Stimulant treatment may cause blurred vision and difficulties with accommodation. Visual disturbance has been reported during postmarketing experience (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

### 3.3.12 Psychiatric Effects

Methylphenidate

Methylphenidate Hydrochloride

#### 3.3.12.A Methylphenidate

Labile affect, Mild

Mania

Psychotic disorder

##### 3.3.12.A.1 Labile affect, Mild

a) Incidence: 6% (Prod Info DAYTRANA(TM) transdermal system, 2006)

b) Mild affect lability occurred in 6% of patients on transdermal methylphenidate compared with 0% of patients on placebo. Of the 6 patients who experienced affect lability, symptoms were characterized as increased emotionally labile affect, and intermittent emotional lability (Prod Info DAYTRANA(TM) transdermal system, 2006).

### 3.3.12.A.2 Mania

a) In a review of 49 randomized, controlled pediatric ADHD clinical trials involving psychostimulant medications (methylphenidate hydrochloride, modafinil and dextromethylphenidate hydrochloride), the rate of psychostimulant-induced mania was 1.48 (95% CI, 0.74 to 2.65) per 100 person-years, with no comparable adverse events reported to the US Food and Drug Administration to manufacturers of marketed ADHD drugs for submission of postmarketing surveillance reports between 2000 and 2005, yielded a total of 865 reports (pediatrics and adults) in which signs and symptoms of mania were reported. The majority of reports involved pediatric subjects, with almost half of the reports in children 10 years of age or younger. Visual and/or tactile sensations of insight were reported. Positive rechallenge was reported for each of the psychostimulant medications (methylphenidate hydrochloride and mixed salts of a single entity amphetamine product) included in the analysis; and in many cases a significant onset of psychiatric symptoms ranged from days to weeks, but in some cases it was months or years from onset (Mosholder et al, 2009).

### 3.3.12.A.3 Psychotic disorder

a) In a review of 49 randomized, controlled pediatric ADHD clinical trials involving psychostimulant medications (methylphenidate hydrochloride, modafinil and dextromethylphenidate hydrochloride), the rate of psychostimulant-induced psychosis was 1.48 (95% CI, 0.74 to 2.65) per 100 person-years, with no comparable adverse events reported to the US Food and Drug Administration to manufacturers of marketed ADHD drugs for submission of postmarketing surveillance reports between 2000 and 2005, yielded a total of 865 reports (pediatrics and adults) in which signs and symptoms of psychosis were reported. The majority of reports involved pediatric subjects, with almost half of the reports in children 10 years of age or younger. Visual and/or tactile sensations of insight were reported. Positive rechallenge was reported for each of the psychostimulant medications (methylphenidate hydrochloride and mixed salts of a single entity amphetamine product) included in the analysis; and in many cases a significant onset of psychiatric symptoms ranged from days to weeks, but in some cases it was months or years from onset (Mosholder et al, 2009).

b) Exacerbation of psychosis (behavior disturbance and thought disorder) has occurred during clinical use of DAYTRANA(TM) transdermal system, 2006).

### 3.3.12.B Methylphenidate Hydrochloride

Aggressive behavior

Agitation

Anxiety

Bruxism

Crying associated with mood

Depression

Disorientated

Feeling angry

Feeling nervous

Irritability

Mania

Mood swings

O/E - hypervigilance

Obsessive-compulsive disorder

Psychotic disorder

Reduced libido

Restlessness

Stuttering

Tension

### **3.3.12.B.1 Aggressive behavior**

a) Incidence: 1.7% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Aggression has occurred in 1.7% of adult patients on methylphenidate hydrochloride extended-release oral tablets on placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

### **3.3.12.B.2 Agitation**

a) Incidence: 2.2% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Agitation has occurred in 2.2% of adult patients on methylphenidate hydrochloride extended-release oral tablets on placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

### **3.3.12.B.3 Anxiety**

a) Incidence: 8.2% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Anxiety has occurred in 8.2% of adult patients on methylphenidate hydrochloride extended-release oral tablets on placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

### **3.3.12.B.4 Bruxism**

a) Incidence: 1.7% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Bruxism has occurred in 1.7% of adult patients on methylphenidate hydrochloride extended-release oral tablets on placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

### **3.3.12.B.5 Crying associated with mood**

a) Incidence: less than 1% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Tearfulness has occurred in less than 1% of patients on methylphenidate hydrochloride extended-release oral tablets on placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

### **3.3.12.B.6 Depression**

a) Incidence: 1.7% to 3.9% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Depression has occurred in 1.7% of adult patients on methylphenidate hydrochloride extended-release oral tablets on placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

2) Depressed mood has occurred in 3.9% of adult patients on methylphenidate hydrochloride extended-release oral tablets on placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

### **3.3.12.B.7 Disorientated**

a) Disorientation has been reported during postmarketing experience with methylphenidate hydrochloride extended-release oral tablets, 2008).

### **3.3.12.B.8 Feeling angry**

a) Incidence: less than 1% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Anger has occurred in less than 1% of patients on methylphenidate hydrochloride extended-release oral tablets on placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

### **3.3.12.B.9 Feeling nervous**

a) Incidence: 3.1% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Nervousness has occurred in 3.1% of adult patients on methylphenidate hydrochloride extended-release oral tablets on placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

### **3.3.12.B.10 Irritability**

a) Incidence: 5.8% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

**b) Adults**

- 1) Irritability has occurred in 5.8% of adult patients on methylphenidate hydrochloride extended-release placebo (n=212), in 2 double-blind, placebo-controlled clinical trials .

**3.3.12.B.11 Mania**

**a)** In a review of 49 randomized, controlled pediatric ADHD clinical trials involving psychostimulant medication (methylphenidate hydrochloride, modafinil and dextromethylphenidate hydrochloride), the rate of psychostimulant active drug was 1.48 (95% CI, 0.74 to 2.65) per 100 person-years, with no comparable adverse events reported to the US Food and Drug Administration to manufacturers of marketed ADHD drugs for submission of postmarketing surveillance events between 2000 and 2005, yielded a total of 865 reports (pediatrics and adults) in which signs and symptoms were reported. The majority of reports involved pediatric subjects, with almost half of the reports in children 10 years of age or younger. Visual and/or tactile sensations of insight were reported. Positive rechallenge was reported for each of the psychostimulant medications (methylphenidate and mixed salts of a single entity amphetamine product) included in the analysis; and in many cases a significant onset of psychiatric symptoms ranged from days to weeks, but in some cases it was months or years from onset (Mosholder et al, 2009).

**b)** Stimulants may induce mixed/manic episodes in patients with comorbid bipolar disorders. Exercise caution (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

**c)** Stimulants may cause treatment-emergent psychotic or manic symptoms (eg, hallucinations, delusional ideas, or manic symptoms). In a pooled analysis of multiple short-term, placebo-controlled studies, the incidence of psychotic symptoms was 0.1% of patients treated with stimulants (n=3482) compared with 0% in placebo treated patients (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

**d)** Methylphenidate was associated with mania in a 10-year-old boy who was treated for severe hyperactivity. He received increasing doses up to 45 milligrams (mg) daily, which resulted in manic episodes during the treatment. He responded to treatment with methylphenidate. The mania resulted in improvement over 2 days and lithium carbonate therapy was initiated. This patient had a positive response to treatment.

**3.3.12.B.12 Mood swings**

**a)** Incidence: less than 1% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

**b)** Mood swings have occurred in less than 1% of patients on methylphenidate hydrochloride extended-release placebo in clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

**3.3.12.B.13 O/E - hypervigilance**

**a)** Incidence: less than 1% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

**b)** Hypervigilance has occurred in less than 1% of patients on methylphenidate hydrochloride extended-release placebo in clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

**3.3.12.B.14 Obsessive-compulsive disorder**

**a)** High-dose methylphenidate was associated with obsessive-compulsive symptoms in a 10-year-old girl with hyperactive disorder (ADHD), for which she was receiving methylphenidate (doses increased gradually to 30 mg/day). For 2 years, the child was uncontrollably stealing from peers, teachers, and family. She was unable to control her urge to steal. The dose of methylphenidate was tapered to 30 mg/day. Her symptoms improved on an occasional basis. She was hospitalized so methylphenidate could be withdrawn under observation; serotonergic symptoms were observed after methylphenidate withdrawal; stealing episodes were further reduced. At 1-year follow-up, symptoms were further reduced (Kotsopoulos & Spivak, 2001).

**3.3.12.B.15 Psychotic disorder**

**a)** In a review of 49 randomized, controlled pediatric ADHD clinical trials involving psychostimulant medication (methylphenidate hydrochloride, modafinil and dextromethylphenidate hydrochloride), the rate of psychostimulant active drug was 1.48 (95% CI, 0.74 to 2.65) per 100 person-years, with no comparable adverse events reported to the US Food and Drug Administration to manufacturers of marketed ADHD drugs for submission of postmarketing surveillance events between 2000 and 2005, yielded a total of 865 reports (pediatrics and adults) in which signs and symptoms were reported. The majority of reports involved pediatric subjects, with almost half of the reports in children 10 years of age or younger. Visual and/or tactile sensations of insight were reported. Positive rechallenge was reported for each of the psychostimulant medications (methylphenidate and mixed salts of a single entity amphetamine product) included in the analysis; and in many cases a significant onset of psychiatric symptoms ranged from days to weeks, but in some cases it was months or years from onset (Mosholder et al, 2009).

**b)** Hallucinations have been reported during postmarketing experience with methylphenidate hydrochloride extended-release oral tablets, 2008).

**3.3.12.B.16 Reduced libido**

**a)** Incidence: 1.7% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

**b) Adults**

- 1) Decreased libido has occurred in 1.7% of adult patients on methylphenidate hydrochloride extended-release placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

**3.3.12.B.17 Restlessness**

**a)** Incidence: 3.1% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

**b) Adults**

1) Restlessness has occurred in 3.1% of adult patients on methylphenidate hydrochloride extended release oral tablets (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

**3.3.12.B.18 Stuttering**

a) Stuttering has been temporally associated with the use of pemoline (9.375 milligrams(mg)/day) and n in a 3-year-old girl. The stuttering stopped with the discontinuation of each drug (Burd & Kerbeshian, 1995).

**3.3.12.B.19 Tension**

a) Incidence: 1.2% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

**b) Adults**

1) Tension has occurred in 1.2% of adult patients on methylphenidate hydrochloride extended-release oral tablets (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

**3.3.13 Renal Effects****3.3.13.A Methylphenidate Hydrochloride****3.3.13.A.1 Urogenital finding**

a) Methylphenidate has been shown to increase urinary catecholamines.

b) Intravenous abuse of methylphenidate can result in the development of a foreign body granuloma in 1 patient (cornstarch) contained in the tablets (Hahn, 1969).

**3.3.14 Reproductive Effects****3.3.14.A Methylphenidate Hydrochloride****3.3.14.A.1 Erectile dysfunction**

a) Incidence: less than 1% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Erectile dysfunction has occurred in less than 1% of patients on methylphenidate hydrochloride in placebo-controlled clinical trials (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

**3.3.15 Respiratory Effects**

Methylphenidate

Methylphenidate Hydrochloride

**3.3.15.A Methylphenidate**

Nasal congestion

Nasopharyngitis

**3.3.15.A.1 Nasal congestion**

a) Incidence: 6% (Prod Info DAYTRANA(TM) transdermal system, 2006)

b) Nasal congestion occurred in 6% of patients on transdermal methylphenidate compared with 1% of patients on placebo (n=183) (Prod Info DAYTRANA(TM) transdermal system, 2006).

**3.3.15.A.2 Nasopharyngitis**

a) Incidence: 5% (Prod Info DAYTRANA(TM) transdermal system, 2006)

b) Nasopharyngitis occurred in 5% of patients on transdermal methylphenidate compared with 2% of patients on placebo (n=183) (Prod Info DAYTRANA(TM) transdermal system, 2006).

**3.3.15.B Methylphenidate Hydrochloride**

Cough

Dyspnea

Respiratory finding

Upper respiratory infection

### 3.3.15.B.1 Cough

a) Incidence: 1.9% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Children

1) Cough has occurred in 1.9% of children and adolescent patients on methylphenidate hydrochloride 0.3% of patients on placebo (n=318), in 4 double-blind, placebo-controlled clinical trials (Prod Info C 2008).

### 3.3.15.B.2 Dyspnea

a) Incidence: less than 1% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Dyspnea has occurred in less than 1% of patients on methylphenidate hydrochloride extended-release oral tablets (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

### 3.3.15.B.3 Respiratory finding

a) Pulmonary dysfunction associated with methylphenidate use is related to inappropriate parenteral abusers dissolve methylphenidate tablets, which contain fillers such as talc, in water and then inject the solution. This has the potential to embolize in the lung and produce pulmonary dysfunction (Hahn et al, 1969). Also with intravenous arterial hypertension and medial hypertrophy of muscular pulmonary arteries, including fibrous intimal proliferation (Arnett, 1976).

### 3.3.15.B.4 Upper respiratory infection

a) Incidence: 2.2% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Adults

1) Upper respiratory infections have occurred in 2.2% of adult patients on methylphenidate hydrochloride 0.9% of patients on placebo (n=212), in 2 double-blind, placebo-controlled clinical trials (Prod Info C 2008).

## 3.3.16 Other

Methylphenidate

Methylphenidate Hydrochloride

### 3.3.16.A Methylphenidate

Drug dependence

Viral disease

#### 3.3.16.A.1 Drug dependence

a) Marked tolerance and psychological dependence with varying degrees of abnormal behavior have been reported with abused methylphenidate. Frank psychotic episodes can occur, particularly with parenteral abuse. Risk factors include alcoholism. Withdrawing methylphenidate in a patient who has abused it may lead to severe depression. Methylphenidate may unmask symptoms of the underlying disorder that may require follow-up (Prod Info DAYTRANA(TM) extended-release oral tablets, 2008).

1) Among children with attention deficit disorder treated with methylphenidate, no strong conclusive evidence was found linking methylphenidate with the occurrence of adult drug abuse.

2) Ingestion of high doses (doses above those normally recommended) of methylphenidate for extended periods may produce the euphoric effect and psychological dependence. Dependence on methylphenidate may be characterized by degrees of abnormal behavior. Intravenous administration of methylphenidate has been reported to produce symptoms of 30 to 100 milligrams (mg)/day for 14 days. Severe depression and amphetamine-like withdrawal symptoms including aggression, belligerence, anxiety, muscular aches, chills, tremors, sleep disturbances, lethargy, exhaustion, and methylphenidate withdrawal. Withdrawal therapy usually consists of adjunctive neuroleptic and/or anticholinergic drugs and gradual methylphenidate withdrawal. The gradual tapering of methylphenidate doses is dependent on the duration of withdrawal symptoms. Further studies are needed to justify any advantage of gradual withdrawal over abrupt withdrawal. This drug may result in toxic psychosis. Multiple organ failure including hepatic, renal, pancreatic, an intravenous or intra-arterial injection of crushed methylphenidate tablets (Keeley & Licht, 1985; Stec & Gunby, 1979; Extein, 1978; Spensley, 1972; Spensley & Rockwell, 1972; AtLee, 1972; Lindell et al, 1970).

#### 3.3.16.A.2 Viral disease

a) During an open-label study (n=191) of 40 months duration with transdermal methylphenidate worn for

of subjects (Prod Info DAYTRANA(TM) transdermal system, 2006).

### 3.3.16.B Methylphenidate Hydrochloride

Drug dependence

Drug tolerance - finding

Fatigue

Fever

#### 3.3.16.B.1 Drug dependence

a) Methylphenidate hydrochloride should be given cautiously to patients with a history of drug dependence to marked tolerance and psychological dependence, with varying degrees of abnormal behavior (Prod Info tablets, 2008).

b) Among children with attention deficit disorder treated with methylphenidate, no strong conclusive evidence of methylphenidate with the occurrence of adult drug abuse.

c) Ingestion of high doses (doses above those normally recommended) of methylphenidate for extended periods may produce euphoric effect and psychological dependence. Dependence on methylphenidate may be characterized by abnormal behavior. Intravenous administration of methylphenidate has been reported to produce dependence. The recommended dose is 54 milligrams (mg)/day for 14 days. Severe depression and amphetamine-like withdrawal symptoms including anxiety, muscular aches, chills, tremors, sleep disturbances, lethargy, exhaustion, and suicidal ideations. Withdrawal therapy usually consists of adjunctive neuroleptic and/or antidepressant therapy along with a gradual tapering of methylphenidate doses in dependent individuals may not alter the severity or duration of withdrawal. The studies are needed to justify any advantage of gradual over abrupt drug withdrawal. Chronic ingestion of methylphenidate may occur following intravenous administration of methylphenidate tablets (Keeley & Licht, 1985; Stecyk, 1985; Anon, 1985; Hodding et al, 1980; Gunby, 1972; Rockwell, 1972; AtLee, 1972; Lindell et al, 1972; Sugar et al, 1971; Hopkins & Taylor, 1970).

#### 3.3.16.B.2 Drug tolerance - finding

a) Two double-blind, randomized, crossover trials evaluating the effectiveness of various drug delivery systems for tolerance to methylphenidate may exist in the treatment of children with attention deficit hyperactivity disorder. In the first study, methylphenidate delivery patterns (twice-daily, flat, and ascending) and placebo were compared. The twice-daily regimen of methylphenidate was designed to produce typical school day peak and trough concentrations. The flat regimen followed by a uniform methylphenidate concentration throughout the day. The ascending regimen produced a low-drug concentration early in the morning to a high-drug concentration by the end of the day. The flat regimen for measures of efficacy than the twice daily regimen in the afternoon, which suggests that acute tolerance may be emerging throughout the day. In Study II, 32 children were assigned three treatment profiles (the timing of the middle bolus of the three-times daily regimen was either 9:30 am (tid-am) or 1:30 pm (tid-pm)). Increases in efficacy were measured in the tid-am regimen after the second dose compared with large increases in efficacy for the tid-pm regimen. The interpretation of these results supports the hypothesis. The results of Study I and Study II support the hypothesis that acute tolerance may contribute to drug delivery compared with immediate-release drug delivery of methylphenidate (Swanson et al, 1999).

#### 3.3.16.B.3 Fatigue

a) Incidence: less than 1% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Fatigue has occurred in less than 1% of patients on methylphenidate hydrochloride extended-release oral tablets (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

#### 3.3.16.B.4 Fever

a) Incidence: 2.2% (Prod Info CONCERTA(R) extended-release oral tablets, 2008)

b) Children

1) Pyrexia has occurred in 2.2% of child and adolescent patients on methylphenidate hydrochloride extended-release oral tablets of patients on placebo (n=318), in 4 double-blind, placebo-controlled clinical trials in placebo-control (Prod Info CONCERTA(R) extended-release oral tablets, 2008).

### 3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

#### A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info Concerta(R), 2001) (All Trim)

a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the risk.

2) Australian Drug Evaluation Committee's (ADEC) Category: B2 (Batagol, 1999)

- a) Drugs which have been taken by only a limited number of pregnant women and women of childbearing age and malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in which available data show no evidence of an increased occurrence of fetal damage.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Unknown

4) Clinical Management

- a) Although a causal relationship between methylphenidate and teratogenic effects has not been found, the relationship has yet to be confirmed. Until additional data are available, caution should be exercised with the use of methylphenidate.

5) Literature Reports

- a) No human studies of pregnancy outcomes after exposure to methylphenidate have been published and there is no data on inadvertent exposure during pregnancy. Adequate studies to establish safe use of methylphenidate during pregnancy (Concerta(R), 2001). One source describes a series of women (n=11) who used methylphenidate (dose unspecified) during pregnancy. No birth defects or other abnormalities were reported in any of the infants and all 11 were considered normal (J Clin Pharmacol, 1993) discussed the outcomes of another 38 women who used methylphenidate during pregnancy. Although some infants were premature, growth retarded, and to show signs of neonatal withdrawal, no increase in congenital abnormalities was observed. No pattern or estimate of risk can be determined at this time.

B) Breastfeeding

1) 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 without weighing potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

2) Clinical Management

- a) It is not known whether methylphenidate is excreted into human breast milk and the potential for adverse effects on the infant are unknown. Given the drug's low molecular weight of approximately 270, transfer into milk would be expected.

3) Literature Reports

- a) No reports describing the use of methylphenidate during human lactation or measuring the amount, if any, in breast milk.

### 3.5 Drug Interactions

Drug-Drug Combinations

Intravenous Admixtures

#### 3.5.1 Drug-Drug Combinations

Amitriptyline

Amoxapine

Brofaromine

Carbamazepine

Citalopram

Clomipramine

Clorgyline

Clovoxamine

Desipramine

Dicumarol

Dothiepin

Doxepin

Escitalopram

Femoxetine  
Fluoxetine  
Fluvoxamine  
Furazolidone  
Imipramine  
Iproniazid  
Isocarboxazid  
Lazabemide  
Linezolid  
Lofepramine  
Moclobemide  
Nefazodone  
Nialamide  
Nortriptyline  
Opipramol  
Pargyline  
Paroxetine  
Phenelzine  
Phenobarbital  
Phenytoin  
Primidone  
Procarbazine  
Protriptyline  
Rasagiline  
Selegiline  
Sertraline  
Toloxatone  
Tranlycypromine

Trimipramine

Tyrosine

Warfarin

Zimeldine

### 3.5.1.A Amitriptyline

- 1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
- 2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs in most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it shows moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCA: monitored for increased cardiovascular effects (hypertension and dysrhythmias).
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if used closely for hypertension and dysrhythmias.
- 7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
- 8) Literature Reports
  - a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agent amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006).
  - b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
  - c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combination methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
  - d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine or fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical effects doubled steady-state plasma levels of desipramine (Price et al, 1990).
  - e) There have been claims based on uncontrolled studies that a better antidepressant response may occur 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated that they appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1990).

### 3.5.1.B Amoxapine

- 1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
- 2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs in most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it shows moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCA: monitored for increased cardiovascular effects (hypertension and dysrhythmias).
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if used closely for hypertension and dysrhythmias.
- 7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
- 8) Literature Reports
  - a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agent amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006).

2006).

**b)** Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

**c)** Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combination. Methylphenidate usually results in the blood pressure returning to normotensive levels; reinstatement of the blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

**d)** Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine or fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical effects. Methylphenidate doubled steady-state plasma levels of desipramine (Price et al, 1990).

**e)** There have been claims based on uncontrolled studies that a better antidepressant response may occur with methylphenidate (Price et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little benefit. Methylphenidate appears to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1990).

### 3.5.1.C Brofaromine

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)

2) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hypertension such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with methylphenidate (Prod Info Concerta(TM), 2000). The concomitant administration of methylphenidate with monoamine oxidase inhibitor must be discontinued, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days (Prod Info DAYTRANA(TM), 2006).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and methylphenidate is contraindicated. The monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.

7) Probable Mechanism: unknown

### 3.5.1.D Carbamazepine

1) Interaction Effect: loss of methylphenidate efficacy

2) Summary: Two case reports describe the loss of methylphenidate efficacy after carbamazepine therapy with cytochrome P450 enzymes, a pathway involved in methylphenidate metabolism. Although methylphenidate plasma levels were measured, they may be helpful in patients receiving carbamazepine who are showing no benefits or side effects (Schaller & Behar, 1999a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Clinicians should monitor patient response to methylphenidate therapy when carbamazepine is administered. Methylphenidate plasma levels may also be helpful. Doses of methylphenidate may need to be increased to maintain efficacy (Behar et al, 1999a).

7) Probable Mechanism: induction by carbamazepine of cytochrome P450 3A4-mediated methylphenidate metabolism

8) Literature Reports

**a)** A 7-year-old male with severe mental retardation and attention deficit disorder was failing to respond to methylphenidate 10 mg daily. Other drug therapy included carbamazepine 1000 mg daily to control grand mal seizures. Plasma levels of methylphenidate were measured two hours after the morning dose. Methylphenidate plasma levels could be found. Doses were increased to methylphenidate 30 mg every four hours and carbamazepine 1000 mg every four hours. Both agents were then discontinued (Behar et al, 1998).

**b)** Attention deficit/hyperactivity disorder (ADHD) was being treated with methylphenidate 20 mg three times daily. Methylphenidate plasma levels and significant impulsivity, carbamazepine was introduced at 200 mg daily. The methylphenidate serum level was 5.3 ng/mL (normal range 5 to 20 ng/mL) at this time. ADHD symptoms began to worsen after carbamazepine was introduced. Six weeks after the start of combination therapy, the patient's methylphenidate and ritalinic acid plasma levels decreased to 4.2 ng/mL. A month later, the carbamazepine dose was increased to 1000 mg daily with a steady-state plasma level of 1200 ng/mL. After another two months, her carbamazepine dose was increased to 1200 mg daily with a steady-state blood level of 60 mg three times daily to regain the benefit from the drug that she had experienced before carbamazepine was introduced (Behar, 1999).

### 3.5.1.E Citalopram

1) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations

2) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of selective serotonin reuptake inhibitors (SSRIs). Downward dose adjustments of the SSRI may be necessary when it is used concurrently with methylphenidate. When discontinuing methylphenidate, the SSRI dose may need to be adjusted as needed (Prod Info METADATE CD(R) extended-release oral capsules, 2007).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution when prescribing methylphenidate to patients who take an SSRI. The concurrent use of methylphenidate and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease in SSRI dose if necessary when initiating or discontinuing methylphenidate (Prod Info METADATE CD(R) extended-release oral capsules, 2007).

7) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by methylphenidate

### 3.5.1.F Clomipramine

- 1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
- 2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs in most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported (Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCA; monitored for increased cardiovascular effects (hypertension and dysrhythmias).
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetics may increase cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if used closely for hypertension and dysrhythmias.
- 7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
- 8) Literature Reports
  - a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agent amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006).
  - b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
  - c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combination. Methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
  - d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine or fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubling steady-state plasma levels of desipramine (Price et al, 1990).
  - e) There have been claims based on uncontrolled studies that a better antidepressant response may occur (Satel & Nelson, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated that they appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1969).

### 3.5.1.G Clorgyline

- 1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
- 2) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hypertensive crisis such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with methylphenidate (Prod Info Concerta(TM), 2000). The concomitant administration of methylphenidate with monoamine oxidase inhibitor must be discontinued for a minimum of 14 days (Prod Info DAYTRANA(TM) transdermal system, 2006).
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and methylphenidate is contraindicated. The monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
- 7) Probable Mechanism: unknown

### 3.5.1.H Clovoxamine

- 1) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations
- 2) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of SSRIs. Downward dose adjustments of the SSRI may be necessary when it is used concurrently with methylphenidate. When discontinuing methylphenidate, the SSRI dose may need to be adjusted as needed (Prod Info METADATE C D(R) extended-release oral capsules, 2007).
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when prescribing methylphenidate to patients who take an SSRI. The concurrent use of methylphenidate and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease in SSRI dose if necessary when initiating or discontinuing methylphenidate.
- 7) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by methylphenidate

### 3.5.1.I Desipramine

- 1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
- 2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported

from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs in most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it shows moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported (Russ & Ackerman, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs; monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents may increase cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if used closely for hypertension and dysrhythmias.

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combination. Methylphenidate usually results in the blood pressure returning to normotensive levels; reinstatement of the pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine or fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical effects, had doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur (Price et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little difference, appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1990).

### 3.5.1.J Dicumarol

1) Interaction Effect: an increased risk of bleeding

2) Summary: Methylphenidate may increase the hypoprothrombinemic effect of dicumarol (Prod Info Dicumarol (TM) oral tablets, 2006). It has been demonstrated that methylphenidate may inhibit the metabolism of coumarin anticoagulants, such as dicumarol. A decrease in the anticoagulant effect may be necessary when it is used concurrently with methylphenidate. Additionally, coagulation times should be monitored with the addition and withdrawal of treatment with methylphenidate, and should be reassessed periodically during concurrent therapy. Dicumarol levels should be monitored in order to maintain the desired level of anticoagulation (Prod Info DAYTRANA(TM) transdermal system, 2006).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of methylphenidate and dicumarol may increase dicumarol levels. In patients receiving oral anticoagulant therapy, the prothrombin time ratio or international normalized ratio should be monitored with the addition and withdrawal of treatment with methylphenidate, and should be reassessed periodically. A decrease in the anticoagulant effect may be necessary in order to maintain the desired level of anticoagulation.

7) Probable Mechanism: inhibition of dicumarol metabolism

### 3.5.1.K Dothiepin

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to increase the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs in most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it shows moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported (Russ & Ackerman, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs; monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents may increase cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if used closely for hypertension and dysrhythmias.

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents.

amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).

**b)** Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

**c)** Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combination methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

**d)** Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine or fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubling of steady-state plasma levels of desipramine (Price et al, 1990).

**e)** There have been claims based on uncontrolled studies that a better antidepressant response may occur (1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1990).

### 3.5.1.L Doxepin

**1)** Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

**2)** Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs in most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it shows moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported (Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is monitored for increased cardiovascular effects (hypertension and dysrhythmias).

**3)** Severity: moderate

**4)** Onset: delayed

**5)** Substantiation: theoretical

**6)** Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetics may increase cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if used closely for hypertension and dysrhythmias.

**7)** Probable Mechanism: synergistic effects on noradrenergic neurotransmission

**8)** Literature Reports

**a)** Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).

**b)** Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

**c)** Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combination methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

**d)** Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine or fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubling of steady-state plasma levels of desipramine (Price et al, 1990).

**e)** There have been claims based on uncontrolled studies that a better antidepressant response may occur (1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1990).

### 3.5.1.M Escitalopram

**1)** Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations

**2)** Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of SSRIs. Downward dose adjustments of the SSRI may be necessary when it is used concurrently with methylphenidate, the SSRI dose may need to be adjusted as needed (Prod Info METADATE CD(R) extended-release oral capsules, 2007).

**3)** Severity: moderate

**4)** Onset: unspecified

**5)** Substantiation: theoretical

**6)** Clinical Management: Use caution when prescribing methylphenidate to patients who take a selective serotonin reuptake inhibitor and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease in the SSRI dose if necessary when initiating or discontinuing methylphenidate (Prod Info METADATE CD(R) extended-release oral capsules, 2007).

**7)** Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by methylphenidate

### 3.5.1.N Femoxetine

- 1) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations
- 2) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism (SSRIs). Downward dose adjustments of the SSRI may be necessary when it is used concurrently with methylphenidate. Discontinuing methylphenidate, the SSRI dose may need to be adjusted as needed (Prod Info METADATE C).
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when prescribing methylphenidate to patients who take an SSRI. The use of methylphenidate and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease in the SSRI dose if coadministered. Additionally, consider adjusting the SSRI dose if necessary when initiating or discontinuing nortriptyline (CD(R) extended-release oral capsules, 2007).
- 7) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by methylphenidate

#### 3.5.1.O Fluoxetine

- 1) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations
- 2) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism (SSRIs). Downward dose adjustments of the SSRI may be necessary when it is used concurrently with methylphenidate. Discontinuing methylphenidate, the SSRI dose may need to be adjusted as needed (Prod Info METADATE C).
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when prescribing methylphenidate to patients who take an SSRI. The use of methylphenidate and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease in the SSRI dose if coadministered. Additionally, consider adjusting the SSRI dose if necessary when initiating or discontinuing nortriptyline (CD(R) extended-release oral capsules, 2007).
- 7) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by methylphenidate

#### 3.5.1.P Fluvoxamine

- 1) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations
- 2) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism (SSRIs). Downward dose adjustments of the SSRI may be necessary when it is used concurrently with methylphenidate. Discontinuing methylphenidate, the SSRI dose may need to be adjusted as needed (Prod Info METADATE C).
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when prescribing methylphenidate to patients who take an SSRI. The use of methylphenidate and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease in the SSRI dose if coadministered. Additionally, consider adjusting the SSRI dose if necessary when initiating or discontinuing nortriptyline (CD(R) extended-release oral capsules, 2007).
- 7) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by methylphenidate

#### 3.5.1.Q Furazolidone

- 1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
- 2) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hypertensive crisis such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with methylphenidate (Prod Info Concerta(TM), 2000). The concomitant administration of methylphenidate with monoamine oxidase inhibitors should not be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days (Prod Info DAY).
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and methylphenidate is contraindicated. The monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
- 7) Probable Mechanism: unknown

#### 3.5.1.R Imipramine

- 1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
- 2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in increased blood pressure (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with amphetamine. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs in most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported (Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs. Monitor for increased cardiovascular effects (hypertension and dysrhythmias).
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetics may result in increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info).

capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agent amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine (VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combination methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine or fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical effects when the plasma levels of desipramine were doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur (1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

### 3.5.1.S Iproniazid

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)

2) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hypertensive crisis such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with methylphenidate (Prod Info Concerta(TM), 2000). The concomitant administration of methylphenidate with monoamine oxidase inhibitor if initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days (Prod Info DAY

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and methylphenidate is contraindicated. The monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.

7) Probable Mechanism: unknown

### 3.5.1.T Isocarboxazid

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)

2) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hypertensive crisis such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with methylphenidate (Prod Info Concerta(TM), 2000). The concomitant administration of methylphenidate with monoamine oxidase inhibitor if initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days (Prod Info DAY

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and methylphenidate is contraindicated. The monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.

7) Probable Mechanism: unknown

### 3.5.1.U Lazabemide

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)

2) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hypertensive crisis such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with methylphenidate (Prod Info Concerta(TM), 2000). The concomitant administration of methylphenidate with monoamine oxidase inhibitor if initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days (Prod Info DAY

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and methylphenidate is contraindicated. The monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.

7) Probable Mechanism: unknown

### 3.5.1.V Linezolid

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)

2) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hypertensive crisis such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with methylphenidate (Prod Info Concerta(TM), 2000). The concomitant administration of methylphenidate with monoamine oxidase inhibitor if initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days (Prod Info DAY

3) Severity: contraindicated

- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and methylphenidate is contra the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
- 7) Probable Mechanism: unknown

#### 3.5.1.W Lofepramine

- 1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
- 2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs in most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it shows moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported (Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs: monitored for increased cardiovascular effects (hypertension and dysrhythmias).
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info VYVANSE(TM) oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.
- 7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
- 8) Literature Reports
  - a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agent amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006).
  - b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
  - c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combination methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
  - d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine or fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubling steady-state plasma levels of desipramine (Price et al, 1990).
  - e) There have been claims based on uncontrolled studies that a better antidepressant response may occur (1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1990).

#### 3.5.1.X Moclobemide

- 1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
- 2) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hypertensive crisis such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with methylphenidate (Prod Info Concerta(TM), 2000). The concomitant administration of methylphenidate with monoamine oxidase inhibitor be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days (Prod Info DAYTRANA(TM) transdermal system, 2006).
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and methylphenidate is contra the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
- 7) Probable Mechanism: unknown

#### 3.5.1.Y Nefazodone

- 1) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations
- 2) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of SSRI. Downward dose adjustments of the SSRI may be necessary when it is used concurrently with methylphenidate. Discontinuing methylphenidate, the SSRI dose may need to be adjusted as needed (Prod Info METADATE C D(R) extended-release oral capsules, 2007).
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when prescribing methylphenidate to patients who take an SSRI. The use of methylphenidate and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease in SSRI dose if coadministered. Additionally, consider adjusting the SSRI dose if necessary when initiating or discontinuing methylphenidate (Prod Info METADATE C D(R) extended-release oral capsules, 2007).
- 7) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by methylphenidate

**3.5.1.Z Nialamide**

- 1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
- 2) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hypertensive crisis such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with methylphenidate (Prod Info Concerta(TM), 2000). The concomitant administration of methylphenidate with monoamine oxidase inhibitor must be discontinued for a minimum of 14 days (Prod Info DAYTRANA(TM), 2006).
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and methylphenidate is contraindicated. The monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
- 7) Probable Mechanism: unknown

**3.5.1.AA Nortriptyline**

- 1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
- 2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs in most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it shows moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported (Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs; monitored for increased cardiovascular effects (hypertension and dysrhythmias).
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetics may increase cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if used concurrently for hypertension and dysrhythmias.
- 7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
- 8) Literature Reports
  - a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agent amphetamine with TCAs such as desipramine or nortriptyline results in sustained increases in d-amphetamine (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006).
  - b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
  - c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure. Effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combination. Methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
  - d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine or fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement (Price et al, 1990).
  - e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with amphetamines (Sattel & Nelson, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated that amphetamines appear to be as effective as the conventional antidepressants in primary depression (Sattel & Nelson, 1969).

**3.5.1.AB Opi Pramol**

- 1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
- 2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs in most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it shows moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported (Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs; monitored for increased cardiovascular effects (hypertension and dysrhythmias).
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetics may increase cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if used concurrently for hypertension and dysrhythmias.
- 7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
- 8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agent amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine (VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combination. Methylphenidate usually results in the blood pressure returning to normotensive levels; reinstatement of the pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine (20 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement) had doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with methylphenidate (1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little benefit, they appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1990).

#### 3.5.1.AC Pargyline

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)

2) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hypertensive crisis such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with methylphenidate (Prod Info Concerta(TM), 2000). The concomitant administration of methylphenidate with monoamine oxidase inhibitor must be discontinued for a minimum of 14 days (Prod Info DAYTRANA(TM) transdermal system, 2006).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and methylphenidate is contraindicated. If the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.

7) Probable Mechanism: unknown

#### 3.5.1.AD Paroxetine

1) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations

2) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of selective serotonin reuptake inhibitors (SSRIs). Downward dose adjustments of the SSRI may be necessary when it is used concurrently with methylphenidate. If discontinuing methylphenidate, the SSRI dose may need to be adjusted as needed (Prod Info METADATE C D(R) extended-release oral capsules, 2007).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution when prescribing methylphenidate to patients who take an SSRI. The concurrent use of methylphenidate and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease in the SSRI dose if necessary when initiating or discontinuing methylphenidate. Additionally, consider adjusting the SSRI dose if necessary when initiating or discontinuing methylphenidate (Prod Info METADATE C D(R) extended-release oral capsules, 2007).

7) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by methylphenidate

#### 3.5.1.AE Phenelzine

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)

2) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hypertensive crisis such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with methylphenidate (Prod Info Concerta(TM), 2000). The concomitant administration of methylphenidate with monoamine oxidase inhibitor must be discontinued for a minimum of 14 days (Prod Info DAYTRANA(TM) transdermal system, 2006).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and methylphenidate is contraindicated. If the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.

7) Probable Mechanism: unknown

#### 3.5.1.AF Phenobarbital

1) Interaction Effect: increased phenobarbital plasma concentrations

2) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of phenobarbital. Downward dose adjustments of phenobarbital may be necessary when it is used concurrently with methylphenidate. If discontinuing methylphenidate, the phenobarbital dose may need to be adjusted as needed (Prod Info DAYTRANA(TM) transdermal system, 2006).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of methylphenidate and phenobarbital may increase phenobarbital plasma concentrations. Consider a decrease in the phenobarbital dose if necessary when initiating or discontinuing methylphenidate.

metabolism by methylphenidate. Consider a decrease in phenobarbital dose when these agents are coadministered. Downward dose adjustments of phenobarbital concentrations when initiating or discontinuing methylphenidate and adjust phenobarbital dose if necessary.

7) Probable Mechanism: inhibition of phenobarbital metabolism by methylphenidate

### 3.5.1.AG Phenytoin

- 1) Interaction Effect: increased phenytoin plasma concentrations
- 2) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of phenytoin. Downward dose adjustments of phenytoin may be necessary when it is used concurrently with methylphenidate. Need to be monitored when initiating or discontinuing methylphenidate and phenytoin dose adjusted as necessary (FDA, 2006).
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of methylphenidate and phenytoin may increase phenytoin levels. Consider a decrease in phenytoin dose when these agents are coadministered. Additionally, monitor phenytoin concentrations when initiating or discontinuing methylphenidate and adjust phenytoin dose if necessary.
- 7) Probable Mechanism: inhibition of phenytoin metabolism by methylphenidate

### 3.5.1.AH Primidone

- 1) Interaction Effect: increased primidone plasma concentrations
- 2) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of primidone. Downward dose adjustments of primidone may be necessary when it is used concurrently with methylphenidate. Need to be monitored when initiating or discontinuing methylphenidate and primidone dose adjusted as necessary (FDA, 2006).
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of methylphenidate and primidone may increase primidone levels. Consider a decrease in primidone dose when these agents are coadministered. Additionally, monitor primidone concentrations when initiating or discontinuing methylphenidate and adjust primidone dose if necessary.
- 7) Probable Mechanism: inhibition of primidone metabolism by methylphenidate

### 3.5.1.AI Procarbazine

- 1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
- 2) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hypertensive crisis such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with methylphenidate (Prod Info Concerta(TM), 2000). The concomitant administration of methylphenidate with monoamine oxidase inhibitor must be discontinued for a minimum of 14 days (Prod Info DAYBINE(TM), 2000).
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and methylphenidate is contraindicated. The monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
- 7) Probable Mechanism: unknown

### 3.5.1.AJ Protriptyline

- 1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
- 2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in increased blood pressure (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with amphetamines. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs in combination with TCAs have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported (Russ & Ackerman, 1988). Caution is advised when concurrent administration of amphetamine-like agents and TCAs. Monitor for increased cardiovascular effects (hypertension and dysrhythmias).
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetics may increase cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if used concurrently with TCAs. Monitor for increased cardiovascular effects (hypertension and dysrhythmias).
- 7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
- 8) Literature Reports
  - a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Coadministration of amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006).
  - b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of amphetamines.

imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

**c)** Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstatement of the pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

**d)** Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine or fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).

**e)** There have been claims based on uncontrolled studies that a better antidepressant response may occur (1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1990).

#### **3.5.1.AK Rasagiline**

- 1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
- 2) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hypertension such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with methylphenidate (Prod Info Concerta(TM), 2000). The concomitant administration of methylphenidate with monoamine oxidase inhibitor must be discontinued for a minimum of 14 days (Prod Info DAYTRANA(TM) transdermal system, 2006).
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and methylphenidate is contraindicated. The monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
- 7) Probable Mechanism: unknown

#### **3.5.1.AL Selegiline**

- 1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
- 2) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hypertension such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with methylphenidate (Prod Info Concerta(TM), 2000). The concomitant administration of methylphenidate with monoamine oxidase inhibitor must be discontinued for a minimum of 14 days (Prod Info DAYTRANA(TM) transdermal system, 2006).
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and methylphenidate is contraindicated. The monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
- 7) Probable Mechanism: unknown

#### **3.5.1.AM Sertraline**

- 1) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations
- 2) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of selective serotonin reuptake inhibitors (SSRIs). Downward dose adjustments of the SSRI may be necessary when it is used concurrently with methylphenidate. When discontinuing methylphenidate, the SSRI dose may need to be adjusted as needed (Prod Info METADATE C-120 extended-release oral capsules, 2007).
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when prescribing methylphenidate to patients who take an SSRI. The concurrent use of methylphenidate and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease in the SSRI dose if necessary when initiating or discontinuing methylphenidate.
- 7) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by methylphenidate

#### **3.5.1.AN Toloxatone**

- 1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
- 2) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hypertension such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with methylphenidate (Prod Info Concerta(TM), 2000). The concomitant administration of methylphenidate with monoamine oxidase inhibitor must be discontinued for a minimum of 14 days (Prod Info DAYTRANA(TM) transdermal system, 2006).
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and methylphenidate is contraindicated. The monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
- 7) Probable Mechanism: unknown

#### **3.5.1.AO Tranylcypromine**

- 1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)

- 2) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hypertensive crisis such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with methylphenidate (Prod Info Concerta(TM), 2000). The concomitant administration of methylphenidate with monoamine oxidase inhibitor should not be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days (Prod Info DAYVONNE(TM), 2000).
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and methylphenidate is contraindicated. The monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
- 7) Probable Mechanism: unknown

### 3.5.1.AP Trimipramine

- 1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
- 2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with amphetamine. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs in most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported (Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs. Monitor for increased cardiovascular effects (hypertension and dysrhythmias).
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetics may increase cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if used closely for hypertension and dysrhythmias.
- 7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
- 8) Literature Reports
  - a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. The combination of amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006).
  - b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
  - c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure. Effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combination. Methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the TCAs usually results in blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
  - d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine or fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement, had their plasma levels of desipramine doubled (Price et al, 1990).
  - e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with the combination (Price et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little benefit, the combination appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1990).

### 3.5.1.AQ Tyrosine

- 1) Interaction Effect: increased adverse effects
- 2) Summary: Tyrosine prolonged the effect of methylphenidate in rats (Woods & Meyer, 1991a).
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Caution is advised if tyrosine and methylphenidate are used together. Monitor the patient for increased methylphenidate effects.
- 7) Probable Mechanism: not specified
- 8) Literature Reports
  - a) Exogenous tyrosine supplementation prolonged the effect of methylphenidate (MPD) in rats. Simultaneous administration of MPD into the nucleus accumbens of Sprague-Dawley rats resulted in potentiation and prolongation of the effect of MPD. The final 20 minutes of infusion when dopamine concentrations already declined during the MPD-alone experiment, the maximum MPD effect was observed (Woods & Meyer, 1991).

### 3.5.1.AR Warfarin

- 1) Interaction Effect: increased warfarin plasma concentrations and an increased risk of bleeding
- 2) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of warfarin. Downward dose adjustments of warfarin may be necessary when it is used concurrently with methylphenidate. Warfarin should be closely monitored, when initiating or discontinuing methylphenidate, and should be reassessed periodically. Dose adjustments may be made as necessary in order to maintain the desired level of anticoagulation (Prod Info DAYVONNE(TM), 2000).

2006).

- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of methylphenidate and warfarin may increase warfarin levels due methylphenidate. Consider a decrease in warfarin dose when these agents are coadministered. Additionally, discontinuing methylphenidate and adjust warfarin dose if necessary.
- 7) Probable Mechanism: inhibition of warfarin metabolism by methylphenidate

### 3.5.1.AS Zimeldine

- 1) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations
- 2) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metab (SSRIs). Downward dose adjustments of the SSRI may be necessary when it is used concurrently with meth discontinuing methylphenidate, the SSRI dose may need to be adjusted as needed (Prod Info METADATE C
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when prescribing methylphenidate to patients who take an selective se use of methylphenidate and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease coadministered. Additionally, consider adjusting the SSRI dose if necessary when initiating or discontinuing n CD(R) extended-release oral capsules, 2007).
- 7) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by methylphenidate

### 3.5.5 Intravenous Admixtures

Drugs

Solutions

#### 3.5.5.1 Drugs

Amobarbital

Dextran

Methohexital

Pentobarbital

Phenobarbital

Procainamide

Procaine

Secobarbital

Thiopental

#### 3.5.5.1.A Amobarbital

- 1) Incompatible
  - a) Methylphenidate (incompatible with amobarbital; conditions not specified) (Kramer et al, 1971)

#### 3.5.5.1.B Dextran

- 1) Compatible
  - a) Dextran 70 6% in Dextrose 5% in water with methylphenidate 30 mg/L, physically compatible for al, 1961b; Smith, 1965)
  - b) Dextran 70 6% in Sodium chloride 0.9% with methylphenidate 30 mg/L, physically compatible for al, 1961b; Smith, 1965)

**3.5.5.1.C Methohexital**

## 1) Incompatible

a) Methohexital (barbiturates physically incompatible with methylphenidate; drug concentrations an

**3.5.5.1.D Pentobarbital**

## 1) Incompatible

a) Pentobarbital (barbiturates physically incompatible with methylphenidate; drug concentrations an

**3.5.5.1.E Phenobarbital**

## 1) Incompatible

a) Methylphenidate 1 mL, reconstituted, with phenobarbital 1 mL, reconstituted, both added to Steri was reported within 2 hours; exact drug concentrations not specified (Misgen, 1965a)

b) Phenobarbital barbiturates physically incompatible with methylphenidate; drug concentrations an

**3.5.5.1.F Procainamide**

## 1) Compatible

a) Methylphenidate 1 mL, reconstituted, with procainamide 1 mL, reconstituted, both added to Steri for 2 hours (Misgen, 1965).

**3.5.5.1.G Procaine**

## 1) Compatible

a) Procaine (0.1% in Sodium chloride 0.9% with methylphenidate 30 mg/L physically compatible; cc

b) Methylphenidate (30 mg/L with procaine 1 g/L physically compatible in Sodium chloride 0.9%; cc

**3.5.5.1.H Secobarbital**

## 1) Incompatible

a) Secobarbital (barbiturates physically incompatible with methylphenidate; drug concentrations an

**3.5.5.1.I Thiopental**

## 1) Incompatible

a) Thiopental (barbiturates physically incompatible with methylphenidate; drug concentrations and c

b) Methylphenidate (incompatible with barbiturates; conditions not specified) (Kramer et al, 1971a)

**3.5.5.2 Solutions**

## ALKALINE SOLUTIONS

Dextrose 10% in lactated Ringer's injection

Dextrose 10% in Ringer's injection

Dextrose 10% in Sodium chloride 0.9%

DEXTROSE 10% in water

Dextrose 2.5% in half-strength lactated Ringer's injection

Dextrose 2.5% in half-strength Ringer's injection

Dextrose 2.5% in Sodium chloride 0.45%

Dextrose 2.5% in Sodium chloride 0.9%

DEXTROSE 2.5% in water

DEXTROSE 20% in water

Dextrose 5% in lactated Ringer's injection

Dextrose 5% in Ringer's injection

Dextrose 5% in sodium chloride 0.225%

Dextrose 5% in Sodium chloride 0.45%

Dextrose 5% in Sodium chloride 0.9%

DEXTROSE 5% in water

DEXTROSE 50% in water

FRUCTOSE 10%

FRUCTOSE 10% IN SODIUM CHLORIDE 0.9%

Invert sugar 10%

Invert sugar 10% in sodium chloride 0.9%

Invert sugar 5%

Invert sugar 5% in sodium chloride 0.9%

IONOSOL(R) B IN DEXTROSE 5%

Ionosol(R) D, modified in invert sugar 10%

IONOSOL(R) DCM

IONOSOL(R) DCM IN DEXTROSE 5%

IONOSOL(R) D IN DEXTROSE 10%

Ionosol(R) D in invert sugar 10%

IONOSOL(R) G IN DEXTROSE 10%

IONOSOL(R) G IN INVERT SUGAR 10%

IONOSOL(R) K IN INVERT SUGAR 10%

IONOSOL(R) MB IN DEXTROSE 5%

IONOSOL(R) PSL

Ionosol(R) T in dextrose 5%

LACTATED RINGER'S INJECTION

RINGER'S INJECTION

SODIUM CHLORIDE 0.45%

SODIUM CHLORIDE 0.9%

SODIUM CHLORIDE 3%

SODIUM CHLORIDE 5%

## SODIUM LACTATE 1/6 M

**3.5.5.2.A ALKALINE SOLUTIONS**

- 1) Incompatible
  - a) Alkaline solutions (physically incompatible with methylphenidate; conditions not specified) (Kram

**3.5.5.2.B Dextrose 10% in lactated Ringer's injection**

- 1) Compatible
  - a) Methylphenidate 30 mg/L is physically compatible with Dextrose 10% in lactated Ringer's injectic

**3.5.5.2.C Dextrose 10% in Ringer's injection**

- 1) Compatible
  - a) Methylphenidate 30 mg/L is physically compatible with Dextrose 10% in Ringer's injection; condi

**3.5.5.2.D Dextrose 10% in Sodium chloride 0.9%**

- 1) Compatible
  - a) Methylphenidate 30 mg/L is physically compatible with Dextrose 10% in Sodium chloride 0.9%; c

**3.5.5.2.E DEXTROSE 10% in water**

- 1) Compatible
  - a) Methylphenidate 30 mg/L is physically compatible with Dextrose 10% in water; conditions not sp

**3.5.5.2.F Dextrose 2.5% in half-strength lactated Ringer's injection**

- 1) Compatible
  - a) Methylphenidate 30 mg/L is physically compatible with Dextrose 2.5% in half-strength lactated R (Kirkland et al, 1961c)

**3.5.5.2.G Dextrose 2.5% in half-strength Ringer's injection**

- 1) Compatible
  - a) Methylphenidate 30 mg/L is physically compatible with Dextrose 2.5% in half-strength Ringer's in 1961c)

**3.5.5.2.H Dextrose 2.5% in Sodium chloride 0.45%**

- 1) Compatible
  - a) Methylphenidate 30 mg/L is physically compatible with Dextrose 2.5% in Sodium chloride 0.45%

**3.5.5.2.I Dextrose 2.5% in Sodium chloride 0.9%**

- 1) Compatible
  - a) Methylphenidate 30 mg/L is physically compatible with Dextrose 2.5% in Sodium chloride 0.9%; i

**3.5.5.2.J DEXTROSE 2.5% in water**

- 1) Compatible
  - a) Methylphenidate 30 mg/L is physically compatible with Dextrose 2.5% in water; conditions not sp

**3.5.5.2.K DEXTROSE 20% in water**

- 1) Compatible
  - a) Methylphenidate 30 mg/L is physically compatible with Dextrose 20% in water; conditions not sp

**3.5.5.2.L Dextrose 5% in lactated Ringer's injection**

- 1) Compatible
  - a) Methylphenidate 30 mg/L is physically compatible with Dextrose 5% in lactated Ringer's injection

**3.5.5.2.M Dextrose 5% in Ringer's injection**

- 1) Compatible
  - a) Methylphenidate 30 mg/L is physically compatible with Dextrose 5% in Ringer's injection; conditi

**3.5.5.2.N Dextrose 5% in sodium chloride 0.225%**

- 1) Compatible
  - a) Methylphenidate 30 mg/L is physically compatible with Dextrose 5% in sodium chloride 0.225%;

**3.5.5.2.O Dextrose 5% in Sodium chloride 0.45%**

- 1) Compatible
  - a) Methylphenidate 30 mg/L is physically compatible with Dextrose 5% in Sodium chloride 0.45%; c

**3.5.5.2.P Dextrose 5% in Sodium chloride 0.9%**

- 1) Compatible

a) Methylphenidate 30 mg/L is physically compatible with Dextrose 5% in Sodium chloride 0.9%; cc

**3.5.5.2.Q DEXTROSE 5% in water**

1) Compatible

a) Methylphenidate 30 mg/L is physically compatible with Dextrose 5% in water; conditions not spec

**3.5.5.2.R DEXTROSE 50% in water**

1) Compatible

a) Methylphenidate 30 mg/L is physically compatible with Dextrose 50% in water; conditions not sp

**3.5.5.2.S FRUCTOSE 10%**

1) Compatible

a) Fructose 10% (with methylphenidate 30 mg/L physically compatible; conditions not specified) (Ki

b) Methylphenidate (30 mg/L in FRUCTOSE 10% or FRUCTOSE 10% IN SODIUM CHLORIDE 0.9 specified) (Kirkland et al, 1961d)

**3.5.5.2.T FRUCTOSE 10% IN SODIUM CHLORIDE 0.9%**

1) Compatible

a) Fructose 10% in sodium chloride 0.9% (with methylphenidate 30 mg/L physically compatible; cor

b) Methylphenidate (30 mg/L in FRUCTOSE 10% or FRUCTOSE 10% IN SODIUM CHLORIDE 0.9 specified) (Kirkland et al, 1961d)

**3.5.5.2.U Invert sugar 10%**

1) Compatible

a) Invert sugar 10% (with methylphenidate 30 mg/L physically compatible; conditions not specified)

b) Methylphenidate (30 mg/L in Invert sugar 10% physically compatible; conditions not specified) (K

**3.5.5.2.V Invert sugar 10% in sodium chloride 0.9%**

1) Compatible

a) Invert sugar 10% in sodium chloride 0.9% (with methylphenidate 30 mg/L physically compatible;

b) Methylphenidate (30 mg/L in Invert sugar 10% in sodium chloride 0.9% physically compatible; cc

**3.5.5.2.W Invert sugar 5%**

1) Compatible

a) Invert sugar 5% (with methylphenidate 30 mg/L physically compatible; conditions not specified) (

b) Methylphenidate (30 mg/L in Invert sugar 5% physically compatible; conditions not specified) (Ki

**3.5.5.2.X Invert sugar 5% in sodium chloride 0.9%**

1) Compatible

a) Invert sugar 5% in sodium chloride 0.9% (with methylphenidate 30 mg/L physically compatible; c

b) Methylphenidate (30 mg/L in Invert sugar 5% in sodium chloride 0.9% physically compatible; cor

**3.5.5.2.Y IONOSOL(R) B IN DEXTROSE 5%**

1) Compatible

a) Ionosol(R) B in dextrose 5% (with methylphenidate 30 mg/L physically compatible; conditions no

**3.5.5.2.Z Ionosol(R) D, modified in invert sugar 10%**

1) Compatible

a) Ionosol(R) D, modified in invert sugar 10% (with methylphenidate 30 mg/L physically compatible;

**3.5.5.2.AA IONOSOL(R) DCM**

1) Compatible

a) Ionosol(R) DCM (with methylphenidate 30 mg/L physically compatible; conditions not specified) (

**3.5.5.2.AB IONOSOL(R) DCM IN DEXTROSE 5%**

1) Compatible

a) Ionosol(R) DCM in dextrose 5% (with methylphenidate 30 mg/L physically compatible; conditions

**3.5.5.2.AC IONOSOL(R) D IN DEXTROSE 10%**

1) Compatible

a) Ionosol(R) D in dextrose 10% (with methylphenidate 30 mg/L physically compatible; conditions n

**3.5.5.2.AD Ionosol(R) D in invert sugar 10%**

1) Compatible

a) Ionosol(R) D in invert sugar 10% (with methylphenidate 30 mg/L physically compatible; condition

**3.5.5.2.AE IONOSOL(R) G IN DEXTROSE 10%**

1) Compatible

a) Ionosol(R) G in dextrose 10% (with methylphenidate 30 mg/L physically compatible; conditions n

**3.5.5.2.AF IONOSOL(R) G IN INVERT SUGAR 10%**

1) Compatible

a) Ionosol(R) G in invert sugar 10% (with methylphenidate 30 mg/L physically compatible; condition

**3.5.5.2.AG IONOSOL(R) K IN INVERT SUGAR 10%**

1) Compatible

a) Ionosol(R) K in invert sugar 10% (with methylphenidate 30 mg/L physically compatible; condition

**3.5.5.2.AH IONOSOL(R) MB IN DEXTROSE 5%**

1) Compatible

a) Ionosol(R) MB in dextrose 5% (with methylphenidate 30 mg/L physically compatible; conditions r

**3.5.5.2.AI IONOSOL(R) PSL**

1) Compatible

a) Ionosol(R) PSL (with methylphenidate 30 mg/L physically compatible; conditions not specified) (f

**3.5.5.2.AJ Ionosol(R) T in dextrose 5%**

1) Compatible

a) Ionosol(R) T in dextrose 5% (with methylphenidate 30 mg/L physically compatible; conditions noi

**3.5.5.2.AK LACTATED RINGER'S INJECTION**

1) Compatible

a) Lactated Ringer's injection (with methylphenidate 30 mg/L physically compatible; conditions not s

**3.5.5.2.AL RINGER'S INJECTION**

1) Compatible

a) Ringer's injection (with methylphenidate 30 mg/L physically compatible; conditions not specified)

**3.5.5.2.AM SODIUM CHLORIDE 0.45%**

1) Compatible

a) SODIUM CHLORIDE 0.45% (with methylphenidate 30 mg/L physically compatible; conditions no

**3.5.5.2.AN SODIUM CHLORIDE 0.9%**

1) Compatible

a) SODIUM CHLORIDE 0.9% (with methylphenidate 30 mg/L physically compatible; conditions not

**3.5.5.2.AO SODIUM CHLORIDE 3%**

1) Compatible

a) SODIUM CHLORIDE 3% (with methylphenidate 30 mg/L physically compatible; conditions not s

**3.5.5.2.AP SODIUM CHLORIDE 5%**

1) Compatible

a) SODIUM CHLORIDE 5% (with methylphenidate 30 mg/L physically compatible; conditions not s

**3.5.5.2.AQ SODIUM LACTATE 1/6 M**

1) Compatible

a) Sodium lactate 1/6 M (with methylphenidate 30 mg/L physically compatible; conditions not specif

b) Methylphenidate (30 mg/L in Sodium lactate 1/6 M physically compatible; conditions not specifie

#### 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) Methylphenidate****1) Therapeutic****a) Physical Findings**

- 1)** Improvement in the mental and behavioral symptoms of attention deficit hyperactivity disorder (ADHD) hyperactivity, and cognitive performance.
- 2)** Periodic reassessment of the need for continued methylphenidate treatment (by temporarily withdraw behavioral symptoms and their severity; slow dose-tapering may be indicated to prevent withdrawal symptom system, 2006).

**2) Toxic****a) Laboratory Parameters**

- 1)** Monitor CBC, differential, and platelet counts periodically during prolonged therapy (Prod Info DAYTF

**b) Physical Findings**

- 1)** The American Academy of Pediatrics (AAP) does not recommend the routine use of electrocardiogram evaluations (which were previously recommended by the American Heart Association (AHA) scientific statement place the child at risk for sudden cardiac death) before initiating stimulant therapy to treat attention-deficit disorder. The APA cited specific reasons for changing the recommendation including: lack of evidence establishing treatment of ADHD and sudden cardiac death (SCD), the frequency of sudden unexpected deaths among patients in the general population of children, and lack of cost-effective analysis to support ECG screening or screening (2008).

- 2)** Based on the American Academy of Pediatrics (AAP) and the American Heart Association (AHA) current monitoring recommendations have been established to assist clinicians in the evaluation of children treated with methylphenidate, for ADHD (Perrin et al, 2008; Vetter et al, 2008):

- Conduct a thorough examination prior to initiating methylphenidate therapy for a diagnosis of ADHD symptoms indicative of a cardiac condition, including palpitations, near syncope, or syncope.
- Obtain a complete family and patient history for conditions associated with SCD, and determine current medications.
- Conduct a complete physical evaluation of the patient for hypertension, cardiac murmurs, physical signs of irregular cardiac rhythms.
- Perform further evaluation if family history, patient history or physical exam is suggestive of cardiac and if indicated, consult pediatric cardiologist.
- Continue to assess the patient for cardiac symptoms and any changes in family history at follow up.
- Blood pressure and heart rate should be evaluated at baseline, during routine follow-up within 1 to 3 months. Increases in blood pressure and heart rate have been reported with stimulant use.

- 3)** Assess growth determinations (body weight and height) periodically (Prod Info DAYTRANA(TM) trans

**B) Methylphenidate Hydrochloride****1) Therapeutic****a) Attention Deficit Hyperactivity Disorder (ADHD)**

- 1)** Improvement in the mental and behavioral symptoms of attention deficit hyperactivity disorder (ADHD) hyperactivity, and cognitive performance.
- 2)** Periodic reassessment of the need for continued methylphenidate treatment (by temporarily withdraw behavioral symptoms and their severity; slow dose-tapering may be indicated to prevent withdrawal symptom release oral tablets, 2007; Prod Info CONCERTA(R) extended-release oral tablets, 2007).

**b) Narcolepsy**

- 1)** Decreased frequency of narcoleptic attacks.

**2) Toxic****a) Laboratory Parameters**

- 1)** Monitor CBC, differential, and platelet counts periodically during prolonged therapy (Prod Info RITALIN release tablet, 2004; Prod Info RITALIN LA(R) oral extended-release capsule, 2004; Prod Info METHYLIN METHYLIN(R) oral solution, 2004; Prod Info CONCERTA(R) extended-release tablets, 2004; Prod Info 2002).

**b) Physical Findings**

- 1)** The American Academy of Pediatrics (AAP) does not recommend the routine use of electrocardiogram evaluations (which were previously recommended by the American Heart Association (AHA) scientific statement place the child at risk for sudden cardiac death) before initiating stimulant therapy to treat attention-deficit disorder. The APA cited specific reasons for changing the recommendation including: lack of evidence establishing treatment of ADHD and sudden cardiac death (SCD), the frequency of sudden unexpected deaths among patients in the general population of children, and lack of cost-effective analysis to support ECG screening or screening (2008).

- 2)** Based on the American Academy of Pediatrics (AAP) and the American Heart Association (AHA) current monitoring recommendations have been established to assist clinicians in the evaluation of children treated with methylphenidate, for ADHD (Perrin et al, 2008; Vetter et al, 2008):

- Conduct a thorough examination prior to initiating methylphenidate therapy for a diagnosis of ADHD symptoms indicative of a cardiac condition, including palpitations, near syncope, or syncope.
- Obtain a complete family and patient history for conditions associated with SCD, and determine current medications.
- Conduct a complete physical evaluation of the patient for hypertension, cardiac murmurs, physical

signs of irregular cardiac rhythms.

- Perform further evaluation if family history, patient history or physical exam is suggestive of cardiac and if indicated, consult pediatric cardiologist .
- Continue to assess the patient for cardiac symptoms and any changes in family history at follow up
- Blood pressure and heart rate should be evaluated at baseline, during routine follow-up within 1 to months. Increases in blood pressure and heart rate have been reported with stimulant use.

3) Assess growth determinations (body weight and height) periodically (Prod Info RITALIN(R) oral tablet 2004; Prod Info RITALIN LA(R) oral extended-release capsule, 2004; Prod Info METHYLIN(R) chewable solution, 2004; Prod Info CONCERTA(R) extended-release tablets , 2004; Prod Info METADATE(R) ER

## 4.2 Patient Instructions

### A) Methylphenidate (Absorbed through the skin) Methylphenidate

Treats attention deficit hyperactivity disorder (ADHD). This medicine is a stimulant.

#### When This Medicine Should Not Be Used:

You should not apply this medicine if you or your child have had an allergic reaction to methylphenidate. You should not apply this medicine if you or your child are anxious, tense, or agitated most of the time. You should not use this medicine if you have muscle tics that causes you to have muscle twitches or to make sounds you are not able to control. Do not use this medicine called an MAO inhibitor (MAOI), such as Eldepryl®, Marplan®, Nardil®, or Parnate®, in the past 14 days. This medicine is not for use in children less than 6 years of age unless your doctor tells you otherwise.

#### How to Use This Medicine:

##### Patch

Your doctor will tell you how many patches to use, where to apply them, and how often to apply them. Do not use more patches than your doctor tells you to.

This medicine should come with a Medication Guide. Read and follow these instructions carefully. Ask your doctor or pharmacist for the Medication Guide if you do not have one. Your doctor might ask you to sign some information.

The Medication Guide will show the body areas where you or your child can wear the patch. When putting on these areas. Do not put the new patch on the same place you or your child wore the last one. Be sure to remove the old patch. Wash your hands with soap and water before and after applying a patch. Make sure the skin area is clean (free of powder, oil, or lotion) before you apply the patch.

Leave the patch in its sealed wrapper until you are ready to put it on. Tear the wrapper open carefully. NEVER use a patch that has been cut by accident.

Apply the patch right away after removing it from the pouch or sealed wrapper.

Do not put the patch over burns, cuts, or irritated skin.

Put on a new patch if the old one has fallen off and cannot be reapplied. Remove the new patch 9 hours after

#### If a Dose is Missed:

If you forget to wear or change a patch, put one on as soon as you can. If it is almost time to put on your next patch, skip the one you missed. Do not apply extra patches to make up for a missed dose.

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

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

Throw any used patch away so that children or pets cannot get to it. There is still enough medicine in a used patch to cause harm. When throwing away a patch, fold it in half with the sticky sides together and flush it down the toilet, and then wash your hands.

When you stop treatment with this medicine, take all of the leftover patches out of the pouches and flush them down the toilet. Put them in a trash can with a cover. You will also need to throw away all of the protective liners down the toilet. Put them in a trash can with a cover. You will also need to throw away all of the 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, or herbal products. Make sure your doctor knows if you or your child are also using cold or allergy medicines, clonidine (Catapres®), a blood thinner (such as warfarin or Coumadin®), a phenytoin, primidone, Dilantin®, or Mysoline®), or medicines to treat depression (such as clomipramine, desipramine, Anafranil®, Celexa®, Effexor®, Lexapro™, Norpramin®, Paxil®, Tofranil®, or Zoloft®).

#### Warnings While Using This Medicine:

Make sure your doctor knows if you or your child are pregnant, planning to become pregnant, or breastfeeding. This medicine may cause dizziness, drowsiness, or blurred vision. Tell your doctor if you experience any of these symptoms. Tell your doctor if you have seizures, heart disease, high blood pressure, depression or mental illness, thyroid problems, skin problems, or alcohol problems.

This medicine may be habit-forming. If you feel that the medicine is not working as well, do not use more than the instructions.

Tell your doctor right away if you or your family notices any unusual changes in behavior, such as an increase in suicidal thinking or behaviors. Also tell your doctor if you have hallucinations or any unusual thoughts, especially if they are scary. This medicine may make you dizzy or drowsy. It may also cause blurred vision or other vision problems. If an

do anything else that could be dangerous if you are not alert or not able to see well.

This medicine may cause slow growth. If your child is using this medicine, the doctor will need to keep track of that your child is growing properly.

This medicine may cause skin irritation. Tell your doctor about any skin rash that occurs where this medicine

Avoid putting this medicine near external sources of direct heat, such as hair dryers, heating pads, electric blankets.

Your doctor will need to check your blood at regular visits while you are using this medicine. Be sure to keep

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

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

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, or changes in vision.

Chest pain or shortness of breath.

Convulsions or tremors.

Fast, pounding, or irregular heartbeat.

Fever, chills, runny or stuffy nose, cough, sore throat, and body aches.

Lightheadedness, dizziness, or fainting.

Mood or mental changes, confusion, or unusual behavior.

Seeing, hearing, or feeling things that are not there.

Severe redness, swelling, itching, or blistering of the skin where the patch is worn.

Uncontrollable muscle movements or twitching.

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

Decreased appetite.

Feeling restless or nervous.

Headache.

Nausea or vomiting.

Trouble sleeping.

Warmth or redness in your child's face, neck, arms, or upper chest.

Weight loss.

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

#### **B) Methylphenidate (By mouth)**

Methylphenidate

Treats attention deficit hyperactivity disorder (ADHD) and narcolepsy (sudden attacks of uncontrollable sleepiness).

#### When This Medicine Should Not Be Used:

You should not use this medicine if you or your child have had an allergic reaction to methylphenidate. You should not use this medicine if you are anxious, tense, or agitated most of the time. You should not use this medicine if you have muscle twitches or that causes you to have muscle twitches or to make sounds you are not able to control. Do not use this medicine called an MAO inhibitor (MAOI), such as Eldepryl®, Marplan®, Nardil®, or Parnate®, in the past 14 days. This medicine is not for use in children under 6 years of age unless your doctor tells you otherwise.

#### How to Use This Medicine:

Long Acting Capsule, Liquid, Tablet, Chewable Tablet, Long Acting Tablet

Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed if it is not the best for you. Do not use more medicine or use it more often than your doctor tells you to.

This medicine should come with a Medication Guide. Read and follow these instructions carefully. Ask your doctor for a copy.

Ask your pharmacist for the Medication Guide if you do not have one. Your doctor might ask you to sign some information.

You may take this medicine with or without food.

It is best to take the immediate-release tablets 30 to 45 minutes before meals. If you or your child have problems with stomach acid, take them before 6 p.m.

The extended-release form of this medicine is taken once a day, usually just before the morning meal. Swallow whole, or crush it. If you or your child cannot swallow the extended-release capsule whole, carefully open the capsule and mix the contents with a

tablespoon of applesauce. Swallow this mixture right away and drink some water. Do not save the mixture for later. Tell your doctor if you or your child cannot swallow the sustained-release tablet whole. A different medicine may be needed.

#### 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, skip the missed dose. Do not use extra medicine to make up for a missed dose.

#### 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 no longer 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 minerals. Make sure your doctor knows if you or your child are also using antacids, certain blood pressure medicines (such as Clorpres®, Combipres®, or Ismelin®), blood thinners (such as warfarin or Coumadin®), cold or allergy medicine (such as amitriptyline, clomipramine, desipramine, imipramine, trazodone, Anafranil®, Celexa®, Effexor®, Luvox®, or Zoloft®), or medicine for seizures (such as phenobarbital, phenytoin, primidone, Dilantin®, or Zoloft®).

**Warnings While Using This Medicine:**

Make sure your doctor knows if you or your child are pregnant, planning to become pregnant, or breastfeeding. Tell your doctor if you or anyone in your family has tried to commit suicide or talked about suicide.

This medicine may be habit-forming. If you feel that the medicine is not working as well, do not use more than the instructions.

This medicine may make you dizzy or drowsy. It may also cause blurred vision or other vision problems. Do not do anything else that could be dangerous if you are not alert or not able to see well.

This medicine may cause slow growth. If your child is using this medicine, the doctor will need to keep track of that your child is growing properly.

Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to keep all appointments.

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

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

Allergic reaction: itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest pain or shortness of breath.

Convulsions or tremors.

Fast, slow, pounding, or irregular heartbeat.

Lightheadedness, dizziness, drowsiness, or fainting.

Mood and mental changes, or unusual behavior.

Seeing, hearing, or feeling things that are not there.

Trouble seeing or blurred vision.

Uncontrollable muscle movements or twitching.

Vomiting, agitation, confusion, sweating, fever, or tremors.

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

Feeling restless or nervous.

Headache.

Nausea, loss of appetite, or stomach pain.

Runny or stuffy nose, cough, or sore throat.

Trouble sleeping.

Weight loss.

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

**4.3 Place In Therapy**

**A)** Oral and transdermal methylphenidate are primarily used as an adjunct to the treatment of attention deficit disorder in children 6 years of age (oral) and 6 to 12 years (transdermal) (Prod Info DAYTRANA(TM) transdermal system, 2006; Prod Info METHYLIN(R) chewable tablets, 2004; Prod Info RITALIN(R) oral tablet, RITALIN-SR(R) oral tablet, 2004; Prod Info RITALIN-SR(R) oral tablet, 2002). Children who exhibit ADHD-like symptoms that are secondary to environmental factors and/or other primary psychiatric conditions may be candidates for use of stimulants such as methylphenidate (Prod Info DAYTRANA(TM) transdermal system, 2006). The Advisory Committee recommends that transdermal methylphenidate be used after oral forms have been considered. The risks of sensitization of the topical form (FDA Advisory Committee, 2005). Patients who develop a contact sensitivity to methylphenidate should be able to take methylphenidate in any form (Prod Info DAYTRANA(TM) transdermal system, 2006). Methylphenidate may cause narcolepsy.

**B)** Sustained-release methylphenidate (MSR) therapy for cognitive impairment in HIV-1-infected substance abusers resulted in improved neuropsychological test performance when compared to placebo treatment in a pilot study. However, when used as a confirmatory study, it did not confirm superiority over placebo (van Dyck et al, 1997).

**C)** Other potential therapeutic uses of methylphenidate include treatment of depression, chronic pain, brain tumors, and cocaine abuse (Frye, 1997; Emptage & Semla, 1996; Plutchik et al, 1998; Grade et al, 1998; Meyers et al, 1998; Levitt et al, 1987; Grubb et al, 1996; Whyte et al, 1997).

**4.4 Mechanism of Action / Pharmacology****A) MECHANISM OF ACTION**

**1)** Methylphenidate is a mild central nervous system stimulant; the drug has similar pharmacological properties and activity and minimal effects on the cardiovascular system. Although its exact mechanism of action is not known, its effects on the brainstem arousal system, cortex, and subcortical structures including the thalamus to produce its stimulant effect. Its behavioral effects in children has not been determined (Prod Info DAYTRANA(TM) transdermal system, 2006).

**B) REVIEW ARTICLES**

**1)** A review of the efficacy and safety of methylphenidate treatment in children with attention deficit disorder, anxiety disorder, cancer, epilepsy, traumatic brain injury, encephalitis, and mental retardation has been provided (Weber & Lutschig, 1997).

- 2) The OROS(R) extended-release formulation of methylphenidate is reviewed, including pharmacodynamics, pharmacokinetics, and safety (Pelham et al, 2001).

#### 4.5 Therapeutic Uses

Methylphenidate

Methylphenidate Hydrochloride

##### 4.5.A Methylphenidate

###### 4.5.A.1 Attention deficit hyperactivity disorder

FDA Labeled Indication

###### a) Overview

FDA Approval: Adult, no; Pediatric, yes ( 6 to 12 years)

Efficacy: Pediatric, Effective

Recommendation: Pediatric, Class IIb

Strength of Evidence: Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

###### b) Summary:

Transdermal methylphenidate, in a 9-hour of delivery once daily dose, is an effective treatment of attention deficit hyperactivity disorder (ADHD) providing symptom reduction (McGough et al, 2006)

Transdermal methylphenidate is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) using the DAYTRANA(TM) transdermal system, 2006)

Transdermal methylphenidate improves behavior measures when compared to placebo (Pelham et al, 2001). Long-term effects (greater than 7 weeks) in children have not been well established (Prod Info DAYTRANA(TM), 2006)

###### c) Pediatric:

1) In pediatric patients age 6 to 12 years with attention deficit hyperactivity disorder (ADHD), the use of a 9-hour transdermal methylphenidate (MTS) patch wear time of 9 hours resulted in optimal treatment results when compared with placebo (PTS), according to a randomized, double-blind, placebo-controlled trial. Patients with a mean age 9.1 years, 72% male, and a total score of 26 or higher on the ADHD rating scale who were known to be responsive to stimulants, or naive to stimulants (37%) were included in the intent-to-treat population. In the optimization phase, patients were randomized to receive one of 4 optimized daily doses of MTS (n=41) compared to the PTS group (n=41). The MTS patch delivering 16 or 20 mg dose over 9 hours. After one week of treatment, patients were randomized to receive one of 4 optimized daily doses of MTS (n=41) compared to the PTS group (n=41) during the 12-week treatment period. All patients attended 2 days of simulated classroom, which provided 12 to 14 hours of performance data. Patients in the MTS group performed significantly better compared with the PTS group (Swanson, Kotkin, Agler, M-Flynn and Pellham Teacher Rating Scale). The least square (LS) mean of the change in ADHD-Rating Scale-IV scores was significantly lower (improved) (3.2 +/- 0.58) compared with the PTS group (8 +/- 0.58, p less than 0.0001) at post-dose assessment at 2 hours, continuing through the final 12 hour postdose assessment. Comparing the number of math problems attempted was 113.8 versus 86.2 (difference of 27.5, 95% CI, 19.48 - 35.59, p less than 0.0001). The number of math problems correct was 109.4 versus 80.7 (difference of 28.7, 95% CI, 21.09 - 35.34, p less than 0.0001). On the parent-rated CGI-I scores of 71.1% versus 15.8% (p less than 0.0001). In the safety assessment, there were no emergent adverse events in 24 patients recorded in the MTS group compared with 25 events in 18 patients in the PTS group occurring 2% or more, comparing the MTS with the PTS group, the incidence of any adverse effect was 3% (nausea) (3% vs 0%) (McGough et al, 2006).

2) Transdermal methylphenidate (MTS) was effective for the treatment of attention deficit hyperactivity disorder (ADHD) in a double-blind, placebo-controlled, randomized trial. All patients received MTS in an open-label phase to determine the optimal dose (15 mg, 20 mg, and 30 mg for 5 weeks). Then patients were randomized to placebo or MTS patch (at the time of application for 9 hours every day, then removed). The primary efficacy outcome was the mean differences in change in ADHD-Rating Scale-IV scores between MTS and placebo. Children were evaluated in a classroom setting. From 2 hours after patch application through 12 hours after application, SKAMP Scores improved significantly in the MTS group compared with the PTS group (Prod Info DAYTRANA(TM) transdermal system, 2006).

3) Transdermal methylphenidate (MTS) was effective for the treatment of attention deficit hyperactivity disorder (ADHD) in a double-blind, placebo-controlled, randomized trial. Children were randomized to placebo or MTS patch in a 9-hour wear time (15 mg, 20 mg, and 30 mg for 5 weeks). Then the patients were followed for 2 weeks during the 9-hour wear time. The patch was worn for 9 hours every day, then removed. The primary efficacy outcome was the mean differences in ADHD-Rating Scale-IV scores between MTS and placebo. ADHD-Rating Scale-IV improved statistically more in the MTS group compared with the PTS group. The study did not allow for evaluation of a dose-response, in general, there did not appear to be improvement in ADHD-Rating Scale-IV scores from 9 hours to 30 mg over 9 hours (Prod Info DAYTRANA(TM) transdermal system, 2006).

4) In a multicenter, double-blind, randomized, dose-ranging study of transdermal methylphenidate (MTS) for the treatment of attention deficit hyperactivity disorder (ADHD), MTS were superior to placebo in behavioral measures. Enrolled in the study were 33 boys and 3 girls, aged 6 to 12 years, in the summer treatment program. Patients were randomized to receive placebo, MTS 6.25 centimeters sq (2), worn for at least 12 hours daily. The time of application was also studied along with the dose and patch wear time. The patch was either administered 60 or 120 minutes before the start of the summer treatment program day. Therefore, there was no overlap of MTS with other medication administered one time to each patient. Patients were instructed to continue their usual medication regimen.

a placebo practice day. During the day patients participated in both academic and nonacademic activities: system that assessed point systems, time outs, and daily report cards. After the 8 study days, the point scores (noncompliance, interruption, complaining, conduct problems, and negative verbalizations) were all significantly improved at all MTS doses compared to placebo in pairwise comparisons ( $p$  less than 0.05). The classroom measures for following rules and the amount of classroom work completed correctly. The daily report cards also showed significant improvement across doses) and trouble sleeping (47% of the children across doses), with incidence increasing with higher doses in 40% to 50% of the patients, more incidence on active MTS than placebo days (Pelham et al, 2005).

5) Transdermal methylphenidate (MTS) combined with behavioral modification produced significant improvement in hyperactivity disorder (ADHD) compared to either treatment alone. The study enrolled 25 boys and 2 girls in a summer treatment program. Patients were randomly assigned to receive placebo, MTS 12.5 centigrams (cm<sup>2</sup>) on Monday through Thursday for 24 days. The drug conditions were double-blind and varied on a drug condition once each week. All of the MTS doses were applied at 7 a.m. and removed at 3:30 p.m. Each day, so each patient had 2 days in each medication condition without behavioral treatment and 4 days with behavioral treatment. The children spent 2 hours each day in an academic setting and the remainder of their day at home. Behavior was assessed using a point system (following activity rules, rule violations, noncompliance, interruptions, and negative verbalizations), classroom measures (rule violations, completed work and accuracy of completed tests showed significant improvement at all three doses of MTS compared to placebo in point system criteria and daily report cards (all doses of MTS compared to placebo in pairwise tests,  $p$  less than 0.05). Exceptions were not statistically significant at any dose of MTS regardless of behavior modification, interruption was not significant at MTS 12.5 cm<sup>2</sup> with no behavioral modification and completion of classroom work was not significant at MTS 12.5 cm<sup>2</sup> with no behavioral modification. An adverse effect that increased as the dose increased was loss of appetite (Pelham et al, 2005).

#### 4.5.B Methylphenidate Hydrochloride

Attention deficit hyperactivity disorder

Autistic disorder

Bipolar disorder; Adjunct

Bulimia nervosa

Cancer; Adjunct

Cataplexy - Narcolepsy

Cerebral palsy - Spasticity; Adjunct

Cocaine dependence

Dementia

Depression, Combination therapy

Depression, Monotherapy

Epilepsy

Fatigue

Finding related to coordination / incoordination - Impaired cognition

Hiccoughs, Intractable

Indifference

Narcolepsy



investigators deemed to be possibly related to OROS methylphenidate (headache, insomnia, decrease were no significant differences found in patients expected height and weight for their age at the end slight changes in blood pressure and heart rate throughout the study with the only significant increase +/- 8.1 mmHg at baseline to 108.1 +/- 8.7 mmHg at end of study; p less than 0.0001). No clinically significant liver function tests were found throughout the trial (Wilens et al, 2005).

**b)** In a 2-week, unpublished double-blind study involving 134 children with ADHD (6 to 12 years), methylphenidate (Ritalin(R) LA) 10 to 40 milligrams (mg) daily were statistically superior to placebo in improving symptoms on the Conners' Global Index (CADS-T) during the second week (first-week data not provided). The dose ranged from 10 to 40 mg daily, as determined in a previous dose-titration phase (Prod Info RITALIN LA(R) oral extended-release capsule, 2004).

**c)** Compared with placebo, a 3-week course of once daily methylphenidate (Metadate CD(R)) significantly improved symptoms of attention-deficit hyperactivity disorder over the course of the multi-center, double-blind, multi-center trial (n=321 children, 6 to 16 years of age). The form of methylphenidate used was the immediate-release formulation (also called 'modified-release'), which released approximately 30% of its dose on an immediate-release basis. Subjects (n=158) randomized to methylphenidate (MPH) initiated therapy as 20 milligrams daily, titrated to effect (maximum 60 mg/day), with the mean dose reaching 40.7 mg/day (1.28 mg/kg/day). The mean teacher-rated Conners' Global Index dropped from 12.7 to 4.9 in the MPH group after 3 weeks, while the mean score in the placebo group was 7.8 (p less than 0.001, MPH versus control (least squares mean)). For MPH-treated children, the mean morning score to 4.8 and the mean afternoon score to 5.4, showing that MPH had a sustained effect throughout the study. The parents demonstrated a similar pattern to that of teachers (a drop of 6.2 versus 2.8 points for MPH on the Clinical Global Impression ratings by investigators classified 64% of the MPH group as responders (with 27% of the placebo group). Most common adverse effects were headache, anorexia, abdominal pain, and constipation, occurring significantly more often in the MPH group than in controls (9.7% vs 2.5%; p=0.007). Two mild adverse events. No serious side effects were reported in either group (Greenhill et al, 2002).

**d)** In a double-blind, cross-over study (n=68), 7-day courses of EXTENDED-RELEASE METHYLPHENIDATE demonstrated equivalent efficacy to IMMEDIATE-RELEASE METHYLPHENIDATE given 3 times a day. MPH was significantly superior to PLACEBO for treatment of attention-deficit/hyperactive disorder (ADHD) who met diagnostic criteria for ADHD (DSM-IV) and who had received a stable dose of MPH for at least 6 weeks at the 3 established MPH dose levels. The dose levels were: (1) Concerta(R) 18 milligrams (mg) once daily; (2) Concerta(R) 36 mg once daily or IR MPH 10 mg 3 times a day; or (3) Concerta(R) 54 mg once daily. The mean total dose in the study was 35 mg of Concerta(R) and 29 mg of immediate release (IR) MPH. Teachers rated the child's behavior on a card which was sent home to the child's parents (who provided rewards for a positive report card). The Conners' Global Index (I/O) with Aggression (IOWA) Conners Rating Scale. Parents also completed the Conners' Global Index (I/O) with Aggression (IOWA) Conners Rating Scale. Parents also completed the Conners' Global Index (I/O) with Aggression (IOWA) Conners Rating Scale. Children attended 3 Saturday Laboratory Sessions, with ratings made on an academic performance scale. On all domain ratings by all reviewers in all settings, Concerta(R) and IR MPH provided significantly better results (p less than 0.001). The only differences between the 2 MPH formulations was in 2 parent ratings (I/O and Aggression) where Concerta(R) was significantly better than IR MPH ratings (p less than 0.05). In the laboratory sessions, rule violations and disruptive behaviors were significantly different for MPH (both forms) compared with placebo. Withdrawals due to adverse events occurred. Most common adverse effects of MPH were headache, irritability, and motor tics, all during IR MPH therapy. Poor sleep was reported in 16%, 7%, and 10% of recipients on Concerta(R), IR MPH, and placebo, respectively. Usual appetite was reported for 77%, 66%, and 59% during the same 3 treatment periods. Diastolic blood pressure were significantly higher in both MPH groups (p less than 0.05), as was mean heart rate (Pelham et al, 2001).

**e)** In a multi-center, double-blind trial (n=277), a 4-week course of Concerta(R) (EXTENDED-RELEASE METHYLPHENIDATE) demonstrated to be significantly more effective than placebo (p less than 0.001), and to have similar efficacy to IR MPH in children 6 to 12 years of age with attention-deficit/hyperactive disorder. Enrollees were randomized to OROS 18 milligrams (mg) once daily or IR MPH 5 mg 3 times a day; (2) OROS 36 mg once daily or IR MPH 15 mg 3 times a day. Children who had not received MPH previously participated in a dose-finding study to determine their MPH dose; those who had previously used MPH were converted to one of the established MPH doses, OROS, IR MPH, or placebo. Average total daily dose was 29.5 mg/day for those taking the immediate-release form-OROS (n=94). The primary efficacy measure was the IOWA Conners Rating Scale (IOWA) Conners Rating Scale and Oppositional/Defiance subscales completed by both teachers and parents. Ratings on the IOWA Conners Rating Scale efficacy for extended-release and immediate-release methylphenidate. Fifty-nine subjects discontinued the study, 11 (16%) from the extended-release group, and 10 (14%) from the immediate-release group. No significant difference between groups was observed in sleep quality; more children were reported as eating less than usual compared with the control group. Five patients had tics reported as adverse events (Wolraich et al, 2001).

## 2) Monotherapy - Immediate Release

### a) General Information

**1)** Controlled, blinded studies have shown methylphenidate to be effective in increasing attention in hyperkinetic children (Barkley & Cunningham, 1979)(Charles et al, 1979a; Klorman et al, 1979). Methylphenidate occurs in restrictive environments, and not in "free play" settings (Barkley & Cunningham, 1979). Methylphenidate drug improves the behavioral style, not learning efficiency (Whalen et al, 1979) and has adverse effects on attention, judgment, and judgmental behavior. Other studies have found that methylphenidate improves attention, motor performance, social behavior, and right hemisphere functioning, but has little effect on learning (Famularo & Fenton, 1987; Werry et al, 1980). Tachyphylaxis may occur (Charles et al, 1979a). Methylphenidate is effective in children with epilepsy who are seizure free, while receiving antiepileptic drugs, before and after surgery (Charles et al, 1997a).

**b)** The racemic mixture of L and D-amphetamine (Adderall(R)) was as least as effective as methylphenidate in children with ADHD (Faraone et al, 1997a).

attention deficit hyperactivity disorder (ADHD), and was more effective at 4 to 5 hours post-administration (duration of action). In this within-subject, double-blind, placebo-controlled, crossover study, 25 children received methylphenidate 10 milligram (mg), 17.5 mg, Adderall(R) 7.5 mg, 12.5 mg, and placebo twice a day in a manner every day for 24 days. Teachers and counselors rated their behavior throughout the day and duration of action (noon and 5 p.m.). Parents rated them at the end of the day and in the evening for placebo, Adderall(R) and methylphenidate significantly improved in-school behaviors ( $p$  less than 0.05), recess violations ( $p$  less than 0.0001), and after-school behaviors ( $p$  less than 0.0001), recess violations ( $p$  less than 0.0001), and after-school behaviors ( $p$  less than 0.01). Adderall(R) consistently resulted in higher effect size consistently resulted in higher ES than lower doses. Adderall(R) was also significantly more effective than placebo ( $p$  less than 0.05). The ES of both drugs dropped at midday and steadily increased in the afternoon dose. Side effects were reported more frequently with Adderall(R) but did not preclude the elimination from the study due to exacerbation of his motor tic condition. Further studies are needed to compare the efficacy of methylphenidate to D-amphetamine (Pelham et al, 1999).

**c)** Two double-blind, randomized, cross-over trials evaluating the effectiveness of various drug delivery patterns (twice-daily, flat, and ascending) and placebo were compared. The methylphenidate was designed to produce typical school day peak and trough concentrations. The flat regimen followed by a uniform methylphenidate concentration throughout the day. The ascending regimen followed by a low drug concentration early in the morning to a high drug concentration by the end of the day. The flat regimen was more efficacious for measures of efficacy than the twice daily regimen in the afternoon, which suggests that methylphenidate concentrations may be emerging throughout the day. In Study II, 32 children were randomized to three regimens (twice-daily, ascending, and placebo) where the timing of the middle bolus of the three-times daily regimen was varied after the 7:30 am dose. Only small increases in efficacy were measured in the tid-am regimen after the first dose in efficacy in the tid-pm regimen following the second dose. Following the administration of the third dose, efficacy was observed in the tid-am regimen compared with small increases in efficacy for the tid-pm regimen. This suggests a consistency with the tolerance hypothesis. The results of Study I and Study II support the hypothesis that the reduced efficacy of sustained-release drug delivery compared with immediate-release drug delivery (Pelham et al, 1999a).

**d)** Methylphenidate 0.4 to 1.2 milligrams/kilogram (mg/kg)/day, in two divided doses, was reported to be effective in children with attention deficit disorder without hyperactivity (ages, 7 to 12 years). During one academic year, children who received methylphenidate resulted in an improvement in school grades, when compared to a preceding grading period and the children who did not receive methylphenidate. Methylphenidate may be useful in this type of attention deficit disorder and controlled studies are needed.

**3) Use In Patients With Epilepsy**

**a)** Use of methylphenidate (0.3 milligram/kilogram once daily) appears to be safe and effective to treat ADHD in children with EPILEPSY who are seizure free, while receiving antiepileptic drugs, before a 6-month study involving 30 children with epilepsy and ADHD, none of the 25 children who were seizure free while taking methylphenidate. Of the 5 children continuing to have seizures despite antiepileptic drugs, none showed no change or a reduction in seizures while receiving methylphenidate. In this study methylphenidate was found to be safe and effective. However, the authors advise that caution is warranted for those children still having seizures while receiving methylphenidate (Pelham et al, 1997a).

**4) Use In Patients With Neurofibromatosis**

**a)** Use of methylphenidate can improve cognitive, academic, and social behavior in children with attention deficit disorder and neurofibromatosis type 1 (NF1). This study involved children with ADHD and NF1 ( $n=20$ ), those with normally developing children ( $n=14$ ). Methylphenidate was given to each child in the ADHD-NF1 group of methylphenidate (5 to 15 milligrams (mg) daily; average 7.5 mg) to children with ADHD and NF1. The study measured variables of Attention (TOVA) scores and the Child Behavior Checklist (CBCL) scores. In addition, social behavior improved and aggressive behavior declined in children with ADHD and NF1. Children in the ADHD-NF1 group showed significant improvement in measured variables (Mautner et al, 2002).

**5) Use In Patients With Tourette's Syndrome Or Tics**

**a)** In children with attention deficit hyperactive disorder (ADHD) and TICS (both by DSM-IV criteria) (MPH) alone, or combination CLONIDINE/MPH provided symptomatic improvement in ADHD without Tourette's Syndrome. CLONIDINE/MPH combination therapy provided the greatest benefit. This finding emanated from a 6-month study of children 6 to 12 years of age ( $n=136$ ). Subjects were randomized to placebo ( $n=32$ ), clonidine alone starting at 0.1 mg/day ( $n=37$ ), or combination clonidine/MPH ( $n=33$ ). Average daily doses were 0.25 mg for clonidine, 25.7 mg for MPH alone, and 26.1 mg for MPH given with clonidine. Based on the primary end point (Teacher Rating Inventory), a significant treatment effect was observed for clonidine (compared to no clonidine;  $p=0.003$ ), and either clonidine or MPH was more effective than placebo (both  $p=0.02$ ). However, the combination of clonidine and MPH was more effective than placebo ( $p$  less than 0.0001 compared to placebo). Worsening of Tourette's Syndrome was seen with combination clonidine/MPH ( $p$  less than 0.0001 compared to placebo). Worsening of Tourette's Syndrome was seen with MPH alone, 6 on combination clonidine/MPH, and 7 receiving placebo. Compared with placebo, the MPH treatment groups according to the Yale Global Tic Severity Scale, the Global Tic Rating Scale, and the Tourette Syndrome Assessment Scale were well tolerated except for sedation caused by clonidine; 48% of those receiving clonidine report sedation. Clonidine seemed to be most helpful for impulsivity and hyperactivity, while MPH appeared most helpful for Tourette's Syndrome.

**b)** Tourette's syndrome may be exacerbated or precipitated by the use of stimulant medications for children. Early signs of Tourette's Syndrome or TICS are difficult to distinguish from hyperactive and conduct disorder and therefore mistakenly be treated with stimulant medications (dextroamphetamine, methylphenidate, and amphetamine). The severe motor and phonic tics requiring discontinuation of the stimulants and possible institution of antipsychotic medication. In children with no symptoms of Tourette's Syndrome but with a familial history of Tourette's Syndrome, methylphenidate may be useful in the treatment of children with attention deficit disorder and Tourette's Syndrome.

The use of stimulants is contraindicated in children with Tourette's Syndrome. If tics occur during sti discontinued (Lowe et al, 1982a).

**c)** Although stimulant therapy was suspected to exacerbate tics, LONG-TERM methylphenidate tre effective in children with attention-deficit hyperactivity disorder (ADHD) AND CHRONIC MULTIPLE In this 2-year non-blinded, prospective, follow-up study, 32 children (age ranging from 6.1 and 11.9 : methylphenidate from a previous trial (mean 16.5 milligrams (mg), range=5 to 40 mg). The children months for 2 years for their on-task, fidgeting, worksheet behaviors, and vocal and motor tic frequen significantly worse at baseline than placebo (p ranging from less than 0.001 to 0.03). There was no methylphenidate. ADHD behaviors were not significantly different between baseline and placebo, wl task during the medication conditions than placebo (p less than 0.001). There was no significant diff when compared to growth table values. Systolic blood pressure and heart rate were significantly inc considered clinically insignificant. Although this study showed methylphenidate did not worsen tics ir the possibility of individual exacerbation of tic cannot be ruled out (Gadow et al, 1999a). In another s syndrome, abrupt withdrawal of methylphenidate and dextroamphetamine in long-term therapy DID frequency (Nolan et al, 1999a).

#### 4.5.B.2 Autistic disorder

##### a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Pediatric, Evidence is inconclusive

Recommendation: Pediatric, Class IIb

Strength of Evidence: Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

##### b) Summary:

Methylphenidate may be useful in the treatment of autism

Methylphenidate may improve concentration, hyperactivity, constructive behavior, and stereotyped r sadness and exacerbate temper tantrums

##### c) Pediatric:

**1)** One group of investigators reported the efficacy of methylphenidate 10 to 50 milligrams daily (mean, ; an open study involving 9 children (4 to 16 years of age). All children improved significantly during treatr movements or significant toxicity. The authors suggest that a placebo-controlled, two month study of hyp evaluate the efficacy of methylphenidate in this patient population (Birmaher et al, 1988).

**2)** Methylphenidate 10 milligrams orally twice daily was reported beneficial in a 6-year-old boy with autis randomly administered methylphenidate or placebo daily, under double-blind conditions. Methylphenidat and hyperactivity, as well as constructive behavior and stereotyped movements; negative effects were of exacerbation of temper tantrums); however, beneficial effects were considered to outweigh these negativ suggests that methylphenidate may not be contraindicated in autistic children. More studies are required in autism.

#### 4.5.B.3 Bipolar disorder; Adjunct

##### a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

##### b) Summary:

Some DEPRESSED patients with bipolar disorder experienced symptomatic improvement with methylph

##### c) Adult:

**1)** In a small 12-week, open-label pilot study (n=14), the addition of METHYLPHENIDATE to mood stab symptoms to some depressed patients with bipolar disorder. Ten patients had bipolar type I illness (DSM had a manic episode secondary to controlled hydrocephalus or antidepressant therapy. All had a score c Depression (HAM-D). Methylphenidate was started at 5 milligrams (mg) twice daily and titrated based or completing the study (9) and 10 mg in those who discontinued (5). Terminations were secondary to deve agitation (1), anxiety (1), alcohol abuse (1), and lost to follow-up (1). HAM-D scores dropped from baseli Psychiatric Symptom Assessment Scale (PSAS) scores dropped from 17.9 to 4.8 (p=0.016) (El-Mallakh,

#### 4.5.B.4 Bulimia nervosa

##### a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

##### b) Summary:

Possibly effective in the treatment of bulimia nervosa with cluster B personality disorder

##### c) Adult:

**1)** Methylphenidate (MPH) was effective in the treatment of 2 patients with bulimia nervosa associated v

Bulimics with cluster B personality disorder responded poorly to psychotherapy and antidepressant treatments and were put on MPH therapy. Patient 1, a 20-year-old woman with 5-year history of bulimic disorders, had symptoms of attention deficient hyperactivity disorder (ADHD) since age 7. She was put on MPH 20 mg at noon, and 5 mg at 5 p.m. At 10 months after discharge, her urges to binge and induce vomiting had sign scale, ranging from 0 to 36, improved from an average 12.6 to 2.6 on the first 3 days of MPH 20 mg/day improved from an average of 28.9 to 16.3. Patient 2, a 38-year-old woman with 20-year history of bulimic generalized anxiety disorder, and major depressive disorder, improved her anxiety and depression with MPH but did not improve on her bingeing and purging. She was treated with MPH 5 mg 3 times per day for 1 month purging, and decreased impulsivity. Her Conner score improved from 34 to 13. A trial of PEMOLINE was not successful. Her symptoms of bulimia nervosa and irritability returned. She was put on long-acting MPH with reduced symptoms. MPH may be useful in the treatment of bulimics with cluster B personality disorder. Further studies are needed. In drug abuse potential in this population, MPH treatment was not recommended by the authors at this time.

#### 4.5.B.5 Cancer; Adjunct

##### a) Overview

FDA Approval: Adult, no; Pediatric, no  
Efficacy: Adult, Evidence is inconclusive  
Recommendation: Adult, Class IIb  
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

##### b) Summary:

Methylphenidate may improve neurobehavioral functioning in patients with malignant brain tumors  
Effective for depression associated with cancer  
Methylphenidate may be effective for alleviating fatigue in patients with advanced cancer  
Methylphenidate may enhance the analgesic efficacy of narcotic analgesics and decrease sedation in patients with advanced cancer

##### c) Adult:

##### 1) BRAIN TUMORS

a) Methylphenidate may improve neurobehavioral functioning in patients with malignant brain tumors as a result of their disease and/or treatment (i.e., radiation and chemotherapy). In this study, patients (n=20) received methylphenidate 10 to 30 milligrams twice daily. Methylphenidate treatment was associated with sustained and daily functioning. Results of neuropsychologic tests indicate improvements in psychomotor speed, motor speed, executive function, and fine-motor coordination. Subjective functional improvements included concentration, brighter mood, improved motivation, and increased stamina. In addition, the majority of patients wished to decrease their dose. Adverse effects were minimal, no patient experienced an increase in seizure activity (Meyers et al, 1998a).

##### 2) DEPRESSION

a) A report of the efficacy of methylphenidate in the treatment of depression in cancer patients has been published. Methylphenidate was given in doses of 10 milligrams orally three times daily initially, with subsequent increases to a maximum of 80 milligrams daily were permitted by week 2 of treatment. Marked improvement, with 13 showing moderate improvement; maximum improvement was general.

##### 3) FATIGUE

a) Methylphenidate may be effective for alleviating fatigue in patients with advanced cancer. In this study, patients with advanced cancer were given methylphenidate 5 to 30 milligrams daily for a mean evaluation period of 4 weeks. Methylphenidate was considered responders (at least 30% improvement). Mean visual analogue scale (VAS) scores for fatigue were 54, respectively (p=0.01). According to log-rank test, there was a significant difference in survival time between the two groups (36 vs 54 days, respectively; p=0.01). Adverse effects were relatively mild and reversible (Sugawara et al, 1998a).

##### 4) PAIN

a) Methylphenidate doses of 15 milligrams (mg) orally daily (10 mg orally at breakfast; 5 mg orally at dinner) was reported to enhance the analgesic efficacy of the narcotic agents and decrease sedation in patients with advanced cancer (Bruera et al, 1987a). Patients were receiving either morphine, hydromorphone, or

#### 4.5.B.6 Cataplexy - Narcolepsy

See Drug Consult reference: NARCOLEPSY AND CATAPLEXY - DRUG THERAPY

#### 4.5.B.7 Cerebral palsy - Spasticity; Adjunct

##### a) Overview

FDA Approval: Adult, no; Pediatric, no  
Efficacy: Adult, Evidence is inconclusive  
Recommendation: Adult, Class III  
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

##### b) Summary:

Effective in relieving spasticity and dystonia in one patient with cerebral palsy

##### c) Adult:

1) Methylphenidate was effective in alleviating SPASTICITY and DYSTONIA in a 44-year-old woman with cerebral palsy in a wheelchair due to marked spasticity of the legs and choreoathetosis of the face, trunk, and upper extremities. Treatment with clonazepam, biperiden, trihexyphenidyl, diazepam, tizanidine, and baclofen had little benefit. Botulinum toxin

successful. Methylphenidate 10 milligrams (mg) twice a day markedly improved her spasticity and chorea returned during an interruption of the treatment. The patient's neurologic condition continued to be stable 1 year. No side effects were noted (Boogerd & Beijnen, 2000).

#### 4.5.B.8 Cocaine dependence

##### a) Overview

FDA Approval: Adult, no; Pediatric, no  
Efficacy: Adult, Evidence is inconclusive  
Recommendation: Adult, Class III  
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

##### b) Summary:

Methylphenidate may be effective in the treatment of adults with attention deficit hyperactivity disorder. Limited data indicate that methylphenidate is ineffective in the treatment of cocaine abusers without

##### c) Adult:

1) Results of a 12-week open trial suggest that methylphenidate combined with relapse prevention therapy for attention deficit hyperactivity disorder (ADHD), cocaine craving, and cocaine use in adults with ADHD and cocaine dependence. Sustained-release methylphenidate 40 to 80 milligrams/day in 2 divided doses along with weekly relapse prevention indicated significant reductions in attention difficulties, hyperactivity, impulsivity, cocaine use, and craving on urinalysis (Levin et al, 1998a).

2) Methylphenidate therapy (5 to 20 milligrams (mg) four times daily) was reported ineffective in the management of cocaine abusers (without attention deficit disorders). Clinical improvement or cocaine abstinence was not reported (al, 1985).

#### 4.5.B.9 Dementia

##### a) Overview

FDA Approval: Adult, no; Pediatric, no  
Efficacy: Adult, Evidence is inconclusive  
Recommendation: Adult, Class III  
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

##### b) Summary:

Efficacy in the treatment of senile dementia is questionable; available data are anecdotal. Some of the negative symptoms associated with vascular dementia or dementia of Alzheimer's type. Withdrawn, non-agitated patients with moderate dementia are most likely to respond to methylphenidate.

##### c) Adult:

1) Results of an open-label, non-blinded preliminary study indicate that the negative symptoms associated with Alzheimer's type dementia respond to methylphenidate (10 to 20 milligrams/day). Results were similar for Alzheimer's type dementia. Depressive symptoms in this population did not respond to methylphenidate. Some cognitive improvement in dementia, but not in those with dementia of Alzheimer's type. It appears that withdrawn, non-agitated patients are most likely to respond to methylphenidate (Galynker et al, 1997a).

2) Methylphenidate has been used to treat senile dementia and is possibly effective; however, there are limited data from clinical experience and anecdotes. Most references to the use of methylphenidate (or amphetamine) in the treatment of dementia (Rossman, 1979; Anon, 1978; Yesavage & Hollister, 1978; Borowitz, 1976; Steinberg, 1976).

#### 4.5.B.10 Depression, Combination therapy

##### a) Overview

FDA Approval: Adult, no; Pediatric, no  
Efficacy: Adult, Evidence is inconclusive  
Recommendation: Adult, Class III  
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

##### b) Summary:

A 4-week, randomized, double-blind, placebo-controlled study of patients with treatment-resistant depression demonstrated no statistically significant benefit with the addition of extended-release methylphenidate to antidepressant therapy (n=60) (Patkar et al, 2006)

The results of a small case series involving 5 patients appear to indicate that methylphenidate (10 mg) augmenting the therapeutic effects of serotonin selective reuptake inhibitors (SSRIs) (eg, fluoxetine) in the treatment of depression (Stoll et al, 1996)

The combination of MAO inhibitors (tranylcypromine, isocarboxazid, phenelzine) and stimulants (amphetamines) as therapy of severe treatment-resistant depression (Feighner et al, 1985)

The combination of MAO inhibitors and stimulants plus tricyclic antidepressants (amitriptyline, protriptyline) is effective and safe in this type of intractable depression (Feighner et al, 1985)

##### c) Adult:

1) A 4-week, randomized, double-blind, placebo-controlled study of patients with treatment-resistant depression demonstrated no statistically significant benefit with the addition of extended-release methylphenidate to antidepressant therapy. Patients (n=60; mean age, 48.5 years) with major depressive disorder who had been on antidepressant therapy were randomized to either methylphenidate (n=30) or placebo (n=30), with methylphenidate dosing

in 18-mg/day increments each week to a maximum dose of 54 mg/day. Subjects maintained their preexi period. The primary efficacy measurement was the change in the 21-item Hamilton Depression Rating S treatment), with a response defined as at least 50% reduction and remission defined as a score of 7 or le were included changes in the Clinical Global Impression-Improvement and Severity (CGI-I and CGI-S, re Depression Inventory-Second Edition (BDI-II) scores. There were no statistically significant differences b primary or secondary efficacy measurements. Changes in the mean HAM-D-21 scores were -6.9 for the group (p=0.22). Patients receiving methylphenidate achieved response and remission (40% and 13.3%, receiving placebo (23.3% and 3.3%, respectively), but the differences were not statistically significant (p-statistically significant differences for changes in CGI-I (p=0.34), changes in CGI-S (p=0.18), or BDI-II (p moderate in severity and the dropout rates were similar between groups (Patkar et al, 2006).

2) The results of a small case series involving 5 patients appear to indicate that methylphenidate (10 to augmenting the therapeutic effects of serotonin selective reuptake inhibitors (SSRIs) (eg, fluoxetine, par depression. In this series, methylphenidate added to ineffective or only partially effective SSRI treatment symptoms, without side effects, significant tolerance, or abuse of methylphenidate (Stoll et al, 1996).

3) The combination of MAO inhibitors (tranylcypromine, isocarboxazid, phenelzine) and stimulants (amp as therapy of severe treatment-resistant depression. In addition, the combination of MAO inhibitors and ( amitriptyline, protriptyline, amoxapine, nortriptyline) has also been effective and safe in this type of intra suggested that the following regimen be utilized when combining these agents: (1) the individual drugs a has had a prior partial response; (2) with combined MAO inhibitor and stimulant therapy, the MAO inhibit dextroamphetamine or methylphenidate in 2.5 milligrams (mg) increments to stabilize blood pressure an administering the combination of MAO inhibitors, stimulants, and antidepressants, the tricyclic antidepres days, adding the MAO inhibitor during the daytime for 4 to 5 days, then adding low doses of the stimulan response is positive. The most frequent complication of this therapy is orthostatic hypotension; other pati and agitation. However, no serious side effects or life-threatening reactions were reported.

#### 4.5.B.11 Depression, Monotherapy

##### a) Overview

FDA Approval: Adult, no; Pediatric, no  
Efficacy: Adult, Evidence favors efficacy  
Recommendation: Adult, Class III  
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

##### b) Summary:

Improves selected types of depression (Ayd, 1985; Janowsky et al, 1973); (Rickels et al, 1970 & 19 Effective for depression in medically ill elderly patients (Frye, 1997a; Emptage & Semla, 1996a) Effective for depression associated with cancer and cardiac surgery (Macleod, 1998; Fernandez et a May be effective for depressive and/or cognitive symptoms in post liver transplant and post-stroke p 1998a)

##### c) Adult:

##### 1) GENERAL INFORMATION

a) Studies have shown that methylphenidate (10 to 30 milligrams (mg)/day) can improve selected c et al, 1973); (Rickels et al, 1970 & 1972). However, 1 study found methylphenidate ineffective for de methylphenidate may exacerbate pre-existing agitation, anxiety, mania, psychosis, or depression. M safe and effective for the treatment of depression in medically ill elderly patients lacking contraindic action, usually within 2 to 5 days, is a potential advantage over other antidepressants in this patient 1996a). Methylphenidate has been effective in the treatment of depression associated with cancer a et al, 1987); (Kaufmann et al, 1984). Methylphenidate may be useful for the treatment of depressive transplant and post-stroke patients (Grade et al, 1998a; Plutchik et al, 1998a).

2) Results of a small, uncontrolled, preliminary study indicate that methylphenidate may be useful for the symptoms in post liver transplant patients. In this study, a positive response was reported in 7 of 8 patier milligrams/day. Methylphenidate was noted to improve cognition, mood, motivation, appetite, and alertne

3) Results of a prospective, randomized, double-blind, placebo- controlled study indicate that methylphe stroke depression. In this study, acute stroke patients (n=21) receiving methylphenidate (30 milligrams/d mood, ability to conduct activities of daily living, and motor function than patients receiving placebo. Trea with an increased number of adverse effects (Grade et al, 1998a).

4) Methylphenidate has been demonstrated to be useful in the treatment of depression following cardiac milligrams (mg) orally twice daily produced improvement in depressive symptoms following cardiovascul considered a viable alternative in patients with contradictions to tricyclic antidepressants.

5) A report of the efficacy of methylphenidate in the treatment of depression in cancer patients has beer Methylphenidate was given in doses of 10 milligrams orally three times daily initially, with subsequent do 2 to 3 days; increases to a maximum of 80 milligrams daily were permitted by week 2 of treatment. Of 3C improvement, with 13 showing moderate improvement; maximum improvement was generally seen by th

6) Methylphenidate in doses of 5 milligrams (mg) orally twice daily, increasing by 5 mg twice daily every ineffective as an antidepressant in a controlled study involving 20 mildly depressed patients (Hamilton D 1985).

#### 4.5.B.12 Epilepsy

##### a) Overview

FDA Approval: Adult, no; Pediatric, no  
 Efficacy: Adult, Evidence is inconclusive  
 Recommendation: Adult, Class III  
 Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

**b) Summary:**

Methylphenidate may reduce sedation and fatigue and improve cognition and quality of life in patients wi

**c) Adult:**

1) Methylphenidate appears to reduce sedation and fatigue and improve cognition and quality of life in p adversely affecting seizure activity. In this open-label, non-randomized, pilot study involving 8 epilepsy p years) on multiple antiepileptic drugs (AEDs), methylphenidate (dosage range 7.5 to 25 milligrams (mg)/ patients' current AED regimens for 3 months. Six of 8 patients were seizure free at baseline, 5 remained experienced an increase, 1 a decrease, and 1 no change in seizure activity. Overall, all quality of life ini scores, and emotional well-being scores showed significant improvement from baseline after methylpher analogue scale fatigue scores decreased 63.3% from baseline (p=0.015). Methylphenidate did not signifi serum concentrations of AEDs changed less than 10% from baseline to the end of the study. No serious 2002).

**4.5.B.13 Fatigue**

**a) Overview**

FDA Approval: Adult, no; Pediatric, no  
 Efficacy: Adult, Evidence favors efficacy  
 Recommendation: Adult, Class IIb  
 Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

**b) Summary:**

May reduce fatigue in some HIV-positive patients  
 Methylphenidate may be effective for alleviating fatigue in patients with advanced cancer

**c) Adult:**

1) Methylphenidate may be effective for alleviating fatigue in patients with advanced cancer. In this preli with advanced cancer were given methylphenidate 5 to 30 milligrams daily for a mean evaluation period responders (at least 30% improvement). Mean visual analogue scale (VAS) scores for fatigue before and (p=0.01). According to log-rank test, there was a significant difference in survival time between responde respectively; p=0.01). Adverse effects were relatively mild and reversible (Sugawara et al, 2002).  
 2) A 6-week course of an oral psychostimulant medication, METHYLPHENIDATE or PEMOLINE, reduc quality of life also tended to improve with methylphenidate and pemoline therapy, and drug-induced side least 5 on a 10-point scale for persistent fatigue. Methylphenidate (n=53) was initiated at 7.5 milligrams ( mg/day (mean end-of-study dose 51 mg/day); pemoline (n=45) was started at 18.75 mg twice daily with study dose 96 mg/day). At 6 weeks, total scores on the Piper Fatigue Scale (patient-rated) were significa pemoline-treated subjects compared with placebo (p=0.04). Also, on the patient-rated visual analog scal significantly higher for those receiving methylphenidate or pemoline (p=0.02). No significant differences v comparing methylphenidate and pemoline. Significant correlations were found between improvement in i dropped out due to side effects (methylphenidate (2), pemoline (2), control (1)). Only jitteriness and hype often by those on methylphenidate or pemoline than those on placebo (Breitbart et al, 2001a).

**4.5.B.14 Finding related to coordination / incoordination - Impaired cognition**

**a) Overview**

FDA Approval: Adult, no; Pediatric, no  
 Efficacy: Pediatric, Evidence favors efficacy  
 Recommendation: Pediatric, Class IIb  
 Strength of Evidence: Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

**b) Summary:**

Methylphenidate may improve cognitive and motor performance in intellectually subaverage childrer  
 May improve attention span in children with neurocognitive impairment related to childhood cancer

**c) Pediatric:**

1) A double-blind, randomized trial (n=32) provided preliminary evidence that METHYLPHENIDATE ma survived childhood malignant brain tumors (n=25) or acute lymphoblastic leukemia (n=7) but who exhibit for the study included estimated intelligence quotient greater than 50; academic achievement in the sixte math, or spelling; and ability to sustain attention on a computerized performance test in the sixteenth per study protocol, enrollees completed a battery of tests on day 1. On day 2, subjects were randomized to p milligram/kilogram (maximum 20 milligrams) (n=15). Approximately 90 minutes after ingestion of methylp selected portions of the battery of tests. Compared with placebo, methylphenidate-treated subjects had e Connors' Continuous Performance Test (CPT) for sustained attention (p=0.015) and overall index of atte not improved by methylphenidate included errors of commission (indicative of impulsiveness) or reaction scores were not significantly different between methylphenidate-treated patients and controls, and, on a greater improvement in the methylphenidate group but it did not reach statistical significance (Thompson 2)  
 2) One group of investigators reported a controlled study of methylphenidate and thioridazine in improvi

intellectually subaverage children. Twenty-seven children with subaverage intelligence quotas (IQs) participated in a cross-over study comparing methylphenidate (0.4 milligrams/kilogram/day) and thioridazine (1.75 milligrams/kg/day) on performance, breadth of attention, and performance on a series of electronically-controlled cognitive-motor tasks, including a memory task, reduced omission errors on an attention task, and reduced seat movements on two tasks. Methylphenidate improved cognitive-motor performance. It did not produce deleterious effects on IQ performance when compared with thioridazine at the given dose did not adversely effect performance on any of the cognitive-motor performance tasks.

#### 4.5.B.15 Hiccoughs, Intractable

##### a) Overview

FDA Approval: Adult, no; Pediatric, no  
Efficacy: Adult, Evidence is inconclusive  
Recommendation: Adult, Class III  
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

##### b) Summary:

Stopped intractable hiccups in one patient in a case report

##### c) Adult:

1) A 56-year-old man with refractory hiccup was treated with a regimen that included methylphenidate 5 mg four times a day as well as haloperidol 4 mg every 8 hours and metoclopramide 10 mg four times a day. The patient was diagnosed with peptic esophagitis and gastroparesis. Oral haloperidol did not stop the hiccups which point the hiccups stopped for 2 days and then restarted. Methylphenidate administration resulted in free of hiccups until his death 6 weeks later (Marechal et al, 2003).

#### 4.5.B.16 Indifference

##### a) Overview

FDA Approval: Adult, no; Pediatric, no  
Efficacy: Adult, Evidence is inconclusive  
Recommendation: Adult, Class IIb  
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

##### b) Summary:

Methylphenidate may improve apathy (Padala et al, 2005)

##### c) Adult:

1) A case report involving a 47-year-old woman found that treatment with methylphenidate significantly improved depression. The patient had a 20 year history of recurrent major depression and was diagnosed with apathy and motivation. She had been treated with several antidepressants in the past and was currently on a regimen of nortriptyline 100 mg in the morning for the past 4 months. Her other current medications included vitamin B12 1000 micrograms (m) 0.25 mg at bedtime as needed, and montelukast sodium 10 mg in the evening as needed. Methylphenidate was increased after one week to 20 mg twice daily due to lack of response. After 4 weeks of treatment in apathy and scored 31 on the Apathy Evaluation Scale (AES), a 46% reduction from baseline. Her subjective interests with a desire to resume previous employment. She was also able to awaken earlier and felt less fatigue. Her depression was assessed by the 21-item Hamilton Rating Scale for Depression and was unchanged from baseline with a HAM-D of 33. The patient denied experiencing any adverse effects from

#### 4.5.B.17 Narcolepsy

##### FDA Labeled Indication

##### a) Overview

FDA Approval: Adult, yes (immediate release formulations and Ritalin(R)-SR only); Pediatric, yes (and Ritalin(R)-SR only)  
Efficacy: Adult, Effective; Pediatric, Effective  
Recommendation: Adult, Class IIa; Pediatric, Class IIa  
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

##### b) Summary:

Methylphenidate is effective for the treatment of narcolepsy in adults and children 6 years and over. Methylphenidate improves performance and ability to stay awake. Methylphenidate has been used for various diseases which exhibit hypersomnia as a prominent clinical feature.

##### c) Adult:

1) Methylphenidate (10 to 60 milligrams/day) is indicated for the treatment of narcolepsy in adults and children 6 years and over. Methylphenidate improves performance and ability to stay awake (Prod Info RITALIN(R) oral tablet, RITALIN-SR(R) oral tablet, 200 1987a; Mittle et al, 1986c; Honda et al, 1979a).

2) Methylphenidate has been shown to be effective in the treatment of post-traumatic narcolepsy. In 1 case, methylphenidate was successfully used to treat narcolepsy resulting from moderate brain injury. Following the treatment with methylphenidate, the patient was completely asymptomatic (Francisco & Ivanhoe, 1996).

3) Methylphenidate has been used for various diseases such as Kleine-Levin syndrome, myotonic dystrophy, and hypersomnia as a prominent clinical feature. The treatment of HYPERSOMNOLENCE follows the same pattern as that of narcolepsy. The response to CNS stimulants including pemoline, methylphenidate, and dextroamphetamine is less

hypersomnolence, pemoline is usually inadequate so methylphenidate, dextroamphetamine, phenmetra: prescribed (Culebrar, 1996; Guilleminault, 1994; Guilleminault, 1994a; Aoyama et al, 1994; Jozefowicz &

a) In hypersomnolence associated with myotonic dystrophy of a central origin rather than due to sle 40 milligrams/day) has resulted in sustained benefit in some patients for several years (2 to 6 years) al, 1986).

b) KLEINE-LEVIN SYNDROME, a periodic hypersomnia, is a rare primary condition featuring episo hyperphagia and hypersexuality. Episodes typically appear in adolescent males and last from sever: remission. In 1 case report, Kleine-Levin syndrome was successfully treated with methylphenidate (: 1976). In another case report, methylphenidate therapy (40 mg/day) was only partially successful in 1978).

#### 4.5.B.18 Paraphilia; Adjunct

##### a) Overview

FDA Approval: Adult, no; Pediatric, no  
Efficacy: Adult, Evidence favors efficacy  
Recommendation: Adult, Class IIb  
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

##### b) Summary:

Effective adjunctive treatment for some cases of paraphilia

##### c) Adult:

1) An 8-week course of sustained release METHYLPHENIDATE added to selective serotonin reuptake i produced additional improvement in some patients with paraphilia (n=14) or paraphilia-related behavior ( study (n=26). Indications for addition of methylphenidate to SSRI therapy included retrospective diagnos residual sexual target symptoms despite SSRI, residual depressive symptoms, relapse of sex/depressive effects such as fatigue. The mean dose of methylphenidate was 40 milligrams (mg)/day (range 20 to 100 outlets per week and minutes per day related to paraphilia decreased significantly during SSRI treatment methylphenidate AND SSRI treatment, further reductions occurred in total sexual outlets per week (p=0.1 (p=0.04). With methylphenidate plus an SSRI, total sexual outlet measure decreased by 39% (p=0.003), behavior decreased by 44% (p=0.04). Side effects of methylphenidate therapy (usually managed by dos (1), increased sex drive (1), shallow sleep (2), distractibility (2), and mild anxiety (2) (Kafka & Hennen, 20

#### 4.5.B.19 Schizophrenia

##### a) Overview

FDA Approval: Adult, no; Pediatric, no  
Efficacy: Adult, Evidence is inconclusive; Pediatric, Evidence is inconclusive  
Recommendation: Adult, Class III; Pediatric, Class III  
Strength of Evidence: Adult, Category C; Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

##### b) Summary:

Methylphenidate has had some success in the treatment of schizophrenia in adults and children  
Methylphenidate may provoke schizophrenic symptoms with intensification of preexisting psychotic :

##### c) Adult:

1) Methylphenidate 40 milligrams intravenously (over 90 seconds) was reported effective in eliminating i schizophrenic patient who had been unresponsive to intravenous phenobarbital (Frost, 1989).  
2) When administered intravenously in a dose of 0.5 milligram/kilogram methylphenidate has provoked : preexisting psychotic symptoms in actively ill patients. It was noted that symptom activation occurred with minutes and persisted 2 to 6 hours. It was also noted that antipsychotic agents did not appear to effect p (Janowsky et al, 1973).

##### d) Pediatric:

1) Methylphenidate in doses of 10 milligrams (mg) twice daily in combination with chlorpromazine has b 11-year-old boy. Prior neuroleptic therapy was ineffective (Rogeness & Macedo, 1983).

#### 4.5.B.20 Selective serotonin re-uptake inhibitor adverse reaction - Sexual dysfunction

See Drug Consult reference: SELECTIVE SEROTONIN REUPTAKE INHIBITOR-INDUCED SEXUAL DYSFI

#### 4.5.B.21 Shivering, Postanesthesia; Treatment and Prophylaxis

##### a) Overview

FDA Approval: Adult, no; Pediatric, no  
Efficacy: Adult, Evidence favors efficacy  
Recommendation: Adult, Class IIb  
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

##### b) Summary:

Methylphenidate appears to be effective in suppressing post-anesthetic shivering

##### c) Adult:

1) In a triple-blind study of 153 patients investigators (Liem & Aldrete, 1974) compared the effectiveness methylphenidate (20 mg), calcium chloride (200 mg) and a placebo (normal saline) in the treatment of pc



Protriptyline

Thioridazine

#### 4.6.A Amphetamine

##### 4.6.A.1 Attention deficit hyperactivity disorder

**a) SUMMARY:** In comparative studies, Adderall(R) (combination AMPHETAMINE/DEXTROAMPHETAMINE) demonstrated superior efficacy in the treatment of attention deficit hyperactive disorder in children. METHYLPHENIDATE requires two daily doses.

**b)** The racemic mixture of L- and D-amphetamine (ADDERALL(R)) was at least as effective as methylphenidate in the treatment of attention deficit hyperactivity disorder (ADHD), and was more effective at 4 to 5 hours post-administration (beyond midday) than methylphenidate in a within-subject, double-blind, placebo-controlled, crossover study, 25 children with ADHD (mean age 9.6 years) received 10 mg, 17.5 mg, Adderall(R) 7.5 mg, 12.5 mg, and placebo twice a day (at 7:45 a.m. and 12:15 p.m.) in a randomized, double-blind, placebo-controlled, crossover study. Teachers and counselors rated their behavior throughout the day and at times beyond methylphenidate's expected duration of action at the end of the day and in the evening for possible rebound effects. When compared to placebo, Adderall(R) improved in-school behaviors (p less than 0.0001 and 0.001, respectively), classroom measures (p less than 0.001 and 0.001, respectively), and after-school behaviors (p less than 0.0001). Drug effects were significantly affected by time (p less than 0.001) with effect size (ES) than methylphenidate and higher doses consistently resulted in higher ES than lower doses. Adderall(R) was more effective than methylphenidate at midday and end of day (p less than 0.05). The ES of both drugs dropped at midday, implicating the possibility of reducing the afternoon dose. Side effects were reported more frequently with Adderall(R) than with methylphenidate. Only 1 patient was eliminated from the study due to exacerbation of his motor tic condition. Further studies are needed to compare the efficacy of methylphenidate to D-amphetamine.

**c)** Once-daily Adderall(R) (combination AMPHETAMINE/DEXTROAMPHETAMINE) appeared to be as effective as twice-daily methylphenidate in the treatment of attention deficit hyperactive disorder in children aged 6 to 12 years, according to a double-blind, randomized, placebo-controlled, crossover study. Also, a mid-afternoon dose of either Adderall or methylphenidate (MPH) produced better evening behavior than placebo, although either active treatment tended to induce loss of appetite and sleep difficulties. In a randomized, double-blind, placebo-controlled, crossover study, 25 children with ADHD received each day 1 of 7 treatment protocols: (1) MPH 0.3 milligram/kilogram (mg/kg) at 7:30, 11:30, and 15:30; (2) MPH 0.15 mg/kg at 15:30; (3) MPH 0.3 mg/kg at 7:30; (4) Adderall 0.3 mg/kg at 7:30 and 15:30; (5) Adderall 0.3 mg/kg at 7:30; (6) Adderall 0.3 mg/kg at 7:30; or (7) placebo. While twice-daily MPH 0.3 mg/kg did not differ significantly from placebo, single morning-dose MPH 0.3 mg/kg produced less significant effects than either once-daily Adderall 0.3 mg/kg or MPH 0.3 mg/kg. MPH began to lose its effectiveness approximately 6.5 hours later. Evening behavior was rated better after MPH than after placebo. No evening differences were seen after mid-afternoon doses of either 0.3 or 0.15 mg/kg. Children showed different responses to MPH, 37% responded more positively to MPH, 37% responded more positively to Adderall, and 38% responded equally to both. In a study comparing MPH to Adderall, one dose of MPH was sufficient to carry them all day and into the evening, while one dose of Adderall needed only once-daily dosing of the drug (Pelham et al, 1999aa).

#### 4.6.B Clonidine

##### 4.6.B.1 Attention deficit hyperactivity disorder

**a)** In children with attention deficit hyperactive disorder (ADHD) and TICS (both by DSM-IV criteria), CLONIDINE or combination CLONIDINE/MPH provided symptomatic improvement in ADHD without causing worsening of tic symptoms. This finding emanated from a double-blind, multi-center trial in children randomized to placebo (n=32), clonidine alone starting at 0.1 milligram (mg)/day (n=34), MPH alone starting at 0.3 mg/kg (n=33), or combination clonidine/MPH (n=33). Average daily doses were 0.25 mg for clonidine alone, 0.28 mg for clonidine given with MPH given with clonidine. Based on the primary endpoint (Conners Abbreviated Questionnaire-Teacher), a significant improvement was seen with clonidine (compared to no clonidine; p=0.002), and for MPH (compared to no MPH; p=0.003), and either clonidine or MPH (both p=0.02). However, the greatest improvement on symptomatic ratings was seen with combination clonidine/MPH. Worsening of tics was reported in 9 receiving clonidine alone, 8 receiving MPH alone, 6 on combination clonidine/MPH. Compared with placebo, severity of tics decreased in all active treatment groups according to the Yale Global Tic Severity Scale and the Tic Symptom Self-Report. Study medications were well tolerated except for sedation caused by clonidine. The authors observed that clonidine seemed to be most helpful for impulsivity and hyperactivity. Inattention was not significantly improved with clonidine or MPH (Anon, 2002).

**b)** An open pilot study compared oral and transdermal clonidine to methylphenidate in attention deficit disorder. Both were more effective than placebo. In another study, MPH acted as a placebo in the treatment of attention deficit and moderate hyperactivity. In ADHD children with symptoms of hyperarousal, hyperactivity, and aggression, MPH was more effective than placebo.

#### 4.6.C Dexmethylphenidate

##### 4.6.C.1 Attention deficit hyperactivity disorder

**a)** No comparisons with methylphenidate have been published, and data released by the manufacturer have not been published. In a completed 4-week, placebo-controlled study described in the package insert (Protonix to 20 milligrams (mg) daily was compared to methylphenidate 10 to 40 mg daily (each in two divided doses) in a randomized, double-blind, placebo-controlled, crossover study. Patients included had all subtypes of ADHD (combined type, inattentive type, hyperactive-impulsive type). MPH demonstrated significantly greater improvement of symptom scores from baseline on the Swanson, Noland, and Pelham (SNAP) than placebo (mean change, -0.7 versus -0.2). Although methylphenidate was the comparator, no results for methylphenidate were reported.



#### 4.6.F Pemoline

Attention deficit hyperactivity disorder

Fatigue

Narcolepsy

##### 4.6.F.1 Attention deficit hyperactivity disorder

a) In a retrospective chart review (n=485), METHYLPHENIDATE (MPD) and PEMOLINE (PEM) were both effective in the treatment of attention deficit hyperactivity disorder (ADHD) and attention deficit disorder (ADD) (DSM- IV) in children 4 to 18 years of age; 1-treatment were shown by more PEM-treated than MPD-treated patients (PEM 225 of 245 (92%); MPD 168 of 245 (68%)). Efficacy ratings for treatment efficacy ranged from 1 to 4; 1-poor or no response; 2-initially good but not sustained; 3-good efficacy ratings for the MPD and PEM groups were 2.7 and 3.5, respectively. Most frequent adverse effects were headache and insomnia and irritability for the PEM group. The rates of drug discontinuation for lack of efficacy were 32% for the MPD and 22% for the PEM group. Discontinuations due to adverse effects were higher in the PEM group (22% compared with 5% for MPD). No significant differences were found between either group. Standard doses were 1.44 milligrams/kilogram (mg/kg) for PEM given once daily and 0.4 mg/kg for the immediate-release form and in 2 or 3 divided doses daily for the immediate-release form. The sustained-release form of the immediate-release form (Andriola, 2000).

##### 4.6.F.2 Fatigue

a) A 6-week course of an oral psychostimulant medication, METHYLPHENIDATE or PEMOLINE, reduced the quality of life also tended to improve with methylphenidate (MPH) and PEMOLINE (PEM) therapy, and drug-induced fatigue score of at least 5 on a 10-point scale for persistent fatigue. MPH (n=53) was initiated at 7.5 milligrams (mg) daily (mean end-of-study dose 51 mg/day); PEM (n=45) was started at 18.75 mg twice daily with maximum titration 40 mg/day. At 6 weeks, total scores on the Piper Fatigue Scale (patient-rated) were significantly improved compared with placebo (p=0.04). Also, on the patient-rated visual analog scale for fatigue (VAS-F), the energy subscore was significantly improved for MPH or PEM (p=0.02). No significant differences were found on any outcome measurement comparing MPH between improvement in fatigue and better quality of life. Five patients dropped out due to side effects (MPH hyperactivity were experienced significantly more often by those on MPH or PEM than those on placebo (Bre

##### 4.6.F.3 Narcolepsy

a) One group of investigators studied the efficacy of methylphenidate, pemoline, and protriptyline in the treatment of narcolepsy. Six subjects received methylphenidate at dosages of 10 milligrams (mg), 30 mg, and 60 mg/day (1 week each dosage); two subjects received pemoline at dosages of 18.75 mg, 56.25 mg, and 112.5 mg/day (1 week at each dosage). Two subjects received protriptyline at dosages of 10 mg, 20 mg, and 40 mg/day (1 week at each dosage). All subjects were randomized from patient to patient. Nine healthy subjects with no sleep disorder received placebos and served as controls. Methylphenidate significantly improves the ability of the narcoleptic to stay awake, pemoline seems to improve the ability to stay awake or perform. More data are needed to confirm these findings, and further

#### 4.6.G Protriptyline

##### 4.6.G.1 Narcolepsy

a) Protriptyline did not improve either the ability to stay awake or perform tasks in a double-blind, parallel (by 1986). Three dose levels of 3 drugs were compared in the treatment of narcolepsy in 17 patients. The drugs compared were protriptyline (10, 30, or 60 mg/day), methylphenidate (10, 30, or 60 mg/day) and pemoline (10, 30, and 60 mg/day). Methylphenidate improved the ability to perform tasks, but not to stay awake.

#### 4.6.H Thioridazine

##### 1) Adverse Effects

a) One group of investigators reported a controlled study of methylphenidate and thioridazine in improving cognitive performance in subaverage children. Twenty-seven children with subaverage IQs participated in a double-blind, placebo-controlled study comparing methylphenidate (0.4 milligrams/kilogram/day) and thioridazine (1.75 milligrams/kilogram/day). The children showed improved attention, and performance on a series of electronically-controlled cognitive-motor tests. Methylphenidate improved omission errors on an attentional task, and reduced seat movements on two tasks. Thioridazine had no significant effect on performance. It did not produce deleterious effects on IQ performance when subjects received reinforcers for correct responses. Methylphenidate did not adversely affect performance on any of the cognitive-motor performance tests (Aman et al, 1991).

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