DRUGDEX® Evaluations

FLUVOXAMINE

0.0 Overview

1) Class
- **a)** This drug is a member of the following class(es):
  Antidepressant
  Central Nervous System Agent
  Serotonin Reuptake Inhibitor

2) Dosing Information
- **a)** Fluvoxamine Maleate
  - **1)** Adult
    - **a)** Depression
      - **1)** 50 to 300 mg/day ORALLY
    - **b)** Obsessive-compulsive disorder
      - **1)** immediate-release, 50 mg/day ORALLY at bedtime; may increase by 50 mg increments every 4-7 days to a MAX dosage of 300 mg/day (usual effective range 100 to 300 mg/day) (Prod Info LUVOX(R) oral tablets, 2007)
      - **2)** extended-release, 100 mg/day ORALLY at bedtime; may increase by 50 mg increments every week to a MAX dosage of 300 mg/day (usual effective range 100 to 300 mg/day) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008)
    - **c)** Panic disorder
      - **1)** 50-300 mg/day ORALLY (mean effective dose is 225 mg/day)
    - **d)** Social phobia
      - **1)** extended-release, 100 mg/day ORALLY at bedtime; may increase by 50 mg increments every week to a MAX dosage of 300 mg/day (usual effective range 100 to 300 mg/day) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008)
  - **2)** Pediatric
    - **a)** extended-release fluvoxamine maleate has not been evaluated for use in pediatric patients (Prod Info LUVOX(R) CR extended-release oral capsules, 2008)
    - **b)** safety and efficacy of immediate release fluvoxamine maleate has not been studied in patients with obsessive compulsive disorder (OCD) less than 8 years of age (Prod Info LUVOX(R) oral tablets, 2007)
      - **1)** Obsessive-compulsive disorder
        - **a)** immediate-release (ages 8-11 yr), 25 mg/day ORALLY at bedtime; may increase by 25 mg increments every 4-7 days to a MAX dosage of 200 mg/day (usual effective range 50 to 200 mg/day) (Prod Info LUVOX(R) oral tablets, 2007)
        - **b)** immediate-release (ages 12-17 yr), 25 mg/day ORALLY at bedtime; may increase by 25 mg increments every 4-7 days to a MAX dosage of 300 mg/day (usual effective range 50 to 200 mg/day) (Prod Info LUVOX(R) oral tablets, 2007)

3) Contraindications
- **a)** Fluvoxamine Maleate
  - **1)** concomitant use with alosetron, pimozide, thioridazine, or tizanidine (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)
  - **2)** concomitant use with a monoamine oxidase inhibitor (MAOI) or within 14 days following treatment with a MAOI (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)
  - **3)** hypersensitivity to fluvoxamine maleate or any other component of the product (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

4) Serious Adverse Effects
- **a)** Fluvoxamine Maleate
  - **1)** Bleeding, Abnormal
  - **2)** Depression, worsening
  - **3)** Extrapyramidal disease
  - **4)** Hyponatremia
  - **5)** Neuroleptic malignant syndrome
  - **6)** Psychotic disorder
  - **7)** Seizure
  - **8)** Serotonin syndrome
  - **9)** Stevens-Johnson syndrome
  - **10)** Stevens-Johnson syndrome
  - **11)** Suicidal thoughts
  - **12)** Syndrome of inappropriate antidiuretic hormone secretion
  - **13)** Toxic epidermal necrolysis
  - **14)** Withdrawal sign or symptom

5) Clinical Applications

a) Fluvoxamine Maleate
1) FDA Approved Indications
a) Obsessive-compulsive disorder
b) Social phobia
2) Non-FDA Approved Indications
a) Depression
b) Panic disorder

1.0 Dosing Information

Drug Properties

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
Fluvoxamine
Fluvoxamine Maleate
C) Physicochemical Properties
1) Molecular Weight
a) Fluvoxamine base: 318.3 (Fleeger, 1994); Fluvoxamine maleate: 434.41 (Canada, 1997)
2) Solubility
a) Systemic: Fluvoxamine maleate is sparingly soluble in water (Prod Info Luvox, 97) and freely soluble in ethanol (Prod Info Luvox, 97).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Geriatric Patients

1.3.1 Normal Dosage

1.3.1.A Fluvoxamine Maleate

1.3.1.A.1 Oral route

Depression

Obsessive-compulsive disorder

Social phobia

1.3.1.A.1.a Depression
1) Doses of 50 to 300 milligrams/day administered orally have been found effective in clinical trials (Ottevanger, 1994; Martin et al, 1987a) (Porro et al, 1988). A single night time dose of fluvoxamine appears to be best tolerated (Siddigui et al, 1985).

1.3.1.A.1.b Obsessive-compulsive disorder
1) Immediate-release Formulation
a) The recommended dose of fluvoxamine maleate for the treatment of obsessions and

compulsions in adult patients with obsessive compulsive disorder (OCD) is 50 milligrams (mg) orally once daily at bedtime initially, titrated by 50 mg increments every 4 to 7 days, as tolerated, to the target dose range of 100 to 300 mg/day. The maximum dose should not exceed 300 mg/day. Treatment with fluvoxamine maleate beyond 10 weeks for OCD has not been studied in controlled trials; therefore, if treatment is necessary beyond 10 weeks, maintain the patient on the lowest effective dose and periodically reassess the need for treatment (Prod Info LUVOX(R) oral tablets, 2007).

2) Extended-release Formulation

a) The recommended dose of extended-release fluvoxamine maleate for the treatment of obsessions and compulsions in adult patients with obsessive compulsive disorder (OCD) is 100 milligrams (mg) orally once daily at bedtime initially, titrated by 50 mg increments every week, as tolerated, to the target dose range of 100 to 300 mg/day. The maximum dose should not exceed 300 mg/day. Treatment with extended-release fluvoxamine maleate beyond 12 weeks for OCD has not been studied in controlled trials; therefore, if treatment is necessary beyond 12 weeks, maintain the patient on the lowest effective dose and periodically reassess the need for treatment (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3) Therapy Withdrawal

a) When discontinuing therapy, a gradual reduction in dose is preferred over abrupt cessation of therapy due to risk of withdrawal symptoms. Monitor for withdrawal symptoms when stopping fluvoxamine maleate therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

1.3.1.A.1.c Social phobia

1) The recommended dose of extended-release fluvoxamine maleate for the treatment of social anxiety disorder (social phobia) in adult patients is 100 milligrams (mg) orally once daily at bedtime initially, titrated by 50 mg increments every week, as tolerated, to the target dose range of 100 to 300 mg/day. The maximum dose should not exceed 300 mg/day. Treatment with extended-release fluvoxamine maleate beyond 12 weeks for social anxiety disorder has not been studied in controlled trials; therefore, if treatment is necessary beyond 12 weeks, maintain the patient on the lowest effective dose and periodically reassess the need for treatment. When discontinuing therapy, a gradual withdrawal is preferred to an abrupt cessation of therapy due to risk of withdrawal symptoms. Monitor for withdrawal symptoms when stopping fluvoxamine maleate therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

1.3.2 Dosage in Renal Failure

A) Fluvoxamine Maleate

1) Renal impairment does not appear to affect the pharmacokinetics of fluvoxamine (Raghoebar & Roseboom, 1988). However, a low starting dosage along with careful monitoring is recommended, especially during the first month of treatment.

1.3.3 Dosage in Hepatic Insufficiency

A) Fluvoxamine Maleate

1) Because fluvoxamine undergoes extensive hepatic metabolism, a reduction in the initial dose and slower dose titration may be required in patients with hepatic insufficiency (Prod Info Luvox(R), 1998); (Harten et al, 1993)(DeBree et al, 1983; Doogan, 1980). A 30% decrease in fluvoxamine clearance was noted in patients with hepatic insufficiency (Prod Info Luvox(R), 1998).

2) The pharmacokinetics of fluvoxamine were studied in 13 patients with biopsy-proven liver cirrhosis (van Harten et al, 1993a). They received a single oral 100 mg dose as an enteric-coated tablet and plasma samples were collected up to one week after administration. The mean elimination half-life was 25 hours and it increased with higher plasma bilirubin levels although no relationship between bilirubin and AUC was observed. The AUC was about 50% higher in patients than in healthy volunteers. The authors recommended that in patients with signs of active liver disease, it is wise to initiate fluvoxamine treatment at a lower daily dose and to carefully monitor the patient during subsequent dose increases.

1.3.4 Dosage in Geriatric Patients

A) Fluvoxamine Maleate

1) Mean fluvoxamine plasma concentrations are reported to be 40% higher in elderly versus young subjects following doses of 50 or 100 mg. Fluvoxamine clearance is also reduced by 50% in the elderly. Fluvoxamine dosage should be slowly titrated in elderly patients (Prod Info Luvox(R), 1998).

1.4 Pediatric Dosage

1.4.1 Normal Dosage

1.4.1.A Fluvoxamine Maleate

1.4.1.A.1 Oral route

1.4.1.A.1.a Obsessive-compulsive disorder

1) The recommended dose of fluvoxamine maleate (immediate-release) for the treatment of obsessions and compulsions in patients aged 8 to 11 years with obsessive compulsive disorder (OCD) is 25 milligrams (mg) orally once daily at bedtime initially, titrated by 25 mg increments every 4 to 7 days, as tolerated, to the target dose range of 50 to 200 mg/day (maximum dose not to exceed 200 mg/day). The recommended dose of fluvoxamine maleate (immediate-release) for the treatment of obsessions and compulsions in patients aged 12 to 17 years with OCD is 25 mg orally once daily at bedtime initially, titrated by 25 mg increments every 4 to 7 days, as tolerated, to the target dose range of 50 to 200 mg/day (maximum dose not to exceed 300 mg/day). Treatment with fluvoxamine maleate beyond 10 weeks for OCD has not been studied in controlled trials; therefore, if treatment is necessary beyond 10 weeks, maintain the patient on the lowest effective dose and periodically reassess the need for treatment. When discontinuing therapy, a gradual withdrawal is preferred to an abrupt cessation of therapy due to risk of withdrawal symptoms. Monitor for withdrawal symptoms when stopping fluvoxamine maleate therapy (Prod Info LUVOX(R) oral tablets, 2007).

2) Extended-release fluvoxamine maleate has not been evaluated for use in pediatric patients and is not indicated for use in this population (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3) The safety and efficacy of immediate-release fluvoxamine maleate has not been evaluated in patients with obsessive compulsive disorder (OCD) less than 8 years of age (Prod Info LUVOX(R) oral tablets, 2007).

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset

1) Fluvoxamine Maleate

a) Initial Response

1) Obsessions: 3 to 10 weeks (Jenike et al, 1990; Goodman et al, 1990).

2) Depression: 2 to 3 weeks (Wilde et al, 1993a).

2.2 Drug Concentration Levels

A) Fluvoxamine Maleate

1) Peak Concentration

a) Immediate-release, Age Differences

1) Adults, 5.7 nanogram/mL; children (6 to 11 years), 14.8 nanogram/mL; adolescents (12 to 17 years), 4.2 to 6.7 nanogram/mL (Prod Info LUVOX(R) oral tablets, 2007).

a) In a multiple-dose study of immediate-release fluvoxamine maleate tablets in children age 6 to 11 years, adolescents age 12 to 17 years, and adults, peak concentrations were widely variable. Following oral administration of 100 mg twice daily, children exhibited a mean Cmax of 14.8 nanogram/milliliter (ng/mL) compared to 4.2 ng/mL in adolescents. Following oral administration of 150 mg twice daily, adolescents exhibited a mean Cmax of 6.7 ng/mL compared to 5.7 ng/mL in adults (Prod Info LUVOX(R) oral tablets, 2007).

b) In a dose proportionality study, following administration of fluvoxamine maleate 100, 200, and 300 mg/day for 10 days in 30 healthy volunteers, the mean maximum plasma concentrations at steady state were 88, 283, and 546 nanograms/mL, respectively (Prod Info LUVOX(R) oral tablets, 2007).

c) In a pharmacokinetics study, mean maximum plasma concentrations were 40% higher in elderly patients (66 to 73 years of age) than in younger subjects (19 to 35 years of age) following administration of immediate-release fluvoxamine 50 mg and 100 mg tablets (Prod Info LUVOX(R) oral tablets, 2007).

d) Immediate-release, Gender Differences

1) Children (6 to 11 years), females, 28.1 nanogram/milliliter; males, 9.1 nanogram/milliliter (Prod Info LUVOX(R) oral tablets, 2007).

a) In a multiple-dose study of 100 mg immediate-release fluvoxamine maleate tablets administered orally twice daily in children age 6 to 11 years and adolescents age 12 to 17 years, female children exhibited a higher mean Cmax compared to male children (28.1 ng/mL versus 9.1 ng/mL, respectively). Gender differences were not noted in adolescents (Prod Info LUVOX(R) oral tablets, 2007).

b) Extended-release

1) In a single-dose crossover study in 28 healthy volunteers, the mean Cmax was 38% lower following administration of extended-release capsules compared with immediate-release tablets. In a dose proportionality study, following administration of fluvoxamine maleate extended-release capsules 100, 200, and 300 mg/day in 20 healthy volunteers, the mean maximum plasma concentrations were 47, 161, and 319 nanograms/mL, respectively. The Cmax increased 5.7-fold following the 3-fold increase in dose from 100 to 300 mg (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

2) In a study of 28 healthy volunteers receiving extended-release fluvoxamine 100 mg, the Cmax was increased by approximately 60% in females compared with males (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

2) Time to Peak Concentration

a) Immediate-release

1) 3 to 8 hours (Prod Info LUVOX(R) oral tablets, 2007)

a) In a dose proportionality study, following administration of 100, 200, and 300 milligrams/day for 10 days in 30 healthy volunteers, the maximum plasma concentrations at steady state were reached within 3 to 8 hours (Prod Info LUVOX(R) oral tablets, 2007).

3) Steady State

a) 7 to 10 days (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

1) Steady-state plasma concentrations were reached following 1 week of dosing with either immediate-release or extended release fluvoxamine maleate according to dose proportionality studies of 100 to 300 mg/day of either extended-release capsules (n=20), or immediate-release tablets (n=30) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

2) In additional studies, steady-state plasma concentrations of fluvoxamine were attained in about 10 days of multiple dosing (Harten, 1995; Wilde et al, 1993a; Vries et al, 1992; Wright et al, 1991).

4) Area Under the Curve

a) Immediate-release, Age Differences

1) Adults, 59.4 nanogram x hour/milliliter; children (6 to 11 years), 155.1 nanogram x hour/milliliter; adolescents (12 to 17 years), 43.9 to 69.6 nanogram x hour/milliliter (Prod Info LUVOX(R) oral tablets, 2007).

a) In a multiple-dose study of immediate-release fluvoxamine maleate tablets in children age 6 to 11 years, adolescents age 12 to 17 years, and adults, AUCs were widely variable. Following oral administration of 100 mg twice daily, children exhibited a mean AUC of 155.1 nanogram x hour/milliliter (ng x hr/mL) compared to 43.9 ng x hr/mL in adolescents. Following oral administration of 150 mg twice daily, adolescents exhibited a mean AUC of 69.6 ng x hr/mL compared to 59.4 ng x hr/mL in adults (Prod Info LUVOX(R) oral tablets, 2007).

b) Immediate-release, Gender Differences

1) Children (6 to 11 years), females, 293.5 nanogram x hour/milliliter; males, 95.8 nanogram x hour/milliliter (Prod Info LUVOX(R) oral tablets, 2007).

a) In a multiple-dose study of 100 mg immediate-release fluvoxamine maleate tablets administered orally twice daily in children age 6 to 11 years and adolescents age 12 to 17 years, female children exhibited a higher AUC compared to male children (293.5 ng x hr/mL versus 95.8 ng x hr/mL, respectively). Gender differences were not noted in adolescents (Prod Info LUVOX(R) oral tablets, 2007).

c) Extended-release

1) In a multiple-dose proportionality study, following administration of fluvoxamine maleate extended-release capsules 100, 200, and 300 mg/day in 20 healthy volunteers, the AUC increased 5.7-fold following the 3-fold increase in dose from 100 to 300 mg (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

2) In a study of healthy volunteers receiving extended-release fluvoxamine 100 mg, the AUC was increased by approximately 60% in females (n=13) compared with males (n=15) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption

A) Fluvoxamine Maleate

1) Bioavailability

a) Oral, immediate-release: 53% (Prod Info LUVOX(R) oral tablets, 2007); extended-release: 84% relative to immediate-release (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

1) The absolute bioavailability of fluvoxamine maleate immediate-release tablets is 53% (Prod Info LUVOX(R) oral tablets, 2007). The bioavailability of fluvoxamine maleate extended-release capsules is 84% relative to immediate-release tablets (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

2) Effects of Food

a) No significant effect (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

1) Food causes the mean AUC and Cmax of fluvoxamine to increase only slightly and does not significantly affect the absorption of fluvoxamine maleate (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

2.3.2 Distribution

A) Distribution Sites

1) Fluvoxamine Maleate

a) Protein Binding

1) 80% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

a) Fluvoxamine maleate is 80% bound to plasma protein, primarily albumin, over a concentration range of 20 to 2000 nanograms/mL (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

B) Distribution Kinetics

1) Fluvoxamine Maleate

a) Volume of Distribution

1) 25 L/kg (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

a) Fluvoxamine maleate exhibits extensive tissue distribution, with a mean apparent Vd of approximately 25 L/kg (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics

1) Fluvoxamine Maleate

a) Liver, extensive (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX (R) oral tablets, 2007).

1) Fluvoxamine is extensively metabolized in the liver (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007) (DeBree et al, 1983a; Doogan, 1980a) via oxidative demethylation and deamination (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

B) Metabolites

1) Fluvoxamine Maleate

a) Fluvoxamine acid (active) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

1) Nine mostly inactive metabolites of fluvoxamine maleate have been identified. One metabolite, fluvoxamine acid, has a weak effect (1-2 orders of magnitude less potent than the parent compound) on the inhibition of serotonin uptake (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

2.3.4 Excretion

A) Kidney

1) Fluvoxamine Maleate

a) Renal Excretion (%)

1) 94% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007; DeBree et al, 1983a; Doogan, 1980a).

a) Following a dose of fluvoxamine maleate 5 mg orally, an average of 94% of drug-related products was recovered in the urine within 71 hours. Two percent is excreted unchanged in the urine (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

b) The mean minimum concentrations were similar after 4 and 6 weeks of treatment with fluvoxamine maleate 50 mg twice day day (n=13) in renally impaired patients with creatinine clearance of 5 to 45 mL/minute, suggesting no accumulation of fluvoxamine in this group (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

B) Total Body Clearance

1) Fluvoxamine Maleate

a) Hepatic Impairment
1) There was a 30% decrease in fluvoxamine clearance in patients with hepatic dysfunction compared with healthy subjects in a cross study (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).
b) Elderly
1) In elderly patients the clearance of fluvoxamine was reduced by 50% so initiation of therapy should be titrated slowly (Prod Info LUVOX(R) oral tablets, 2007)

2.3.5 Elimination Half-life
A) Parent Compound
1) Fluvoxamine Maleate
a) Immediate-release, 15.6 hours (Prod Info LUVOX(R) oral tablets, 2007); extended-release, 16.3 hours (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
1) Immediate-release
a) The mean plasma half-life of fluvoxamine at steady state following multiple dose oral administration of immediate-release tablets 100 mg/day in young, healthy volunteers was 15.6 hours (Prod Info LUVOX(R) oral tablets, 2007).
b) In a study comparing administration of immediate-release fluvoxamine 50 mg and 100 mg to elderly patients (66 to 73 years of age) and younger subjects (19 to 35 years of age), the elimination half-life following multiple doses was 17.4 and 25.9 hours in elderly patients compared with 13.6 and 15.6 hours in younger subjects, respectively (Prod Info LUVOX(R) oral tablets, 2007).
2) Extended-release
a) The mean plasma half-life of fluvoxamine following a single oral dose of a 100-mg extended release capsule in healthy volunteers was 16.3 hours (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING
1) Fluvoxamine Maleate
a) Oral (Capsule, Extended Release; Tablet)
Suicidality and Antidepressant Drugs
Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of fluvoxamine maleate extended-release capsules or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007). Fluvoxamine maleate extended-release capsules are not approved for use in pediatric patients (Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Fluvoxamine maleate tablets are not approved for use in pediatric patients except for patients with obsessive compulsive disorder (OCD) (Prod Info LUVOX(R) oral tablets, 2007).

3.1 Contraindications
A) Fluvoxamine Maleate
1) concomitant use with alosetron, pimozide, thioridazine, or tizanidine (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)
2) concomitant use with a monoamine oxidase inhibitor (MAOI) or within 14 days following treatment with a

MAOI (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)
3) hypersensitivity to fluvoxamine maleate or any other component of the product (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

3.2 Precautions

A) Fluvoxamine Maleate

1) suicidal ideation and behavior or worsening depression has been reported, particularly in children, adolescents, and young adults during the first few months of therapy or following changes in dosage; monitoring recommended (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)
2) abnormal bleeding, sometimes fatal, has occurred; risk may be increased with concomitant use of drugs that affect coagulation (eg, NSAIDs, aspirin, warfarin) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)
3) abrupt discontinuation; serious discontinuation symptoms have been reported with abrupt fluvoxamine maleate withdrawal; monitoring recommended; reduce dose gradually if possible (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)
4) bipolar disorder, in patients at risk (eg, major depressive disorder (MDD) may be the initial presentation of bipolar disorder); may cause a mixed/manic episode (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)
5) concomitant use with antipsychotic agents; may increase the risk of neuroleptic malignant syndrome (NMS) or NMS-like events (eg, hyperthermia, muscle rigidity, autonomic instability, mental status changes); use with caution (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)
6) concomitant use with serotonergic drugs (eg, SSRIs, serotonin-norepinephrine reuptake inhibitors), diazepam, ramelteon, or serotonin precursors (eg, tryptophan) is not recommended (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)
7) concomitant use with 5-hydroxytryptamine receptor agonists (triptans); risk of serotonin syndrome; monitoring recommended if concurrent use is clinically warranted (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)
8) hyponatremia and/or syndrome of inappropriate antidiuretic hormone secretion (SIADH) has occurred, greater risk in patients who are volume-depleted, elderly, or receiving concurrent diuretic therapy; discontinue if symptomatic hyponatremia occurs (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)
9) liver dysfunction; lower doses may be necessary (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)
10) mania, history of; may cause an activation of mania or hypomania (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)
11) seizure disorder, history of (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

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

3.3.1.A Fluvoxamine Maleate

Abnormal ECG

Hypotension

Pulse irregular

Sudden cardiac death

3.3.1.A.1 Abnormal ECG

a) Fluvoxamine maleate use was not associated with important changes in ECG variables during short-term, placebo-controlled trials involving patients with obsessive-compulsive disorder or depression (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).
b) Premature ventricular contractions (PVCs) not requiring therapy have been occasionally reported (Garnier et al, 1993).
c) In a pooled analysis of ECG data from several studies, fluvoxamine caused slight increases in the R-R, QT, and QTc intervals (Guelfi et al, 1983a; DeWilde & Doogan, 1982; De Wilde et al, 1983a; Benfield & Ward, 1986b). Fluvoxamine did not change T wave configurations as seen after tricyclic antidepressant administration (Roos, 1983a).
d) In 25 healthy males, fluvoxamine 50 to 100 mg three times daily for 9 days produced a mean decrease in heart rate of 5 beats/minute compared with placebo (Robinson & Doogan, 1982).

3.3.1.A.2 Hypotension

a) Incidence: 1% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)
b) Hypotension was reported in at least 1% of patients with major depressive disorder or obsessive-compulsive disorder who took immediate-release fluvoxamine maleate during premarketing clinical trials (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).
c) Orthostatic hypotension, which improved upon dose reduction, was reported with fluvoxamine therapy in patients with obsessive-compulsive disorder (Price et al, 1987).
d) Fluvoxamine did not produce any significant changes in systolic and diastolic blood pressure or mean arterial pressure in a study using single doses of 50, 75, and 100 mg administered to 17 healthy volunteers (Wilson et al, 1983).

3.3.1.A.3 Pulse irregular

a) Incidence: 0.1% to 1% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)
b) Irregular pulse was reported in 0.1% to 1% of patients with major depressive disorder or obsessive-compulsive disorder who took immediate-release fluvoxamine maleate during premarketing clinical trials (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).
c) fluvoxamine maleate did not produce any significant changes in pulse rate in a study using single doses of 50, 75, and 100 mg administered to 17 healthy volunteers (Wilson et al, 1983).

3.3.1.A.4 Sudden cardiac death

a) In a large cohort study including 481,744 persons and 1487 cases of sudden cardiac death occurring in a community setting, the use of SSRIs was not associated with an increased risk of sudden cardiac death (rate ratio, 0.95; 95% CI, 0.42 to 2.15). In contrast, users of tricyclic antidepressants in doses of 100 mg or higher (amitriptyline or its equivalent) had a 41% increased rate of sudden cardiac death

(rate ratio, 1.41; 95% CI, 1.02 to 1.95) (Ray et al, 2004).

3.3.2 Dermatologic Effects

3.3.2.A Fluvoxamine Maleate

Alopecia

Rash

Stevens-Johnson syndrome

Sweating

Toxic epidermal necrolysis

3.3.2.A.1 Alopecia

a) Incidence: 0.1% to 1% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) Alopecia was reported in between 0.1% and 1% of patients with major depressive disorder or obsessive-compulsive disorder who took immediate-release fluvoxamine maleate during premarketing clinical trials (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

c) A case of patchy baldness was observed following 6 months of therapy with fluvoxamine. A 41-year-old male had taken the medication in varying dosages from 50 to 250 mg/day for treatment of obsessive-compulsive disorder. Three months following discontinuation of fluvoxamine, regrowth of fine white hair was noted over the alopecic patches (Parameshwar, 1996).

3.3.2.A.2 Rash

a) In a placebo-controlled study involving pediatric patients with obsessive-compulsive disorder, rash was reported in 5% or more of patients treated with immediate-release fluvoxamine maleate. This was at least twice the rate found in placebo-treated patients (Prod Info LUVOX(R) oral tablets, 2007).

3.3.2.A.3 Stevens-Johnson syndrome

a) Stevens-Johnson syndrome has been reported during postmarketing use of immediate-release fluvoxamine maleate, although a causal relationship has not been established (Prod Info LUVOX(R) oral tablets, 2007; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3.3.2.A.4 Sweating

a) Incidence: immediate-release, 7%; extended-release (social anxiety disorder), 6%; extended-release (obsessive-compulsive disorder), 7% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, sweating was reported in 7% of fluvoxamine maleate patients (n=892) compared with 3% of placebo patients (n=778) (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 6% of fluvoxamine maleate patients (n=279) reported sweating compared with 2% of placebo patients (n=276). For use in OCD treatment, 7% of fluvoxamine maleate patients (n=124) reported sweating compared with less than 1% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3.3.2.A.5 Toxic epidermal necrolysis

a) Toxic epidermal necrolysis has been reported during postmarketing use of immediate-release fluvoxamine maleate, although a causal relationship has not been established (Prod Info LUVOX(R) oral tablets, 2007; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

b) A case of severe toxic epidermal necrolysis (TEN) was reported in a 16-year-old girl following treatment with fluvoxamine. The patient had been treated with clomipramine 100 mg/day and clorazepate 50 mg/day, and metoclopramide had been given once. After one week of clomipramine, it was withdrawn and replaced by fluvoxamine 100 mg/day. Within 8 days of fluvoxamine, the patient developed a widespread bullous eruption with mucous membrane involvement. Two days later, she showed epidermal detachment of the trunk, face, and proximal limbs involving 30% of the body surface area. This rapidly progressed to include 60% of body surface area. Histological examination of the skin showed total necrosis of the epidermis typical of TEN. Extensive epidemiologic data ruled out other

drugs as causative agents. Fluvoxamine has been previously associated with a case of Stevens-Johnson syndrome (Wolkenstein et al, 1993).

3.3.3 Endocrine/Metabolic Effects

3.3.3.A Fluvoxamine Maleate

Excessive thirst

Galactorrhea

Hyperglycemia

Hyponatremia

Ineffective thermoregulation

Syndrome of inappropriate antidiuretic hormone secretion

Weight loss

3.3.3.A.1 Excessive thirst

a) There was a two-fold increase in the rate of thirst during studies of obsessive-compulsive disorder (OCD) treatment compared with studies of OCD and depression (Prod Info LUVOX(R) oral tablets, 2007).

b) Polydipsia occurred in 3 women after taking fluvoxamine 100 mg/day. One patient developed polydipsia on the second day of treatment. She was also taking levosulpiride and alprazolam. The symptoms disappeared on withdrawal of fluvoxamine but recurred when the drug was restarted 2 weeks later. The adverse effect disappeared when the drug was stopped 1 week later. Water ingestion also increased markedly in a 30-year-old woman with dysthymia and a 40-year-old woman with panic disorder and agoraphobia shortly after they started fluvoxamine treatment. Symptoms rapidly disappeared in these 2 women after the drug was discontinued (Benazzi & Mazzoli, 1993).

3.3.3.A.2 Galactorrhea

a) Galactorrhea and amenorrhea associated with fluvoxamine were reported in a 38-year-old woman with refractory bipolar affective disorder; this patient had been treated for over a decade with several psychotropic agents. The patient had been maintained for an undetermined length of time on loxapine 150 mg daily, oxazepam 30 mg three times daily, and zopiclone 7.5 mg at bedtime. Fluvoxamine was prescribed for depression, and the dose was titrated to 150 mg daily while the loxapine dosage was decreased to 75 mg daily. Six weeks after starting fluvoxamine, she complained of amenorrhea followed soon by galactorrhea. Thorough evaluation ruled out an underlying organic etiology; however, the serum prolactin level was 80 mcg/L (normal, 4 to 30 mcg/L). Galactorrhea resolved 3 weeks after stopping fluvoxamine, and menstruation resumed a week later. The temporal relationship between fluvoxamine and the onset of galactorrhea and amenorrhea suggests a possible etiologic role for fluvoxamine (Jeffries et al, 1992). The probable mechanism for SSRI-induced galactorrhea is an increase in serum prolactin. This may result from direct stimulation of postsynaptic serotonin receptors in the hypothalamus or presynaptic serotonin receptor mediated inhibition of dopamine release (Bronzo & Stahl, 1993).

3.3.3.A.3 Hyperglycemia

a) Incidence: less than 0.01% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) Hyperglycemia was reported in less than 0.1% of patients with major depressive disorder or obsessive-compulsive disorder who took immediate-release fluvoxamine maleate during premarketing clinical trials (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

c) A 60-year-old woman with well-controlled insulin-dependent diabetes developed hyperglycemia following fluvoxamine administration for the treatment of major depression. Five days following initiation of fluvoxamine (100 mg/day) therapy, the woman's blood glycemia began to increase significantly without change in diet or compliance. Glycemia increased from 120 mg/dL at baseline to 210 mg/dL at days 19 and 21. Hyperglycemia persisted for 9 days before the patient discontinued fluvoxamine and the blood glycemia returned to baseline level. Twenty-two days later, fluvoxamine therapy was reinitiated and glycemia increased to the same range as the initial episode. Fluvoxamine was again

stopped and glycemia returned to normal within 2 days (Oswald et al, 2003).

3.3.3.A.4 Hyponatremia

a) Hyponatremia (serum sodium less than 110 mmol/L) has occurred in patients receiving fluvoxamine maleate, possibly as a result of SIADH. Symptoms included headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness. Severe hyponatremia signs/symptoms have included hallucination, syncope, seizure, coma, respiratory arrest, and death. Patients at highest risk include the elderly, volume-depleted, or those taking diuretics. Consider drug discontinuation with symptomatic hyponatremia (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

b) Of the 63 case reports of fluoxetine-induced SIADH reported to the US Food and Drug Administration, the majority occurred in patients over 70 years of age. Based on published reports, the onset of the SIADH was between 3 days and 4 months after starting therapy. Symptoms included confusion, lethargy, dizziness, fatigue, anorexia, delirium, and abdominal pain. Abnormal laboratory findings consisted of a decreased serum osmolality (median 251 milliosmoles/liter (mOsm/L); range 214 to 272 mOsm/L), decreased serum sodium concentration (median 118 mEq/L; range 98 to 130 milliequivalents/liter (mEq/L)), and urine osmolality (median 392.5 mOsm/L; 229 to 613 mOsm/L). In all but 1 case report, the SSRI was stopped, and fluid restriction was required before hyponatremia resolved; 1 patient was also treated with sodium chloride 3%. Patients in their fifties generally recovered in 2 to 4 days versus patients in their eighties who required up to 14 days for complete recovery. Of the 6 patients rechallenged with an SSRI, 3 developed a decrease in serum sodium consistent with SIADH, and 3 tolerated rechallenge without adverse events. In many case reports, inadequate reporting of symptoms, laboratory results, and exclusion of other causes were NOT included making it difficult to attribute SIADH to the SSRI (Woo & Smythe, 1997).

3.3.3.A.5 Ineffective thermoregulation

a) Three women developed diaphoresis, shivering, restlessness, anxiety, and subnormal body temperature, followed by low-grade fever, within 30 minutes of taking a first dose of fluvoxamine 25 mg in combination with a benzodiazepine (medazepam or ethyl loflazepate) in the evening. The women were being treated for either panic disorder or anxiety disorder, with associated depressive symptoms. Symptoms abated and disappeared by the next morning. One woman took a second dose and had the same experience. In all cases, symptoms did not reappear after discontinuation of fluvoxamine (Okada & Okajima, 2001).

3.3.3.A.6 Syndrome of inappropriate antidiuretic hormone secretion

a) SIADH with hyponatremia (serum sodium less than 110 mmol/L) has occurred in patients receiving fluvoxamine maleate. Symptoms included headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness. Severe hyponatremia signs/symptoms have included hallucination, syncope, seizure, coma, respiratory arrest, and death. Patients at highest risk include the elderly, volume-depleted, or those taking diuretics. Consider drug discontinuation with symptomatic hyponatremia (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

b) Of the 63 case reports of fluoxetine-induced SIADH reported to the US Food and Drug Administration, the majority occurred in patients over 70 years of age. Based on published reports, the onset of the SIADH was between 3 days and 4 months after starting therapy. Symptoms included confusion, lethargy, dizziness, fatigue, anorexia, delirium, and abdominal pain. Abnormal laboratory findings consisted of a decreased serum osmolality (median 251 milliosmoles/liter (mOsm/L); range 214 to 272 mOsm/L), decreased serum sodium concentration (median 118 mEq/L; range 98 to 130 milliequivalents/liter (mEq/L)), and urine osmolality (median 392.5 mOsm/L; 229 to 613 mOsm/L). In all but 1 case report, the SSRI was stopped, and fluid restriction was required before hyponatremia resolved; 1 patient was also treated with sodium chloride 3%. Patients in their fifties generally recovered in 2 to 4 days versus patients in their eighties who required up to 14 days for complete recovery. Of the 6 patients rechallenged with an SSRI, 3 developed a decrease in serum sodium consistent with SIADH, and 3 tolerated rechallenge without adverse events. In many case reports, inadequate reporting of symptoms, laboratory results, and exclusion of other causes were NOT included making it difficult to attribute SIADH to the SSRI (Woo & Smythe, 1997).

c) A patient treated with fluvoxamine developed SIADH, which presented as profound confusion. Drug withdrawal resulted in rapid resolution of the CNS and biochemical abnormalities (McHardy, 1993).

3.3.3.A.7 Weight loss

a) Incidence: immediate-release, at least 1%; extended-release (obsessive-compulsive disorder), 2% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) Weight loss was reported in at least 1% of patients with major depressive disorder or obsessive-compulsive disorder (OCD) who took immediate-release fluvoxamine maleate during premarketing clinical trials. There was a two-fold increase in the rate of weight loss in studies of OCD treatment compared with studies of OCD and depression (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term,

placebo-controlled trials of social anxiety disorder (SAD) and OCD. Weight loss was not reported during SAD treatment. For use in OCD treatment, 2% of fluvoxamine maleate patients (n=124) reported weight loss compared with less than 1% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
c) Decreased appetite and weight loss have occurred in children taking SSRIs, including fluvoxamine maleate. Regular monitoring of growth is recommended. Weight loss was more frequent in pediatric OCD patients (n=57) taking immediate-release fluvoxamine maleate than in patients taking placebo (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

3.3.4 Gastrointestinal Effects

3.3.4.A Fluvoxamine Maleate

Constipation

Diarrhea

Dysphagia

Flatulence

Gastrointestinal hemorrhage

Indigestion

Loss of appetite

Nausea

Taste sense altered

Vomiting

Xerostomia

3.3.4.A.1 Constipation
a) Incidence: immediate-release, 10%; extended-release (social anxiety disorder), 6%; extended-release (obsessive-compulsive disorder), 4% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)
b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, constipation was reported in 10% of fluvoxamine maleate patients (n=892) compared with 8% of placebo patients (n=778) (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 6% of fluvoxamine maleate patients (n=279) reported constipation compared with 5% of placebo patients (n=276). For use in OCD treatment, 4% of fluvoxamine maleate patients (n=124) reported constipation compared with less than 1% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
c) Constipation was reported by 18% of fluvoxamine-treated patients (n=222) from pooled data of 10 double-blind, placebo-controlled studies comparing fluvoxamine and imipramine. Constipation was reported by 20% and 7% of patients treated with imipramine and placebo, respectively (Benfield & Ward, 1986b).

3.3.4.A.2 Diarrhea
a) Incidence: immediate-release, 11%; extended-release (social anxiety disorder), 14%; extended-release (obsessive-compulsive disorder), 18% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)
b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, diarrhea was reported in 11% of fluvoxamine maleate patients (n=892) compared with 7% of placebo patients (n=778) (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day

extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 14% of fluvoxamine maleate patients (n=279) reported diarrhea compared with 5% of placebo patients (n=276). For use in OCD treatment, 18% of fluvoxamine maleate patients (n=124) reported diarrhea compared with 8% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3.3.4.A.3 Dysphagia

a) Incidence: immediate-release, 2% (Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, dysphagia was reported in 2% of fluvoxamine maleate patients (n=892) compared with 1% of placebo patients (n=778). There was a two-fold decrease in the rate of dysphagia in studies of OCD treatment compared with studies of OCD and depression (Prod Info LUVOX(R) oral tablets, 2007).

3.3.4.A.4 Flatulence

a) Incidence: immediate-release, at least 4% (Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, flatulence was reported in 4% of fluvoxamine maleate patients (n=892) compared with 3% of placebo patients (n=778) (Prod Info LUVOX(R) oral tablets, 2007).

c) In a placebo-controlled study involving pediatric patients with obsessive-compulsive disorder, flatulence was reported in 5% or more of patients treated with immediate-release fluvoxamine maleate. This was at least twice the rate found in placebo-treated patients (Prod Info LUVOX(R) oral tablets, 2007).

3.3.4.A.5 Gastrointestinal hemorrhage

See Drug Consult reference: CONCOMITANT USE OF SSRIs AND NSAIDs - INCREASED RISK OF GASTROINTESTINAL BLEEDING

3.3.4.A.6 Indigestion

a) Incidence: immediate-release, 10%; extended-release (social anxiety disorder), 10%; extended-release (obsessive-compulsive disorder), 8% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, dyspepsia was reported in 10% of fluvoxamine maleate patients (n=892) compared with 5% of placebo patients (n=778) (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 10% of fluvoxamine maleate patients (n=279) reported dyspepsia compared with 4% of placebo patients (n=276). For use in OCD treatment, 8% of fluvoxamine maleate patients (n=124) reported dyspepsia compared with 5% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3.3.4.A.7 Loss of appetite

a) Incidence: immediate-release, 6%; extended-release (social anxiety disorder), 14%; extended-release (obsessive-compulsive disorder), 13% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, anorexia was reported in 6% of fluvoxamine maleate patients (n=892) compared with 2% of placebo patients (n=778) (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 14% of fluvoxamine maleate patients (n=279) reported anorexia compared with 1% of placebo patients (n=276). For use in OCD treatment, 13% of fluvoxamine maleate patients (n=124) reported anorexia compared with 5% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

c) Anorexia was reported by 15% of patients receiving fluvoxamine, according to the pooled results of 10 placebo-controlled, double-blind studies comparing fluvoxamine and imipramine (Benfield & Ward, 1986b).

3.3.4.A.8 Nausea

a) Incidence: immediate-release, 40%; extended-release (social anxiety disorder), 39%; extended-release (obsessive-compulsive disorder), 34% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, nausea was reported in 40% of fluvoxamine maleate patients (n=892) compared with 14% of placebo patients (n=778). There was an approximate 25% decrease in the rate of nausea in studies of OCD

treatment compared with studies of OCD and depression (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 39% of fluvoxamine maleate patients (n=279) reported nausea compared with 11% of placebo patients (n=276). For use in OCD treatment, 34% of fluvoxamine maleate patients (n=124) reported nausea compared with 13% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

c) SSRIs produce nausea and vomiting in 20% to 25% and 2% to 3% of patients, respectively. In the majority of patients, nausea gradually decreases or resolves over approximately 3 weeks. However, in others, reduction of the dose or discontinuation of the drug is required. For this group, ondansetron or cisapride administered for a few weeks may facilitate continued treatment with the SSRI. Limited data suggest that ondansetron is more effective; however, it is also more expensive. Use of cisapride with careful monitoring for arrhythmias may be more cost effective and open therapy to a broader group of patients. The proposed mechanism for SSRI-induced nausea and vomiting is increased serotonin levels within the chemoreceptor trigger zone and area postrema in the brainstem, the primary areas within the brain associated with nausea and vomiting (McManis & Talley, 1997).

d) Approximately 12.7% of patients with depression receiving fluvoxamine reported nausea as an adverse effect during an open, large-scale study of over 5000 patients. Nausea was the stated reason for withdrawing from this study in 5.6% of all patients (Martin et al, 1987).

e) Event monitoring in Great Britain of fluvoxamine use in 10,401 patients revealed the most commonly reported individual event to be nausea and vomiting (13%) (Edwards et al, 1994).

3.3.4.A.9 Taste sense altered

a) Incidence: immediate-release, 3%; extended-release, 2% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, taste perversion was reported in 3% of fluvoxamine maleate patients (n=892) compared with 1% of placebo patients (n=778) (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 2% of fluvoxamine maleate patients (n=279) reported taste perversion compared with less than 1% of placebo patients (n=276). For use in OCD treatment, 2% of fluvoxamine maleate patients (n=124) reported taste perversion compared with less than 1% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3.3.4.A.10 Vomiting

a) Incidence: immediate-release, 5%; extended-release (social anxiety disorder), 0%; extended-release (obsessive-compulsive disorder), 6% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, vomiting was reported in 5% of fluvoxamine maleate patients (n=892) compared with 2% of placebo patients (n=778) (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. Vomiting did not occur during SAD treatment. For use in OCD treatment, 6% of fluvoxamine maleate patients (n=124) reported vomiting compared with 2% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

c) SSRIs produce nausea and vomiting in 20% to 25% and 2% to 3% of patients, respectively. In the majority of patients, nausea gradually decreases or resolves over approximately 3 weeks. However, in others, reduction of the dose or discontinuation of the drug is required. For this group, ondansetron or cisapride administered for a few weeks may facilitate continued treatment with the SSRI. Limited data suggest that ondansetron is more effective; however, it is also more expensive. Use of cisapride with careful monitoring for arrhythmias may be more cost effective and open therapy to a broader group of patients. The proposed mechanism for SSRI-induced nausea and vomiting is increased serotonin levels within the chemoreceptor trigger zone and area postrema in the brainstem, the primary areas within the brain associated with nausea and vomiting (McManis & Talley, 1997).

d) Vomiting was reported by 3.6% of patients and led to the discontinuation of therapy in 2.8% of all patients in a open, large-scale study of over 5000 patients with depression (Martin et al, 1987).

e) Event monitoring in Great Britain of fluvoxamine use in 10,401 patients revealed the most commonly reported individual event to be nausea and vomiting (13%) (Edwards et al, 1994).

3.3.4.A.11 Xerostomia

a) Incidence: immediate-release, 14%; extended-release (social anxiety disorder), 11%; extended-release (obsessive-compulsive disorder), 10% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression,

dry mouth was reported in 14% of fluvoxamine maleate patients (n=892) compared with 10% of placebo patients (n=778) (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 11% of fluvoxamine maleate patients (n=279) reported dry mouth compared with 8% of placebo patients (n=276). For use in OCD treatment, 10% of fluvoxamine maleate patients (n=124) reported dry mouth compared with 9% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
c) From pooled data of 10 double-blind, placebo-controlled studies comparing fluvoxamine and imipramine, dry mouth was experienced by 26% of the patients treated with fluvoxamine (n=222), which was significantly less than the incidence of 51% in patients who were receiving imipramine (n=221). Twenty-six percent of patients receiving placebo also complained of dry mouth (Benfield & Ward, 1986b).
d) During an open, large-scale study of over 5000 patients with depression, dry mouth was reported by 3.7% of patients but led to the discontinuation of therapy in only 0.8% of all patients (Martin et al, 1987).
e) Fluvoxamine failed to demonstrate any significant differences in salivary flow when compared to placebo. The study administered single doses of fluvoxamine 50, 75, and 100 mg to 17 healthy volunteers (Wilson et al, 1983).

3.3.5 Hematologic Effects

3.3.5.A Fluvoxamine Maleate

3.3.5.A.1 Bleeding, Abnormal

a) In case reports and epidemiological studies, drugs which interfere with serotonin reuptake (eg, SSRIs and serotonin-norepinephrine-reuptake inhibitors (SNRIs)) have been associated with an increased incidence of gastrointestinal bleeding. Bleeding events, including ecchymoses, hematomas, epistaxis, petechiae, gastrointestinal bleeding, and life-threatening hemorrhages have been reported with SSRI and SNRI use. Because the risk of bleeding may be increased by the concomitant use of drugs that affect coagulation (eg, NSAIDs, aspirin, warfarin), use caution when these agents are co-administered with fluvoxamine maleate. Additionally, patients receiving concurrent warfarin therapy should be monitored when fluvoxamine maleate is started or discontinued (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).
b) Epistaxis was more frequent in pediatric obsessive-compulsive disorder patients (n=57) taking immediate-release fluvoxamine maleate than in patients taking placebo (Prod Info LUVOX(R) oral tablets, 2007).
c) SSRIs reduce uptake of serotonin by platelets; therefore, reduction in granular storage of serotonin is observed. Serotonin-mediated platelet aggregation may be decreased. For minor bleeding diatheses (ie, bruising), treatment is usually unnecessary because it usually resolves with continued treatment. However, if bleeding is clinically significant, occurs with other underlying medical illnesses, or fails to improve with time, the drug should be discontinued. Many cases of bleeding have occurred in patients taking doses at the higher end of the dose range. Bleeding is more common in patients with underlying diseases; 1 case occurred in a patient with HIV (Berk & Jacobson, 1998).
d) A 33-year-old woman began taking paroxetine 40 mg daily for panic attacks and noted spontaneous bruising on her arms and legs and excessive menstrual bleeding within 2 weeks. No gynecologic or hematologic abnormalities were identified. Vitamin C added to paroxetine stopped bleeding in 3 weeks; discontinuation of vitamin C resulted in recurrent bleeding. Her medication was switched to fluvoxamine which also caused bleeding that resolved with vitamin C (Tielens, 1997).

3.3.6 Hepatic Effects

3.3.6.A Fluvoxamine Maleate

3.3.6.A.1 Liver function tests abnormal

a) Incidence: extended-release, 2% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008)
b) In 2 short-term, placebo-controlled clinical trials evaluating extended-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of social anxiety disorder, abnormal results of liver function tests were reported in 2% of fluvoxamine maleate patients (n=279) compared with less than 1% of placebo patients (n=276) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
c) A 57-year-old man experienced a 3-fold increase in gamma glutamyl transferase (GGT) of 176 international units/L over baseline (50 international units/L) after 3 weeks of fluvoxamine maleate 100 mg twice daily. An enlarged liver with evidence of fatty changes was observed on abdominal ultrasound and examination. GGT levels returned to near baseline levels 5 weeks after discontinuing therapy (Green, 1988).

3.3.7 Immunologic Effects

3.3.7.A Fluvoxamine Maleate

3.3.7.A.1 Stevens-Johnson syndrome

a) Stevens-Johnson syndrome has been reported during postmarketing use of immediate-release fluvoxamine maleate, although a causal relationship has not been established (Prod Info LUVOX(R) oral tablets, 2007; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3.3.8 Musculoskeletal Effects

3.3.8.A Fluvoxamine Maleate

Fracture of bone

Fracture of bone, Nonvertebral

Leg cramp

Myalgia

3.3.8.A.1 Fracture of bone

a) Incidence: less than 0.1% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) Pathological fracture was reported in less than 0.1% of patients with major depressive disorder or obsessive-compulsive disorder who took immediate-release fluvoxamine maleate during premarketing clinical trials (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

c) In a population-based, randomized, prospective cohort study adjusted for potential covariates, an increased risk of fragility fracture was reported at the 5-year follow-up in patients 50 years of age and older who used daily SSRIs (n=137; mean age of 65.1 years), including fluvoxamine, compared with those who did not use an SSRI (n=4871; mean age of 65.7 years). Daily SSRI use was associated with a significant 2.1-fold increased risk of fragility fracture (95% confidence interval (CI), 1.3 to 3.4). Daily SSRI users who were recurrent (ie, treated with SSRIs at baseline and at 5-year follow-up) had a significant 2.1-fold increased risk of fragility fracture (95% CI, 1.1 to 4.0). Fractures were reported at the following sites: forearm (40%), ankle and foot (21%), hip (13%), rib (13%), femur (9%), and back (4%). None were reported at the skull, toes, or fingers (Richards et al, 2007).

3.3.8.A.2 Fracture of bone, Nonvertebral

a) In a prospective, population-based, cohort study (n=7983) with a mean follow-up of 8.4 years, there was an increased risk of nonvertebral fracture in adult participants older than 55 years of age (mean age of 77.5 years) who were currently using an SSRI (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, or sertraline) compared to those who were not exposed to antidepressants. Current SSRI use was associated with an increased risk of nonvertebral fracture (adjusted hazard ratio (HR), 2.35; 95% confidence interval (CI), 1.32 to 4.18) compared with no antidepressant use. Current SSRI use was also associated with an increased risk of nonvertebral fracture (adjusted HR, 2.07; 95% CI, 1.23 to 3.5) compared with past antidepressant use (n=1217). In addition, duration of SSRI use showed a 9% increase in fracture risk per extra month on an SSRI (95% CI, 3% to 16%; p for trend=0.004). Fractures of the hip (most frequent), wrist, humerus, and pelvis were reported (Ziere et al, 2008).

3.3.8.A.3 Leg cramp

a) There was a two-fold increase in the rate of leg cramps in studies of obsessive-compulsive disorder (OCD) treatment compared with studies of OCD and depression (Prod Info LUVOX(R) oral tablets, 2007).

3.3.8.A.4 Myalgia

a) Incidence: extended-release (obsessive-compulsive disorder), 5% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008)

b) The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and obsessive-compulsive disorder (OCD). For use in OCD treatment, 5% of fluvoxamine maleate patients (n=124) reported myalgia compared with 2% of placebo patients (n=124). Myalgia was not reported during SAD treatment (Prod Info LUVOX(R) CR extended-release oral capsules, 2008). In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of OCD, myalgia was reported at a rate that was two-fold higher than the rate reported in OCD and depression trials (Prod Info LUVOX(R) oral tablets, 2007).

3.3.9 Neurologic Effects

Fluvoxamine

Fluvoxamine Maleate

3.3.9.A Fluvoxamine

3.3.9.A.1 Seizure

See Drug Consult reference: COMPARATIVE INCIDENCE OF SEIZURES FROM ANTIDEPRESSANTS

3.3.9.B Fluvoxamine Maleate

Asthenia

Dizziness

EEG abnormality

Extrapyramidal disease

Headache

Hyperactive behavior

Insomnia

Myoclonus

Seizure

Serotonin syndrome

Sleep disorder

Somnolence

Tremor

3.3.9.B.1 Asthenia

a) Incidence: immediate-release, 14%; extended-release (social anxiety disorder), 24%; extended-release (obsessive-compulsive disorder), 26% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, asthenia was reported in 14% of fluvoxamine maleate patients (n=892) compared with 6% of placebo patients (n=778). There was a two-fold increase in the rate of asthenia in studies of OCD treatment compared with studies of OCD and depression (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 24% of fluvoxamine maleate patients (n=279) reported asthenia compared with 10% of placebo patients (n=276). For use in OCD treatment, 26% of fluvoxamine maleate patients (n=124) reported asthenia compared with 8% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3.3.9.B.2 Dizziness

a) Incidence: immediate-release, 11%; extended-release (social anxiety disorder), 15%; extended-release (obsessive-compulsive disorder), 12% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate

(100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, dizziness was reported in 11% of fluvoxamine maleate patients (n=892) compared with 6% of placebo patients (n=778) (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 15% of fluvoxamine maleate patients (n=279) reported dizziness compared with 7% of placebo patients (n=276). For use in OCD treatment, 12% of fluvoxamine maleate patients (n=124) reported dizziness compared with 10% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

c) Event monitoring in Great Britain of fluvoxamine use in 10,401 patients revealed the most common category of adverse events to be neuropsychiatric. Dizziness was reported in 3.3% of patients (Edwards et al, 1994).

d) In an open study of more than 5000 patients with depression, dizziness was reported by 4.5% of patients (Martin et al, 1987).

e) Dizziness was reported in 14% of patients who received fluvoxamine (n=222) during 10 double-blind, placebo-controlled studies comparing fluvoxamine and imipramine in patients with depression (Benfield & Ward, 1986b).

3.3.9.B.3 EEG abnormality

a) EEG profiles of patients being treated with fluvoxamine showed concomitant increases of slow and fast activities and a decrease in alpha activity indicating sedative qualities. Single doses of fluvoxamine 75 mg were administered to 10 healthy volunteers. The EEG studies showed that fluvoxamine induced less augmentation of slow activity than imipramine, indicating fewer sedative properties with fluvoxamine (Saletu et al, 1983).

3.3.9.B.4 Extrapyramidal disease

a) Incidence: 0.1% to 1% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) Extrapyramidal syndrome was reported in 0.1% to 1% of patients with major depressive disorder or obsessive-compulsive disorder who took immediate-release fluvoxamine maleate during premarketing clinical trials (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

c) Dystonic reactions, parkinsonism, akathisia, and dyskinesias have been described, with the earliest onset noted at 5 days (Bronner & Vanneste, 1998) and latest onset at 4 months (Chong, 1995).

d) Extrapyramidal reactions (EPR) have been reported with 1 or more SSRIs. The majority of case reports involved fluoxetine; however, all of the SSRIs were implicated in at least 1 EPR. Duration of symptoms with treatment was usually a few days. Symptoms occurred weekly for the first 4 weeks of treatment and periodically thereafter. For most cases, treatment was limited to reducing the dose or stopping the SSRI (Caley, 1997; Gill et al, 1997).

e) In a limited number of case reports, propranolol and/or benzodiazepines were used to treat SSRI-induced akathisia; the dose of propranolol ranged from 40 to 90 mg daily (Gill et al, 1997).

f) In case reports, dystonic reactions responded to an unspecified dose of intramuscular trihexyphenidyl or diphenhydramine 50 mg (Gill et al, 1997; George & Trimble, 1993).

g) Possible mechanisms by which SSRIs cause extrapyramidal reactions (EPR) include: (1) central serotonergic activity which inhibits dopaminergic activity; and (2) concurrent use of an SSRI and antipsychotic may cause EPRs by a pharmacokinetic interaction, a pharmacodynamic interaction, or a combination of the two (Caley, 1997).

h) Three days after starting concomitant fluvoxamine and metoclopramide, a 14-year-old boy developed acute dystonia of the extensor muscles of the neck, back, and upper extremities; jaw rigidity; horizontal nystagmus; dysarthria; and uncontrolled movement of the tongue. He was treated with fluvoxamine 50 mg/day and metoclopramide 10 mg 3 times daily. Treatment with intramuscular biperiden 5 mg completely relieved symptoms within 30 minutes. Previous treatment with metoclopramide did NOT produce dystonia (Palop et al, 1999).

i) A 71-year-old woman developed involuntary movements of the head, neck, and extremities, especially the arms, 5 days after she began taking fluvoxamine 50 mg daily for depression. Upon examination in the emergency department, the movements occurred at rest and were NOT suppressible; they were described as dystonic contractures and myoclonic jerks. Treatment consisted of IV clonazepam 1 mg which resulted in improvement within 10 minutes; 2 hours later, myoclonus recurred and responded to oral clonazepam 2 mg. Fluvoxamine was stopped and myoclonus resolved. One week later, this woman was rechallenged with fluvoxamine 50 mg daily which resulted in a similar reaction 11 days later. The abnormal movements resolved after administering oral clonazepam 2 mg. After stopping fluvoxamine, the movements disappeared and did NOT recur during 6 months of follow-up. Of note, this woman was also taking diltiazem, which inhibits the cytochrome P450 enzyme 1A2 (the enzyme responsible for metabolizing fluvoxamine). This may have resulted in increased fluvoxamine bioavailability (Bronner & Vanneste, 1998).

j) About 4 months after starting fluvoxamine 100 mg daily, a 38-year-old woman complained of periauricular pain and headache which progressed to tightening of jaw muscles and teeth clenching over the next month. She also had difficulty chewing solid foods. Upon reduction of the fluvoxamine dose to 50 mg, her complaints lessened but did NOT completely resolve until she stopped fluvoxamine.

This patient did NOT have a history of previous psychiatric illnesses or dystonias (Chong, 1995).

3.3.9.B.5 Headache

a) Incidence: immediate-release, 22%; extended-release (social anxiety disorder), 35%; extended-release (obsessive-compulsive disorder), 32% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, headache was reported in 22% of fluvoxamine maleate patients (n=892) compared with 20% of placebo patients (n=778) (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 35% of fluvoxamine maleate patients (n=279) reported headache compared with 30% of placebo patients (n=276). For use in OCD treatment, 32% of fluvoxamine maleate patients (n=124) reported headache compared with 31% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

c) Event monitoring in Great Britain of fluvoxamine use in 10,401 patients revealed the most common category of adverse events to be neuropsychiatric. Headache was reported in 3.9% of patients (Edwards et al, 1994).

d) In an open study of more than 5000 patients with depression, headache was reported by 5% of patients, causing withdrawal from the study in 2.7% (Martin et al, 1987).

e) Headache was reported in 22% of patients who received fluvoxamine (n=222) during 10 double-blind, placebo-controlled studies comparing fluvoxamine and imipramine in patients with depression (Benfield & Ward, 1986b).

3.3.9.B.6 Hyperactive behavior

a) In a placebo-controlled study involving pediatric patients with obsessive-compulsive disorder, hyperkinesia was reported in 5% or more of patients treated with immediate-release fluvoxamine maleate. This was at least twice the rate found in placebo-treated patients (Prod Info LUVOX(R) oral tablets, 2007).

3.3.9.B.7 Insomnia

a) Incidence: immediate-release, 21%; extended-release (social anxiety disorder), 32%; extended-release (obsessive-compulsive disorder), 35% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, insomnia was reported in 21% of fluvoxamine maleate patients (n=892) compared with 10% of placebo patients (n=778) (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 32% of fluvoxamine maleate patients (n=279) reported insomnia compared with 13% of placebo patients (n=276). For use in OCD treatment, 35% of fluvoxamine maleate patients (n=124) reported insomnia compared with 20% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

c) Event monitoring in Great Britain of fluvoxamine use in 10,401 patients revealed the most common category of adverse events to be neuropsychiatric. Insomnia was reported in 2.4% of patients (Edwards et al, 1994).

d) Insomnia was reported in 15% of patients who received fluvoxamine (n=222) during 10 double-blind, placebo-controlled studies comparing fluvoxamine and imipramine in patients with depression (Benfield & Ward, 1986b).

3.3.9.B.8 Myoclonus

a) There was a two-fold increase in the rate of myoclonus/twitch in studies of obsessive-compulsive disorder (OCD) treatment compared with studies of OCD and depression. Myoclonus was reported in at least 1% and twitching was reported in 0.1% to 1% of patients with major depressive disorder or OCD who took immediate-release fluvoxamine maleate during premarketing clinical trials (Prod Info LUVOX (R) oral tablets, 2007). Twitching was reported in 2% of patients with OCD who were treated with fluvoxamine maleate extended-release 100 mg/day to 300 mg/day (n=124) compared with 0% of placebo-treated patients (n=124) during short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. Twitching was not reported in patients with SAD (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

b) A 71-year-old woman developed involuntary movements of the head, neck, and extremities, especially the arms, 5 days after she began taking fluvoxamine 50 mg daily for depression. Upon examination in the emergency department, the movements occurred at rest and were NOT suppressible; they were described as dystonic contractures and myoclonic jerks. Treatment consisted of IV clonazepam 1 mg which resulted in improvement within 10 minutes; 2 hours later, myoclonus recurred and responded to oral clonazepam 2 mg. Fluvoxamine was stopped and myoclonus resolved. One week later, this woman was rechallenged with fluvoxamine 50 mg daily which resulted in a similar reaction 11 days later. The abnormal movements resolved after administering oral clonazepam 2 mg.

After stopping fluvoxamine, the movements disappeared and did NOT recur during 6 months of follow-up. Of note, this woman was also taking diltiazem, which inhibits the cytochrome P450 enzyme 1A2 (the enzyme responsible for metabolizing fluvoxamine). This may have resulted in increased fluvoxamine bioavailability (Bronner & Vanneste, 1998).

3.3.9.B.9 Seizure

a) Incidence: 0.2% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX (R) oral tablets, 2007)

b) Seizures occurred in 0.2% of patients treated with immediate-release fluvoxamine maleate during premarketing trials. Cautious administration is recommended in patients with controlled epilepsy or a history of convulsions. Avoid treatment in unstable epilepsy. Discontinue fluvoxamine maleate if seizures occur or increase in frequency (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

c) A 49-year-old male who had been seizure-free for 10 years with anticonvulsant therapy experienced a generalized seizure 3 days after beginning fluvoxamine therapy, 150 mg at bedtime. Following an increase in dose of the anticonvulsant therapy, the patient did not experience any more seizures (Kim et al, 2000).

3.3.9.B.10 Serotonin syndrome

a) Serotonin syndrome, which may include mental status changes (eg, agitation, hallucination, and coma), autonomic instability (eg, tachycardia, hyperthermia, and labile blood pressure), neuromuscular aberrations, and gastrointestinal symptoms (eg, nausea, vomiting, and diarrhea), may occur with fluvoxamine maleate. This syndrome could be life-threatening. Risk is increased with concomitant use of SSRIs, serotonin norepinephrine reuptake inhibitors (SNRI), triptans, and MAOIs (contraindicated). If concomitant use with SSRIs, SNRIs, or a triptan is warranted, increased monitoring is advised (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

b) A serotonin syndrome has been described with administration of fluvoxamine. Symptoms include anxiety, coma, confusion, diaphoresis, disorientation, hyperreflexia, hypertension, hyperthermia, myoclonus, rigidity, seizures, and tremor. Incidence is rare (less than 0.1%). In severe cases, hospitalization has been required for treatment (Gill et al, 1999).

c) An 11-year-old boy developed serotonin syndrome (SS) 1 hour after receiving fluvoxamine 50 mg for attention deficit disorder. He was also receiving perphenazine and benztropine, which had been used for 2 years. Symptoms of SS included agitation, unresponsiveness to verbal or painful stimuli, fluctuating blood pressure and heart rate, jaw myoclonus, shivering, fever to 103.5 degrees Fahrenheit, and hyperreflexia with rigidity of the lower extremities. Initial treatment consisted of diazepam 10 mg and lorazepam 21 mg in incremental intravenous doses. Due to a rise in temperature, he was paralyzed with rocuronium 50 mg and intubated; sedation and pharmacologic paralysis were continued for 24 hours. Full recovery occurred 48 hours after hospitalization (Gill et al, 1999).

3.3.9.B.11 Sleep disorder

a) Incidence: 0.1% to 1% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) Sleep disorder was reported in 0.1% to 1% of patients with major depressive disorder or obsessive-compulsive disorder who took immediate-release fluvoxamine maleate during premarketing clinical trials (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

c) Fluvoxamine 100 to 150 mg tended to increase rapid eye movement (REM) sleep latency, increase stage 3 sleep, and shorten REM time in a placebo-controlled trial of healthy volunteers. The overall quality of sleep deteriorated, and subjects complained of feeling worse in the mornings (Benfield & Ward, 1986b).

3.3.9.B.12 Somnolence

a) Incidence: immediate-release, 22%; extended-release (social anxiety disorder), 26%; extended-release (obsessive-compulsive disorder), 27% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, somnolence was reported in 22% of fluvoxamine maleate patients (n=892) compared with 8% of placebo patients (n=778) (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 26% of fluvoxamine maleate patients (n=279) reported somnolence compared with 9% of placebo patients (n=276). For use in OCD treatment, 27% of fluvoxamine maleate patients (n=124) reported somnolence compared with 11% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

c) In an open study of more than 5000 patients with depression, somnolence was reported by 3.8% of patients (Martin et al, 1987).

d) Somnolence was reported in 26% of patients who received fluvoxamine (n=222) during 10 double-blind, placebo-controlled studies comparing fluvoxamine and imipramine in patients with depression

(Benfield & Ward, 1986b).

3.3.9.B.13 Tremor

a) Incidence: immediate-release, 5%; extended-release (social anxiety disorder), 8%; extended-release (obsessive-compulsive disorder), 6% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, tremor was reported in 5% of fluvoxamine maleate patients (n=892) compared with 1% of placebo patients (n=778) (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 8% of fluvoxamine maleate patients (n=279) reported tremor compared with less than 1% of placebo patients (n=276). For use in OCD treatment, 6% of fluvoxamine maleate patients (n=124) reported tremor compared with 0% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3.3.10 Ophthalmic Effects

3.3.10.A Fluvoxamine Maleate

Blurred vision

Raised intraocular pressure

3.3.10.A.1 Blurred vision

a) Incidence: immediate-release, 3%; extended-release (obsessive-compulsive disorder), 2%(Prod Info LUVOX(R) oral tablets, 2007; Prod Info LUVOX(R) CR extended-release oral capsules, 2008)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, amblyopia (mostly "blurred vision") was reported in 3% of fluvoxamine maleate patients (n=892) compared with 2% of placebo patients (n=778). There was a two-fold decrease in the rate of amblyopia (mostly "blurred vision") in studies of OCD treatment compared with studies of OCD and depression (Prod Info LUVOX(R) oral tablets, 2007). Amblyopia was reported in 2% of patients with OCD who were treated with fluvoxamine maleate (n=124) compared with less than 1% of placebo-treated patients (n=124) during short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. Amblyopia was not reported in patients with SAD (Prod Info LUVOX(R) oral tablets, 2007).

3.3.10.A.2 Raised intraocular pressure

a) Aggravation of glaucoma and mydriasis in one patient was attributed to fluvoxamine given to treat tension headache. A 66-year-old woman who was being treated with timolol 0.25% twice per day for narrow-angle glaucoma developed severe orbital pain and blurred vision 2 months after initiation of treatment with fluvoxamine 50 mg/day for tension headache and depression. The headache and mood disorder improved with fluvoxamine. However, she was found to have increased ocular pressure, mydriasis, and a closed angle. The eye problems were treated with intravenous glycerol 50%, acetazolamide 1.5 mg/kg, and pilocarpine 2% 4 applications/day for 1 day. The usual dose of timolol was continued. Intraocular pressure was reduced by the treatment but rose again after 3 days. Discontinuation of fluvoxamine resulted in normalization of intraocular pressure and resolution of orbital pain and blurred vision within 2 days (Jimenez-Jimenez et al, 2001).

3.3.12 Psychiatric Effects

3.3.12.A Fluvoxamine Maleate

Agitation

Anxiety

Depression, worsening

Feeling nervous

Frontal lobe syndrome

Hypomania

Mania

Psychiatric sign or symptom

Psychotic disorder

Suicidal thoughts

3.3.12.A.1 Agitation

a) Incidence: immediate-release, 2%; extended-release (social anxiety disorder), 3%; extended-release (obsessive-compulsive disorder), 2% (Prod Info LUVOX(R) oral tablets, 2007; Prod Info LUVOX(R) CR extended-release oral capsules, 2008)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, agitation was reported in 2% of fluvoxamine maleate patients (n=892) compared with 1% of placebo patients (n=778). There was a two-fold increase in the rate of agitation in studies of OCD treatment compared with studies of OCD and depression(Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 3% of fluvoxamine maleate patients (n=279) reported agitation compared with less than 1% of placebo patients (n=276). For use in OCD treatment, 2% of fluvoxamine maleate patients (n=124) reported agitation compared with less than 1% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

c) Severe agitation was reported in an 11-year-old boy following the ingestion of one therapeutic (50 mg) fluvoxamine tablet (Gill et al, 1999).

d) A 68-year-old male experienced severe agitation and restlessness within one week of beginning fluvoxamine therapy, 50 mg daily. The akathisia began to subside gradually following discontinuation of the fluvoxamine and administration of diazepam (Chong & Cheong, 1999).

e) Agitation was noted in 16% of patients taking fluvoxamine therapeutically (Benfield & Ward, 1986b).

3.3.12.A.2 Anxiety

a) Incidence: immediate-release, 5%; extended-release (social anxiety disorder), 8%; extended-release (obsessive-compulsive disorder), 6% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, anxiety was reported in 5% of fluvoxamine maleate patients (n=892) compared with 3% of placebo patients (n=778). There was a two-fold increase in the rate of anxiety in studies of OCD treatment compared with studies of OCD and depression(Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 8% of fluvoxamine maleate patients (n=279) reported anxiety compared with 5% of placebo patients (n=276). For use in OCD treatment, 6% of fluvoxamine maleate patients (n=124) reported anxiety compared with 2% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

c) Event monitoring in Great Britain of fluvoxamine use in 10,401 patients revealed the most common category of adverse events to be neuropsychiatric. Anxiety was reported in 2.6% of patients (Edwards et al, 1994).

3.3.12.A.3 Depression, worsening

a) Adult and pediatric patients being treated with antidepressants for major depressive disorder who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, or mania may be at risk of suicidal ideation and behavior (suicidality). This same concern applies to patients being treated for other psychiatric and nonpsychiatric disorders. If these symptoms are observed, therapy should be re-evaluated, and it may be necessary to discontinue medications when symptoms are severe, sudden in onset, or were not part of the patient's initial symptoms. The dose should be tapered off, avoiding abrupt discontinuation whenever possible. Patients and their caregivers should be provided with the Medication Guide that is available for this drug (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007; Anon, 2004).

3.3.12.A.4 Feeling nervous

a) Incidence: immediate-release, 12%; extended-release (social anxiety disorder), 10% (Prod Info

LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)
b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, nervousness was reported in 12% of fluvoxamine maleate patients (n=892) compared with 5% of placebo patients (n=778) (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 10% of fluvoxamine maleate patients (n=279) reported nervousness compared with 9% of placebo patients (n=276). Nervousness was not reported as an adverse effect in OCD treatment (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3.3.12.A.5 Frontal lobe syndrome
a) A patient developed a frontal lobe syndrome (apathy, indifference) while taking moderate doses of fluvoxamine 150 mg/day and sulpiride, a dopamine (D-2) antagonist, at 400 mg/day. It was theorized that serotonergic agents may cause this syndrome via reduction of frontal blood flow and that dopamine-blocking agents may modulate this effect (George & Trimble, 1992).
b) Apathy, indifference, loss of initiative, and disinhibition were reported in association with fluvoxamine treatment of 2 patients with panic disorder. The effects appeared to be dose-related and disappeared rapidly when the dose of fluvoxamine, which has a short elimination half-life, was reduced. Patients' behavior seemed to resemble that of people with frontal lobe dysfunction (Hoehn-Saric et al, 1990).

3.3.12.A.6 Hypomania
a) Incidence: 1% (Prod Info LUVOX(R) oral tablets, 2007; Prod Info LUVOX(R) CR extended-release oral capsules, 2008)
b) Mania or hypomania was reported in 1% of patients with primarily depression who took fluvoxamine maleate during premarketing clinical trials (Prod Info LUVOX(R) oral tablets, 2007; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
c) During an 8-week, placebo-controlled study of fluvoxamine for obsessive-compulsive disorder (OCD), 5 of 20 patients became manic (2) or hypomanic (3). This is inconsistent with prior experience with other serotonin re-uptake inhibitors. The rate of hypomania associated with fluvoxamine when treating major depression is 0.4%, that for clomipramine when treating OCD is 0.4%, and that for fluoxetine in the treatment of depression is 0.98%. The high percentage (25%) in this study may reflect the presence of bipolar type II patients in the sample as these patients show a greater frequency of cycling (Jefferson et al, 1991).

3.3.12.A.7 Mania
a) Incidence: 1% to 4% (Prod Info LUVOX(R) oral tablets, 2007; Prod Info LUVOX(R) CR extended-release oral capsules, 2008)
b) Mania or hypomania was reported in 1% of patients with primarily depression who took fluvoxamine maleate during premarketing clinical trials. Manic reactions were reported in 4% of pediatric patients with obsessive-compulsive disorder who were given fluvoxamine maleate (n=57) during a ten-week study, compared with no manic reactions in patients who received placebo (n=63). Caution is advised when fluvoxamine maleate is used in patients with a history of mania (Prod Info LUVOX(R) oral tablets, 2007; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
c) Mania occurred in 3 patients who were treated with a combination of fluvoxamine and lithium. Dosage of fluvoxamine was 100 to 200 mg/day and lithium levels were low, ie, 0.5, 0.55, 0.6 mmol/L. This may represent a "switch" from depression into mania induced by fluvoxamine (Burrai et al, 1991c).
d) During an 8-week, placebo-controlled study of fluvoxamine for obsessive-compulsive disorder (OCD), 5 of 20 patients became manic (2) or hypomanic (3). This is inconsistent with prior experience with other serotonin re-uptake inhibitors. The rate of hypomania associated with fluvoxamine when treating major depression is 0.4%, that for clomipramine when treating OCD is 0.4%, and that for fluoxetine in the treatment of depression is 0.98%. The high percentage (25%) in this study may reflect the presence of bipolar type II patients in the sample as these patients show a greater frequency of cycling (Jefferson et al, 1991).

3.3.12.A.8 Psychiatric sign or symptom
a) Behavioral and mood changes (such as motor activation, impulsivity, aggression, and dysphoria) were observed in 5 patients treated with fluvoxamine (200 to 300 mg/day) for obsessive-compulsive disorders. The authors recommended reduction, but not discontinuation, of fluvoxamine, with addition of carbamazepine (Diaferia et al, 1994).

3.3.12.A.9 Psychotic disorder
a) Incidence: at least 1% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)
b) Psychotic reaction was reported in at least 1% of patients with major depressive disorder or obsessive-compulsive disorder who took immediate-release fluvoxamine maleate during premarketing clinical trials (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

c) Acute exacerbation of schizophrenic symptoms (hallucinations, attacks of anger) occurred in a 53-year-old woman with chronic schizophrenia since age 30 when fluvoxamine 150 mg/day was added to her treatment program for depression. After discontinuation of fluvoxamine and increase of perphenazine (from 16 to 32 mg/day), the patient was free of psychotic symptoms (Rocco & De Leo, 1992).
d) A 17-year-old male with mild mental retardation experienced an acute psychotic reaction resulting in hospitalization for 6 days following a single dose of fluvoxamine 50 mg for depression and anxiety symptoms. The subject experienced agitation, insomnia, auditory and visual hallucinations, fearful mood, paranoid delusions, and episodes of catatonia within 24 hours of taking fluvoxamine. Forty-eight hours after the fluvoxamine dose the subject was hospitalized with an unremarkable physical examination, negative drug screen, and normal laboratories. He was treated with haloperidol 2 mg, lorazepam 1 mg, and chlorpromazine 50 mg. Psychotic symptoms improved within 72 hours of admission and after an additional 72 hours of observation, the subject was discharged on no medication. Medical history was negative for past psychotic presentations and substance abuse history (Sim & Massabki, 2000).

3.3.12.A.10 Suicidal thoughts

a) Adult and pediatric patients being treated with antidepressants for major depressive disorder who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, or mania may be at risk of suicidal ideation and behavior (suicidality). This same concern applies to patients being treated for other psychiatric and nonpsychiatric disorders. If these symptoms are observed, therapy should be re-evaluated, and it may be necessary to discontinue medications when symptoms are severe, sudden in onset, or were not part of the patient's initial symptoms. The dose should be tapered off, avoiding abrupt discontinuation whenever possible. Patients and their caregivers should be provided with the Medication Guide that is available for this drug (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007; Anon, 2004; Anon, 2004).
b) A causal role for antidepressants in inducing suicidality has been established in children, adolescents, and young adults (up to 24 years old). Anyone considering the use of antidepressants in a child, adolescent, or young adult must balance this risk with the clinical need. Families and caregivers should be encouraged to observe the patient carefully for emerging symptoms and unexpected behavior. This causal role in children and adolescents was determined from pooled analyses of 24 short-term, placebo-controlled trials of 9 antidepressants (SSRIs and others) which included over 4400 patients with major depressive disorder, obsessive-compulsive disorder (OCD), or other psychiatric disorders. The causal role in adults was determined from pooled analyses of 295 short-term, placebo-controlled trials of 11 antidepressants which included over 77,000 patients with major depressive disorder or other psychiatric disorders. The risk of suicidal thinking and behavior was increased in children, adolescents, and young adults up to 24 years old. This increased risk did not exist in adults over 24 years old, and the risk was lower in adults over 65 years old. The risk was highest in patients with major depressive disorder, but there were signs of risk emerging from trials in other psychiatric indications, such as OCD and social anxiety disorder. No suicides occurred in the pediatric trials. The risk of suicidality during longer-term use (ie, beyond several months) is not known (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007; Anon, 2004).

3.3.13 Renal Effects

3.3.13.A Fluvoxamine Maleate

3.3.13.A.1 Urinary retention

a) Incidence: immediate-release, 1% (Prod Info LUVOX(R) oral tablets, 2007)
b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, urinary retention was reported in 1% of fluvoxamine maleate patients (n=892) compared with 0% of placebo patients (n=778). There was a two-fold increase in the rate of urinary retention in studies of OCD treatment compared with studies of OCD and depression (Prod Info LUVOX(R) oral tablets, 2007).

3.3.14 Reproductive Effects

Fluvoxamine

Fluvoxamine Maleate

3.3.14.A Fluvoxamine

3.3.14.A.1 Sexual dysfunction

See Drug Consult reference: DRUG-INDUCED SEXUAL DYSFUNCTION
See Drug Consult reference: SELECTIVE SEROTONIN REUPTAKE INHIBITOR-INDUCED SEXUAL DYSFUNCTION

3.3.14.B Fluvoxamine Maleate

Abnormal ejaculation

Amenorrhea

Dysmenorrhea

Impotence

Increased libido

Orgasm incapacity

Priapism

Reduced libido

Sexual dysfunction

3.3.14.B.1 Abnormal ejaculation

a) Incidence: immediate-release, 8%; extended-release (social anxiety disorder), 11%; extended-release (obsessive-compulsive disorder), 10% (Prod Info LUVOX(R) oral tablets, 2007; Prod Info LUVOX(R) CR extended-release oral capsules, 2008)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, abnormal ejaculation (mostly delayed ejaculation) was reported in 8% of male fluvoxamine maleate patients compared with 1% of placebo patients. There was a two-fold increase in the rate of abnormal ejaculation (mostly delayed ejaculation) in studies of OCD treatment compared with studies of OCD and depression(Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 11% of male fluvoxamine maleate patients reported abnormal ejaculation compared with 2% of placebo patients (n=276). For use in OCD treatment, 10% of male fluvoxamine maleate patients reported abnormal ejaculation compared with 0% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

c) Cyproheptadine, 1 mg per 25 mg of fluvoxamine taken 2 hours prior to intercourse was effective in reversing ejaculatory failure secondary to fluvoxamine in a 63-year-old man with recurrent unipolar depression. Eventually, 150 mg fluvoxamine per day was effective in controlling the patient's affective symptoms and 6 mg of cyproheptadine was effective in preventing ejaculatory failure (Arnatt & Nutt, 1994).

3.3.14.B.2 Amenorrhea

a) Amenorrhea has been listed in postmarketing reports of immediate-release fluvoxamine maleate use, although a causal relationship has not been established (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

b) Galactorrhea and amenorrhea associated with fluvoxamine were reported in a 38-year-old woman with refractory bipolar affective disorder; this patient had been treated for over a decade with several psychotropic agents. The patient had been maintained for an undetermined length of time on loxapine 150 mg daily, oxazepam 30 mg three times daily, and zopiclone 7.5 mg at bedtime. Fluvoxamine was prescribed for depression, and the dose was titrated to 150 mg daily while the loxapine dosage was decreased to 75 mg daily. Six weeks after starting fluvoxamine, she complained of amenorrhea followed soon by galactorrhea. Thorough evaluation ruled out an underlying organic etiology; however, the serum prolactin level was 80 mcg/L (normal, 4 to 30 mcg/L). Galactorrhea resolved 3 weeks after stopping fluvoxamine, and menstruation resumed a week later. The temporal relationship between fluvoxamine and the onset of galactorrhea and amenorrhea suggests a possible etiologic role for fluvoxamine (Jeffries et al, 1992).

3.3.14.B.3 Dysmenorrhea

a) In a placebo-controlled study involving pediatric patients with obsessive-compulsive disorder, dysmenorrhea was reported in 5% or more of patients treated with immediate-release fluvoxamine maleate. This was at least twice the rate found in placebo-treated patients (Prod Info LUVOX(R) oral tablets, 2007).

3.3.14.B.4 Impotence

a) Incidence: immediate-release, 2% (Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, impotence was reported in 2% of male fluvoxamine maleate patients compared with 1% of male placebo patients. There was a two-fold increase in the rate of impotence in studies of OCD treatment compared with studies of OCD and depression (Prod Info LUVOX(R) oral tablets, 2007). Impotence was reported in 2% of males treated with extended-release fluvoxamine maleate (n=403) compared with 3% of males treated with placebo (n=400) in trials of social anxiety disorder and OCD treatment (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3.3.14.B.5 Increased libido

a) A 65-year-old female experienced increased sexual desire after 1 week of treatment with fluvoxamine 25 mg twice daily, medazepam 5 mg twice daily, and flunitrazepam 2 mg once daily for the treatment of depression and insomnia. Her depressive symptoms dramatically improved; however, sexual desire increased daily over the second week of therapy. Fluvoxamine was discontinued and treatment with sulpiride 100 mg twice daily, amoxapine 10 mg twice daily, medazepam 5 mg twice daily, and flunitrazepam 2 mg once daily were initiated. Symptoms of increased sexual desire disappeared and did not recur. The subject's past sexual history included cessation of her sexual relationship with her husband for 10 years prior to this event (Okada & Ikajima, 2000).

3.3.14.B.6 Orgasm incapacity

a) Incidence: immediate-release, 2%; extended-release, 5% (Prod Info LUVOX(R) oral tablets, 2007; Prod Info LUVOX(R) CR extended-release oral capsules, 2008)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, anorgasmia was reported in 2% of fluvoxamine maleate patients (n=892) compared with 0% of placebo patients (n=778). There was a two-fold increase in the rate of anorgasmia (in males) in studies of OCD treatment compared with studies of OCD and depression(Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 5% of fluvoxamine maleate patients (n=279) reported anorgasmia compared with 1% of placebo patients (n=276). For use in OCD treatment, 5% of fluvoxamine maleate patients (n=124) reported anorgasmia compared with 0% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

c) A 22-year-old woman who had been taking fluvoxamine for 2 months experienced anorgasmia which was unresponsive to treatment with cyproheptadine 8 and 12 mg; therefore, a reduction in fluvoxamine dosage was tried. Decreasing the weekend dose to 150 or 200 mg did NOT result in normal sexual function; a reduction in dose to fluvoxamine 200 mg daily resulted in a return of obsessive symptoms. In this patient, a partial drug holiday resulted in normal sexual function (Nemeth et al, 1996).

3.3.14.B.7 Priapism

a) Incidence: immediate release, 2% (Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, priapism was reported in 2% of fluvoxamine maleate patients (n=892) compared with 1% of placebo patients (n=778) (Prod Info LUVOX(R) oral tablets, 2007).

3.3.14.B.8 Reduced libido

a) Incidence: immediate-release, 2%; extended-release (social anxiety disorder), 6%; extended-release (obsessive-compulsive disorder), 6% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, decreased libido was reported in 2% of fluvoxamine maleate patients (n=892) compared with 1% of placebo patients (n=778). There was a two-fold increase in the rate of decreased libido in studies of OCD treatment compared with studies of OCD and depression(Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 6% of fluvoxamine maleate patients (n=279) reported decreased libido (8% in males and 4% in females) compared with 4% of placebo patients (n=276) (6% in males and 3% in females). For use in OCD treatment, 6% of fluvoxamine maleate patients (n=124) reported decreased libido (10% in males

and 4% in females) compared with 2% of placebo patients (n=124) (5% in males and 1% in females) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3.3.14.B.9 Sexual dysfunction

a) Incidence: extended-release (social anxiety disorder), 2% (males), 3% (females); extended-release (obsessive-compulsive disorder), 4% (males)(Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007)

b) The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 3% of fluvoxamine maleate patients (n=279) reported abnormal sexual function (2% in males and 3% in females) compared with less than 1% of placebo patients (n=276) (1% in males). For use in OCD treatment, 4% of male fluvoxamine maleate patients reported abnormal sexual function compared with 3% of male placebo patients. The incidence was 0% in females (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

c) Of 20 healthy volunteers enrolled in a phenotyping study using fluvoxamine, 7 (35%) reported sexual dysfunction after 4 weeks of fluvoxamine treatment. Fluvoxamine 100 mg daily on Friday and Saturday followed by 300 mg daily Sunday through Thursday resulted in normal sexual function with adequate control of depression and obsessive-compulsive symptoms. In humans, it is postulated that serotonin has an inhibitory effect on sexual function by direct effects on the central, spinal, or peripheral receptors (Nafziger et al, 1999).

3.3.15 Respiratory Effects

3.3.15.A Fluvoxamine Maleate

Pharyngitis

Rhinitis

Upper respiratory infection

Yawning

3.3.15.A.1 Pharyngitis

a) Incidence: extended-release (obsessive-compulsive disorder), 6% (Prod Info LUVOX(R) CR extended-release oral capsules, 2008)

b) The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and obsessive-compulsive disorder (OCD). For use in OCD treatment, 6% of fluvoxamine maleate patients (n=124) reported pharyngitis compared with less than 1% of placebo patients (n=124). For use in SAD treatment, the incidence was less than or equal to placebo (Prod Info LUVOX(R) CR extended-release oral capsules, 2008). In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of OCD, pharyngitis was reported at a rate that was two-fold higher than the rate reported in OCD and depression trials (Prod Info LUVOX(R) oral tablets, 2007).

3.3.15.A.2 Rhinitis

a) Incidence: immediate-release (obsessive-compulsive disorder), at least 5% (Prod Info LUVOX(R) oral tablets, 2007)

b) In 2 short-term, placebo-controlled studies involving patients with obsessive-compulsive disorder, rhinitis was reported in 5% or more of patients treated with immediate-release fluvoxamine maleate. This was at least twice the rate found in placebo-treated patients, and there was a two-fold increase in the rate of rhinitis in studies of OCD treatment compared with studies of OCD and depression(Prod Info LUVOX(R) oral tablets, 2007).

3.3.15.A.3 Upper respiratory infection

a) Incidence: immediate-release, 9% (Prod Info LUVOX(R) oral tablets, 2007)

b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, upper respiratory infection was reported in 9% of fluvoxamine maleate patients (n=892) compared with 5% of placebo patients (n=778) (Prod Info LUVOX(R) oral tablets, 2007).

3.3.15.A.4 Yawning

a) Incidence: immediate-release, 2%; extended-release (social anxiety disorder), 5%; extended-release (obsessive-compulsive disorder), 2% (Prod Info LUVOX(R) oral tablets, 2007; Prod Info LUVOX(R) CR

extended-release oral capsules, 2008)
b) In short-term, placebo-controlled clinical trials evaluating immediate-release fluvoxamine maleate (100 mg/day to 300 mg/day) for the treatment of obsessive-compulsive disorder (OCD) or depression, yawning was reported in 2% of fluvoxamine maleate patients (n=892) compared with 0% of placebo patients (n=778) (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in SAD treatment, 5% of fluvoxamine maleate patients (n=279) reported yawning compared with less than 1% of placebo patients (n=276). For use in OCD treatment, 2% of fluvoxamine maleate patients (n=124) reported yawning compared with 0% of placebo patients (n=124) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3.3.16 Other

Fluvoxamine

Fluvoxamine Maleate

3.3.16.A Fluvoxamine

3.3.16.A.1 Drug withdrawal
See Drug Consult reference: WITHDRAWAL SYNDROME OF SELECTIVE SEROTONIN REUPTAKE INHIBITORS

3.3.16.B Fluvoxamine Maleate

Accidental injury

Neuroleptic malignant syndrome

Withdrawal sign or symptom

3.3.16.B.1 Accidental injury
a) Incidence: immediate-release, at least 1%; extended-release (obsessive-compulsive disorder), 5% (Prod Info LUVOX(R) oral tablets, 2007; Prod Info LUVOX(R) CR extended-release oral capsules, 2008)
b) Accidental injury was reported in at least 1% of patients with major depressive disorder or obsessive-compulsive disorder (OCD) who took immediate-release fluvoxamine maleate during premarketing clinical trials (Prod Info LUVOX(R) oral tablets, 2007). The use of 100 mg/day to 300 mg/day extended-release fluvoxamine maleate has been evaluated in short-term, placebo-controlled trials of social anxiety disorder (SAD) and OCD. For use in OCD treatment, 5% of fluvoxamine maleate patients (n=124) reported accidental injury compared with 3% of placebo patients (n=124). For use in SAD treatment, the incidence was less than or equal to placebo (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3.3.16.B.2 Neuroleptic malignant syndrome
a) Incidence: rare (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX (R) oral tablets, 2007)
b) While most reports of neuroleptic malignant syndrome (NMS) involved concomitant administration of fluvoxamine maleate and an antipsychotic drug, a small number of NMS cases have been associated with the administration of fluvoxamine maleate alone. Symptoms included hyperthermia, muscle rigidity, autonomic instability, changes in vital signs, and mental status changes (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).
c) Neuroleptic malignant syndrome has been described, with the earliest onset noted at 5 days (Bronner & Vanneste, 1998), and latest onset at 4 months (Chong, 1995). Duration of symptoms with treatment is usually a few days (Caley, 1997; Gill et al, 1997).

3.3.16.B.3 Withdrawal sign or symptom
a) Withdrawal symptoms including dysphoric mood, irritability, agitation, dizziness, sensory disturbances (eg, paresthesias, including electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania have occurred when immediate-release fluvoxamine maleate was discontinued, primarily if discontinuation is abrupt. These events may be serious, although they are usually self-limiting. A gradual reduction in dose is recommended and, if intolerable symptoms develop, a temporary resumption of therapy with the prescribed dose may be

warranted, followed by a more gradual reduction (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

b) On the fourth day following the abrupt discontinuation of fluvoxamine (200 mg/day), a 12-year-old boy experienced nausea, poor concentration, lightheadedness, fatigue, headache, gait instability, and insomnia. Fluvoxamine was restarted at the same dose and the patient's discontinuation symptoms resolved within 2 days. A second 12-year-old boy developed discontinuation symptoms of headache, poor concentration, irritability, dizziness, fatigue, and shock-like sensation in the brain 5 days after stopping fluvoxamine 200 mg/day. Reinstitution of fluvoxamine at the former dose resulted in resolution of withdrawal symptoms in 3 days (Diler & Avci, 2002).

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 LUVOX(R) oral tablets, 2008) (All Trimesters)

a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

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) Although human and animal studies of fluvoxamine use during pregnancy did not reveal substantial teratogenicity (Kulin et al, 1998), nonteratogenic effects (pulmonary hypertension of the newborn (PPHN) and clinical findings consistent with serotonin syndrome) and increased special or intensive unit care of the infant were demonstrated following maternal use of fluvoxamine during the third trimester of pregnancy (Prod Info LUVOX(R) oral tablets, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Malm et al, 2005). A study of prospectively collected data suggests antenatal use of selective serotonin-reuptake inhibitor (SSRI) antidepressants is associated with QTc interval prolongation in exposed neonates (Dubnov-Raz et al, 2008). One study revealed that women who discontinued antidepressant medication during pregnancy had a greater likelihood of relapse compared with those who continued antidepressant therapy throughout the pregnancy (Prod Info LUVOX(R) oral tablets, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Therefore, when deciding whether to treat a pregnant woman with fluvoxamine during the third trimester, evaluate the potential risk to the fetus and the potential benefit to the mother. Consider tapering the fluvoxamine dose during the third trimester of pregnancy (Prod Info LUVOX (R) oral tablets, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

5) Literature Reports

a) A study of prospectively collected data suggests antenatal use of selective serotonin-reuptake inhibitor (SSRI) antidepressants is associated with QTc interval prolongation in exposed neonates. Between January 2000 and December 2005, researchers compared 52 neonates exposed to SSRI antidepressants (paroxetine (n=25), citalopram (n=13), fluoxetine (n=12), fluvoxamine (n=1), and venlafaxine (n=1)) in the immediate antenatal period to 52 matched neonates with no exposure. Prolonged QTc is defined as an interval of greater than 460 milliseconds (msec) (the widely used upper limit cited by authorities in both pediatric cardiology and neonatology). A pediatric cardiologist blinded to drug exposure, interpreted all electrocardiograms (ECGs) using standard statistical analyses. ECG recordings revealed markedly prolonged mean QTc intervals in exposed neonates compared to unexposed neonates (mean; 409 +/- 42 msec versus 392 +/- 29 msec, p=0.02). The mean uncorrected QT interval was 7.5% longer among exposed neonates (mean; 280 +/- 31 msec versus 261 +/- 25 msec, p less than 0.001). Ten percent (n=5) of exposed neonates had a notable increase in QTc interval prolongation (greater than 460 msec) compared to none of the unexposed neonates. The longest QTc interval observed was 543 msec (Dubnov-Raz et al, 2008).

b) Neonates exposed to fluvoxamine and other SSRIs late in the third trimester have developed complications, including respiratory distress, seizures, vomiting, tremor, and irritability that were consistent with either SSRI toxicity or a possible drug discontinuation syndrome. In some cases, clinical findings were consistent with serotonin syndrome (Prod Info LUVOX(R) oral tablets, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

c) In a case control study of women who delivered infants with pulmonary hypertension of the newborn (PPHN; n=377) and women who delivered healthy infants (n=836), the risk for developing PPHN was approximately six-fold higher in infants exposed to SSRIs after week 20 of gestation compared with infants not exposed to SSRIs during gestation. This study demonstrates a potential increased risk of PPHN, associated with considerable neonatal morbidity and mortality, in infants exposed to SSRIs later in the pregnancy. In the general population, PPHN occurs in 1 to 2 per 1000 live births (Prod Info LUVOX(R) oral tablets, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

d) In a prospective longitudinal study of 201 women with a history of major depression and no signs of depression at the beginning of pregnancy, there was a greater likelihood of relapse of major depression in those who discontinued antidepressant drugs during pregnancy compared with those who continued antidepressant drugs throughout the pregnancy (Prod Info LUVOX(R) oral tablets, 2008; Prod Info LUVOX

(R) CR extended-release oral capsules, 2008).

e) A population-based study of 1782 pregnant women exposed to SSRIs found no increased risk of adverse perinatal outcome except for treatment in the neonatal intensive or special care unit, particularly with third trimester exposure. Using 1996-2001 data derived from a government project involving 4 birth or medication registries in Finland, women who had at least one purchase (a 3-month supply) of an SSRI during the period of one month before pregnancy and the day pregnancy ended were compared with 1782 controls with no reimbursed drug purchases during the same peripartum period. The mean age of both cohorts was 30 years (+/- 7). There were more than twice as many smokers and six times as many pregnancies induced by artificial reproductive techniques in the SSRI group compared to controls (p less than 0.001), and mean length of gestation and birth weight were lower (p less than 0.001) in the SSRI group. Malformations, however, were not more common in the SSRI group (p = 0.4). Purchases of SSRIs (citalopram, fluoxetine, paroxetine, sertraline and fluvoxamine) were more common in the first trimester than later in pregnancy, with 65 women purchasing fluvoxamine during the first trimester, 23 during the second trimester, 27 during the third, and 10 throughout pregnancy. When compared with first trimester exposure, treatment in a special or intensive care unit was more common for the infants exposed during the third trimester (11.2% and 15.7%, respectively; p = 0.009). Even after adjusting for confounding variables, this difference remained statistically significant (OR 1.6; 95% CI 1.1-2.2) (Malm et al, 2005).

f) In a cohort study (n=267), the pregnancy outcome did not differ between women treated with sertraline (n=147), paroxetine (n=97), or fluvoxamine (n=26) versus controls. Rates of major malformations, stillbirth, and spontaneous and elective abortions were similar between the 2 groups as were the mean birth rate and gestational age. Nine major malformations were detected in infants exposed to a selective serotonin reuptake inhibitor (SSRI) and in control infants. Of the 49 women who were treated throughout pregnancy with an SSRI, there were also no differences in outcome compared to women treated only during the first trimester. The majority of women took sertraline 50 mg/day, paroxetine 30 mg/day, and fluvoxamine 50 mg/day (Kulin et al, 1998).

g) Treatment with fluvoxamine 200 mg/day and quetiapine 400 mg/day in a 33-year-old woman during her second pregnancy resulted in an uneventful pregnancy and the birth of a healthy female infant. The patient was being treated with fluvoxamine and quetiapine when she was diagnosed with a severe postpartum psychotic depression after the birth of her first child; multiple attempts at reducing her medication led to relapse. After being informed of the risks-benefits of fluvoxamine/quetiapine exposure during pregnancy, the patient decided to go forward with a second pregnancy while maintaining her drug regimen of fluvoxamine and quetiapine with the addition of folate 5 mg/day throughout the pregnancy. The patient gained 9 kg with no symptoms of psychiatric instability. Routine biochemical tests were within the normal range and 5 echographic reports found no fetal abnormalities. The presence of an intrauterine myoma led to an elective caesarean-section. A healthy female infant weighing 2600 g and measuring 49 cm in length was delivered, with Apgar scores of 9 and 10 at 1 minute and 5 minutes, respectively (Gentile, 2006).

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) The American Academy of Pediatrics considers antidepressants to be drugs worthy of concern in the nursing infant, particularly during long-term use (Anon, 2001). The long-term effects of exposure to SSRIs via breast milk on the cognitive development of the infant have not been determined. Although fluvoxamine appeared in the breast milk of two nursing mothers, the drug was not observed in the plasma of either infant and both developed normally with no adverse effects (Kristensen et al, 2002). Similarly, in a case report of a nursing woman being treated with fluvoxamine/quetiapine, the nursing infant received breast milk supplemented with formula for 3 months and showed no developmental abnormalities (Gentile, 2006). Because fluvoxamine is secreted in human breast milk and there is potential for serious adverse effects in the nursing infant, a decision should be made whether to discontinue the drug or discontinue nursing, taking into consideration the potential risk to the fetus as well as the potential benefit to the mother (Prod Info LUVOX(R) oral tablets, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Kristensen et al, 2002).

4) Literature Reports

a) Treatment with fluvoxamine 200 mg/day and quetiapine 400 mg/day in a 33-year-old woman during her second pregnancy resulted in an uneventful pregnancy and the birth of a healthy female infant weighing 2600 g and measuring 49 cm in length with Apgar scores of 9 and 10 at 1 minute and 5 minutes, respectively. The patient chose to breast-feed; however, formula was required to supplement her breast milk due to insufficient milk production. In the 3 months that the infant received breast milk supplemented with formula, no adverse effects were detected and the infant continues to develop normally (Gentile, 2006).

b) In a study of 2 mother-infant pairs, there were no adverse effects from fluvoxamine found in either nursing infant. The infants were 26 months and 0.75 months of age at the time of the study, which involved collecting venous blood samples and breast milk over a 24 hour dosing interval. Assuming a milk intake for both infants of 0.15 L/kg/day, the infant dose calculated as a percentage of the weight-adjusted maternal dose were 1.38% (26 month old infant) and 0.8% (0.75 month old infant). The milk to plasma ratios were

1.34 and 1.21, respectively. Fluvoxamine was not detected in the plasma of either infant. The 26-month-old infant had a Denver developmental assessment with a quotient of 115, indicating that the infant achieved the anticipated milestones. The 0.75-month-old infant was too young to have a meaningful Denver assessment, so a detailed pediatric examination was performed and found no abnormalities. Both mothers reported that the health and progress of their infants was satisfactory (Kristensen et al, 2002).

5) Drug Levels in Breastmilk
- **a)** Fluvoxamine Maleate
  - **1)** Parent Drug
    - **a)** Percent Adult Dose in Breastmilk
      - **1)** In a study of 2 mother-infant pairs, the infant dose calculated as a percentage of the weight adjusted maternal dose were 0.8% (0.75 month old infant) and 1.38% (26 month old infant). These values assume an average milk intake of 0.15 liters/kilogram (L/kg) per day (Kristensen et al, 2002).
    - **b)** Milk to Maternal Plasma Ratio
      - **1)** In a study of 2 mother-infant pairs, the milk to maternal plasma ratio were 1.21 (0.75 month old infant) and 1.34 (26 month old infant) (Kristensen et al, 2002).
    - **c)** Time to Peak Concentration in Milk
      - **1)** In a study of 2 mother-infant pairs, the time after dose at which maximum fluvoxamine concentrations were achieved in breast milk were 2.1 hours (0.75 month old infant) and 4.2 hours (26 month old infant) (Kristensen et al, 2002).

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Food Combinations

Drug-Tobacco Combinations

3.5.1 Drug-Drug Combinations

Abciximab

Aceclofenac

Acemetacin

Acenocoumarol

Alclofenac

Almotriptan

Alosetron

Alprazolam

Amitriptyline

Anagrelide

Ancrod

Anisindione

Antithrombin III Human

Ardeparin

Aspirin

Astemizole

Bendamustine

Benoxaprofen

Bivalirudin

Bromfenac

Bufexamac

Bupropion

Cannabis

Carbamazepine

Carprofen

Celecoxib

Certoparin

Cilostazol

Cisapride

Clomipramine

Clonixin

Clopidogrel

Clopidogrel

Clorgyline

Clozapine

Cyclosporine

Dalteparin

Danaparoid

Defibrotide

Dehydroepiandrosterone

Dermatan Sulfate

Desipramine

Desirudin

Desvenlafaxine

Dexfenfluramine

Dexketoprofen

Diazepam

Diclofenac

Dicumarol

Diflunisal

Dihydroergotamine

Diltiazem

Dipyridamole

Dipyrone

Droperidol

Droxicam

Duloxetine

Eletriptan

Eltrombopag

Enoxaparin

Epoprostenol

Eptifibatide

Ergoloid Mesylates

Ergonovine

Ergotamine

Estazolam

Etodolac

Etofenamate

Etoricoxib

Felbinac

Fenbufen

Fenfluramine

Fenoprofen

Fentiazac

Floctafenine

Flufenamic Acid

Flurbiprofen

Fondaparinux

Fosphenytoin

Frovatriptan

Furazolidone

Galantamine

Ginkgo

Glimepiride

Guarana

Haloperidol

Heparin

Hydroxytryptophan

Ibuprofen

Iloprost

Imipramine

Indomethacin

Indoprofen

Iproniazid

Isocarboxazid

Isoxicam

Ketoprofen

Ketorolac

Lamifiban

Levomethadyl

Lexipafant

Linezolid

Lithium

Lornoxicam

Maprotiline

Mate

Meclofenamate

Mefenamic Acid

Melatonin

Meloxicam

Methadone

Methylergonovine

Methylphenidate

Metoprolol

Mexiletine

Midazolam

Milnacipran

Mirtazapine

Moclobemide

Morniflumate

Nabumetone

Nadroparin

Naproxen

Naratriptan

Nialamide

Niflumic Acid

Nimesulide

Olanzapine

Oxaprozin

Oxycodone

Parecoxib

Pargyline

Parnaparin

Pentosan Polysulfate Sodium

Phenelzine

Phenindione

Phenprocoumon

Phenylbutazone

Phenytoin

Pirazolac

Piroxicam

Pirprofen

Procarbazine

Propranolol

Propyphenazone

Proquazone

Ramelteon

Rasagiline

Reviparin

Rizatriptan

Rofecoxib

Ropivacaine

Selegiline

Sibrafiban

Sibutramine

St John's Wort

Sulfinpyrazone

Sulindac

Sulodexide

Sumatriptan

Suprofen

Tacrine

Tapentadol

Tenidap

Tenoxicam

Terfenadine

Theophylline

Thioridazine

Tiaprofenic Acid

Ticlopidine

Tinzaparin

Tirofiban

Tizanidine

Tolmetin

Toloxatone

Tramadol

Tranylcypromine

Triazolam

Tryptophan

Valdecoxib

Warfarin

Xemilofiban

Zolmitriptan

Zomepirac

3.5.1.A Abciximab

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.B Aceclofenac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.C Acemetacin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate

an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.D Acenocoumarol

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.E Alclofenac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.F Almotriptan

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Concomitant use of almotriptan and selective serotonin reuptake inhibitors (SSRI's) has been reported to cause weakness, hyperreflexia, and incoordination (Prod Info Axert(TM), 2001). Concurrent use of a triptan and an SSRI may result in serotonin syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndrome with patients who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administration, 2006).
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of a triptan, such as almotriptan, and an SSRI may result in a life-threatening condition called serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) Concomitant administration of fluoxetine and almotriptan is well tolerated and fluoxetine has only a modest effect on almotriptan maximum plasma concentration (Cmax). Other almotriptan pharmacokinetics are not significantly affected. A randomized, open-label, two-way crossover study involving 14 healthy volunteers has been conducted. Subjects received each of the following treatments with a minimum 3-week washout between periods: (1) three 20 mg fluoxetine capsules on day 1 to 8 and one dose almotriptan 12.5 mg on day 8, (2) one dose of almotriptan 12.5 mg on day 8 with no treatment on days 1 through 7. Peak almotriptan concentrations were 18% higher following concomitant administration of fluoxetine than after almotriptan administration alone. This difference was statistically significant (p equal 0.023). Mean almotriptan area under the concentration-time curve (AUC) and oral clearance were borderline statistically different between treatment groups. Mean half-life was not statistically different between the treatment groups. During fluoxetine coadministration, Tmax was shorter, suggesting that the absorption rate of almotriptan may have been increased by fluoxetine. The author concludes that based on the results of this study and the lack of effect of fluoxetine on almotriptan pharmacokinetics, almotriptan and fluoxetine can be safely used concomitantly in migraine management (Fleishaker et al, 2001).

3.5.1.G Alosetron

1) Interaction Effect: increased alosetron exposure and increased side effects
2) Summary: Fluvoxamine is a potent inhibitor of the CYP1A2-mediated metabolism of alosetron. In a pharmacokinetic study of 40 healthy female subjects, fluvoxamine increased mean alosetron AUC by 6-fold and prolonged alosetron half-life by 3-fold. Concomitant use of fluvoxamine and alosetron is contraindicated due to the increased risk of serious bowel side effects, including ischemic colitis (Prod Info LOTRONEX(R), 2005).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: established
6) Clinical Management: Concomitant use of alosetron and fluvoxamine is contraindicated. Monitor patient for bowel side effects including constipation, abdominal or gastrointestinal pain or discomfort, nausea,

abdominal distention, reflux and hemorrhoids. Watch for signs and symptoms of ischemic colitis including rectal bleeding, bloody diarrhea or new or worsening abdominal pain.
7) Probable Mechanism: inhibition by fluvoxamine of CYP1A2-mediated alosetron metabolism
8) Literature Reports
a) Fluvoxamine inhibits the CYP1A2-mediated metabolism of alosetron. In a pharmacokinetic study involving 40 healthy female subjects, participants received an escalating dose of fluvoxamine 50 to 200 mg daily for 16 days. On the final day, participants also received a single 1 mg dose of alosetron. The area under the concentration-time curve (AUC) and half-life of alosetron increased 6-fold and 3-fold, respectively (Prod Info LOTRONEX(R), 2005).

3.5.1.H Alprazolam
1) Interaction Effect: elevated plasma alprazolam levels and an increased risk of side effects (CNS depression)
2) Summary: Fluvoxamine coadministration (100 mg daily) with alprazolam 1 mg four times daily resulted in a 2-fold increase in alprazolam steady-state plasma concentrations, area under the concentration-time curve (AUC), maximum concentration (Cmax), and half-life. Elevated plasma levels of alprazolam were associated with impaired psychomotor performance and memory. This effect may be even more pronounced with higher fluvoxamine doses (300 mg daily) (Prod Info Luvox(R), 1997x).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If alprazolam is given to a patient already on fluvoxamine, the initial alprazolam dose should be reduced by 50% due to the possibility of significant alprazolam accumulation. Monitor for signs of alprazolam intoxication (eg, sedation, dizziness, ataxia, weakness, decreased cognition or motor performance) or consider switching to a benzodiazepine eliminated by glucuronidation (eg, lorazepam, oxazepam, temazepam).
7) Probable Mechanism: inhibition by fluvoxamine of cytochrome P4503A4-mediated alprazolam metabolism

3.5.1.I Amitriptyline
1) Interaction Effect: amitriptyline toxicity (dry mouth, urinary retention, sedation)
2) Summary: Coadministration of fluvoxamine and amitriptyline was found to significantly increase plasma levels of amitriptyline (Bertschy et al, 1991a). A bidirectional effect was suggested in which fluvoxamine increased amitriptyline concentrations (by interfering with N-demethylation) and amitriptyline increased fluvoxamine levels (Hartter et al, 1993a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients for signs of amitriptyline and fluvoxamine toxicity; lower doses of one or both agents may be required with concomitant therapy.
7) Probable Mechanism: decreased amitriptyline metabolism
8) Literature Reports
a) Fluvoxamine has been shown to significantly increase plasma levels of amitriptyline and clomipramine and to mildly increase levels of their metabolites nortriptyline and desmethylclomipramine, respectively. This may be due to competitive inhibition of oxidative metabolism in the liver (Bertschy et al, 1991).
b) Metabolism of tricyclic antidepressants coadministered with fluvoxamine was studied in eight depressed patients (one patient received amitriptyline) (Hartter et al, 1993). Fluvoxamine was found to interfere with N-demethylation of amitriptyline. The combination of fluvoxamine and amitriptyline led to increased plasma levels of amitriptyline and decreased concentrations of amitriptyline's N-demethylated metabolite, nortriptyline. In addition, plasma levels of fluvoxamine were increased.

3.5.1.J Anagrelide
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.K Ancrod

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
7) Probable Mechanism: unknown
8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.L Anisindione

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
3) Severity: major

4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.M Antithrombin III Human
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean

age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.N Ardeparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.O Aspirin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.P Astemizole

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Fluvoxamine should not be used in combination with astemizole. Fluvoxamine appears to be a potent inhibitor of the cytochrome P450IIIA4 isozyme, the enzyme primarily responsible for metabolizing astemizole. Inhibition of this enzyme may result in elevated astemizole concentrations; increased plasma concentrations of astemizole are associated with QT prolongation and torsades de pointes, which can be fatal (Prod Info Luvox(R), 1997j; Prod Info Hismanal(R), 1998).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of astemizole and fluvoxamine is contraindicated.

7) Probable Mechanism: inhibition by fluvoxamine of astemizole metabolism

3.5.1.Q Bendamustine

1) Interaction Effect: increased bendamustine levels and decreased levels of active minor metabolites of bendamustine

2) Summary: Alternative treatments should be considered when concomitant use of bendamustine with a CYP1A2 inhibitor is necessary. Based on in vitro data, bendamustine is primarily metabolized via CYP1A2 into 2 active minor metabolites (M3 and M4). However, the cytotoxic efficacy is primarily due to the parent compound as the active metabolites have very low plasma concentrations. Concomitant administration of a strong CYP1A2 inhibitor, such as fluvoxamine, may result in increased bendamustine concentrations and decreased concentrations of the metabolites (Prod Info TREANDA(R) IV injection, 2008). If used concomitantly, patients should be closely monitored for increased incidence of bendamustine adverse events (myelosuppression, infection, skin reactions) and doses should be adjusted appropriately.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Consider alternative treatment when concomitant use of bendamustine with a strong CYP1A2 inhibitor, such as fluvoxamine, is required. However, use caution if bendamustine and fluvoxamine are coadministered (Prod Info TREANDA(R) IV injection, 2008). Monitor the patient for increased bendamustine adverse events (myelosuppression, infection, skin reactions) and adjust doses as necessary.

7) Probable Mechanism: inhibition of the CYP1A2-mediated bendamustine metabolism

3.5.1.R Benoxaprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.S Bivalirudin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of

treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.T Bromfenac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.U Bufexamac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.V Bupropion

1) Interaction Effect: increased plasma levels of bupropion

2) Summary: In vitro studies suggest that fluvoxamine inhibits the hydroxylation of bupropion which may result in increased bupropion concentrations when the two agents are used concurrently. Use caution when bupropion and fluvoxamine are coadministered and monitor patients for excessive bupropion adverse effects (agitation, anxiety, insomnia, hallucinations) (Prod Info WELLBUTRIN(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of bupropion and fluvoxamine may cause elevated bupropion concentrations. Monitor patients for excessive bupropion adverse effects (agitation, anxiety, insomnia, hallucinations) when fluvoxamine is being administered concurrently (Prod Info WELLBUTRIN(R) oral tablets, 2008).
7) Probable Mechanism: inhibition of the hydroxylation of bupropion by fluvoxamine
8) Literature Reports
a) In vitro studies suggest that fluvoxamine inhibits the hydroxylation of bupropion. No clinical studies have been conducted to verify this finding (Prod Info WELLBUTRIN(R) oral tablets, 2008).

3.5.1.W Cannabis

1) Interaction Effect: manic symptoms
2) Summary: One case of mania following use of marijuana with fluoxetine therapy has been reported (Stoll et al, 1991a). Although an interaction is proposed, the authors also state the manic symptoms could have resulted from the fluoxetine or marijuana alone. Caution is advised for patients using marijuana and taking fluoxetine or other serotonin reuptake inhibitors.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Caution patients taking selective serotonin reuptake inhibitors to avoid concomitant use of marijuana.
7) Probable Mechanism: additive serotonergic stimulation
8) Literature Reports
a) A 21-year-old female presented with mania, agitation, and grandiose delusions following use of marijuana with fluoxetine therapy. She had been taking fluoxetine 20 mg daily for 4 weeks and reported smoking 2 "joints" during a 36-hour period. Over the next 24 hours, she developed increased energy, hypersexuality, pressured speech, and grandiose delusions. Lorazepam and perphenazine were given for agitation and excitement which gradually resolved over 4 days. She remained hospitalized for 36 days. Fluoxetine 20 mg every other day was reintroduced one week prior to discharge. One week after discharge, she discontinued fluoxetine due to insomnia and feeling "hyper". These symptoms resolved rapidly upon discontinuation of fluoxetine. Due to the rapid switch to mania after smoking marijuana with fluoxetine, the manic symptoms were associated with the concomitant use of fluoxetine and marijuana, though mania could have developed from either fluoxetine or marijuana alone (Stoll et al, 1991).

3.5.1.X Carbamazepine

1) Interaction Effect: carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizures, coma)
2) Summary: Several cases have been reported in which fluvoxamine appeared to cause increased carbamazepine levels and symptoms of carbamazepine toxicity (Martinelli et al, 1993; Fritze et al, 1991a). However, one study of eight epileptic patients found no such increase in carbamazepine levels with three weeks of concurrent use (Spina et al, 1993e).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Due to the potential to increase carbamazepine levels, patients should be monitored for evidence of carbamazepine toxicity when fluvoxamine is added to therapy. Carbamazepine levels should be considered when adding or discontinuing fluvoxamine, with dosage adjustments made as indicated.
7) Probable Mechanism: decreased carbamazepine metabolism
8) Literature Reports
a) The addition of fluvoxamine to a constant dosage of carbamazepine in three patients caused an increase in carbamazepine levels resulting in symptoms of toxicity (Fritze et al, 1991). The authors concluded that this resulted from inhibition of carbamazepine metabolism. However, (Spina et al, 1993d) found no increase in carbamazepine levels in eight epileptic patients who were given fluvoxamine 100 mg daily or fluoxetine 20 mg daily with carbamazepine for three weeks.

3.5.1.Y Carprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM),

2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.Z Celecoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.AA Certoparin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
7) Probable Mechanism: unknown
8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.AB Cilostazol

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.AC Cisapride

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Fluvoxamine should not be used in combination with cisapride. Although there is no direct experience with this combination, fluvoxamine appears to be a potent inhibitor of the cytochrome P450 3A4 isozyme, the enzyme primarily responsible for the metabolism of cisapride. Inhibition of this enzyme may result in elevated cisapride concentrations; increased plasma concentrations of cisapride are associated with QT prolongation and torsades de pointes, which can be fatal (Prod Info Luvox(R), 1997u).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of fluvoxamine and cisapride is contraindicated.

7) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated cisapride metabolism

3.5.1.AD Clomipramine

1) Interaction Effect: clomipramine toxicity (dry mouth, urinary retention, sedation)

2) Summary: Coadministration of fluvoxamine and clomipramine was found to significantly increase plasma levels of clomipramine (Bertschy et al, 1991c). A bidirectional effect was suggested in which fluvoxamine increased clomipramine concentrations (by interfering with N-demethylation) and clomipramine increased fluvoxamine levels (Hartter et al, 1993c).

3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients for signs of clomipramine and fluvoxamine toxicity; lower doses of one or both agents may be required with concomitant therapy.
7) Probable Mechanism: decreased clomipramine metabolism
8) Literature Reports
a) Fluvoxamine has been shown to significantly increase plasma levels of amitriptyline and clomipramine and to mildly increase levels of their metabolites nortriptyline and desmethylclomipramine, respectively. This may be due to competitive inhibition of oxidative metabolism in the liver (Bertschy et al, 1991b).
b) Metabolism of tricyclic antidepressants coadministered with fluvoxamine was studied in eight depressed patients (four patients received clomipramine). Fluvoxamine was found to interfere with N-demethylation and 8-hydroxylation of clomipramine. The combination of fluvoxamine and clomipramine led to increased plasma levels of clomipramine and decreased concentrations of clomipramine's N-demethylated metabolite, desmethylclomipramine. In addition, plasma levels of fluvoxamine were increased (Hartter et al, 1993b).

3.5.1.AE Clonixin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.AF Clopidogrel
1) Interaction Effect: reduction in clinical efficacy of clopidogrel
2) Summary: Clopidogrel is metabolized to its active metabolite by CYP2C19. Concomitant use of CYP2C19 inhibitors, such as fluvoxamine, would be expected to result in reduced levels of the active metabolite, and therefore a reduction the clinical efficacy of clopidogrel. Concomitant use of CYP2C19 inhibitors with clopidogrel is discouraged (Prod Info PLAVIX(R) oral tablet, 2009).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of clopidogrel and fluvoxamine is discouraged (Prod Info PLAVIX (R) oral tablet, 2009).
7) Probable Mechanism: inhibition of CYP2C19- mediated clopidogrel metabolism by fluvoxamine

3.5.1.AG Clopidogrel
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for

signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.AH Clorgyline
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with fluvoxamine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Luvox(R), 1997k; Lappin & Auchincloss, 1994e; Graber et al, 1994e; Suchowersky & de Vries, 1990e). Concomitant use is not recommended.
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of fluvoxamine and a MAO inhibitor should be avoided. Wait at least two weeks after discontinuing an MAO inhibitor before initiating therapy with fluvoxamine. Wait at least two weeks after discontinuing fluvoxamine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: serotonin reuptake inhibition
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991d). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement in symptoms after the second dose (Lappin & Auchincloss, 1994d).
c) A drug interaction occurred in a 61-year old woman whose regimen of sertraline 100 mg twice daily was added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least 5 half-lives of the parent drug and any active metabolites (Graber et al, 1994d).
d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990d). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.AI Clozapine
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), 2002; 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.AJ Cyclosporine

1) Interaction Effect: an increased risk of cyclosporine toxicity (renal dysfunction, cholestasis, paresthesias)

2) Summary: Fluvoxamine was reported to increase cyclosporine trough serum levels in a 62-year-old female. Fluvoxamine is an inhibitor of cytochrome P450 3A4 enzymes, which are required for cyclosporine metabolism (Vella & Sayegh, 1998a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Closely monitor cyclosporine serum concentrations when fluvoxamine therapy is initiated, altered, or discontinued.

7) Probable Mechanism: inhibition of cytochrome P450 3A4 enzymes by fluvoxamine decreases cyclosporine metabolism

8) Literature Reports

a) A 62-year-old female received a cadaveric renal allograft nine years prior to initiating fluvoxamine therapy for depression. Her baseline cyclosporine trough level ranged from 200 ng/mL to 250 ng/mL, and serum creatinine was 1.5 mg/dL. Medications included cyclosporine 300 mg daily, prednisone, atenolol, levothyroxine, bumetanide, rocaltrol, and omeprazole. Fluvoxamine 100 mg daily was started for symptoms of depression, and two weeks later the patient complained of shivering and exhibited a fine tremor. Cyclosporine trough level was 380 ng/mL and serum creatinine had increased to 1.9 mg/dL. Cyclosporine dosage was decreased to 200 mg daily, and both the cyclosporine trough level and serum creatinine returned to their baseline values (Vella & Sayegh, 1998).

3.5.1.AK Dalteparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis,

hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.AL Danaparoid

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued.

Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.AM Defibrotide

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4

and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.AN Dehydroepiandrosterone

1) Interaction Effect: development of manic symptoms

2) Summary: A case has been reported in which concomitant dehydroepiandrosterone (DHEA) and sertraline use was suggested to precipitate a manic episode in a patient with a history of bipolar disorder (Dean, 2000a). DHEA was also noted to cause mania in a patient with no previous personal or family history of bipolar disorder (Markowitz et al, 1999). Elevated DHEA levels have been found in patients with mental disorders; DHEA suppression has lead to improvement in psychotic symptoms (Howard, 1992). DHEA possesses proserotonergic activity which may predispose patients to manic episodes (Majewska, 1995). DHEA is a precursor to androgenic steroids, which in high doses may precipitate mania (Markowitz et al, 1999). Patients taking medication for bipolar disorder or patients with a personal and/or family history of bipolar disorder should not take DHEA until further data is available to characterize this drug-herb interaction. Concomitant use of DHEA with selective serotonin reuptake inhibitors (SSRIs) should be avoided due to the potential additive precipitation of mania.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and selective serotonin reuptake inhibitors. If patients present with manic symptoms (i.e. agitation, anger, irritability, aggressive behavior), determine if the patient is using DHEA and discontinue DHEA.

7) Probable Mechanism: serotonergic activity of dehydroepiandrosterone, possibly increased androgen levels

8) Literature Reports

a) A 31-year-old male was admitted following threats to commit suicide and injure family members. He had self-initiated sertraline 100 milligrams (mg) daily for the previous 2 to 3 weeks for depression. Sertraline had been prescribed 3 years prior when he was diagnosed with bipolar disorder, which he discontinued after 2 weeks. He had also taken dehydroepiandrosterone (DHEA) 300 mg to 500 mg daily for the previous 2 months apparently for weight training. Following use of DHEA for a short time, he became more irritable, was not sleeping well, and began threatening a female friend and family members. He also drank alcohol occasionally and reportedly had difficulty controlling his anger when intoxicated. Sertraline was stopped and the patient was treated with valproic acid with the dose titrated to 500 mg twice daily. The combination of DHEA, sertraline, and alcohol was suggested responsible for the developing of the manic episode (Dean, 2000).

3.5.1.AO Dermatan Sulfate

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and

prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.AP Desipramine
1) Interaction Effect: desipramine toxicity (dry mouth, urinary retention, sedation)
2) Summary: While an early report on fluvoxamine combined with desipramine or imipramine found increased TCA concentrations (Spina et al, 1992a), later studies by the same investigators reported that fluvoxamine caused no significant alterations in desipramine pharmacokinetics (Spina et al, 1993a; Spina et al, 1993aa).
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor patients for signs of desipramine and fluvoxamine toxicity; lower doses of one or both agents may be required with concomitant therapy.
7) Probable Mechanism: decreased desipramine metabolism
8) Literature Reports
a) The addition of fluvoxamine to imipramine or desipramine in four patients was reported to result in greatly increased tricyclic antidepressant plasma levels (Spina et al, 1992). Three of the four patients showed signs of tricyclic toxicity.
b) A controlled study in eight depressed patients found a slight, but insignificant, increase in desipramine concentrations, after 10 days, when fluvoxamine was added to desipramine therapy (Spina et al, 1993a).
c) A pharmacokinetic study in 12 healthy volunteers reviewed concurrent use of desipramine and fluvoxamine (Spina et al, 1993). No significant alterations in the pharmacokinetics of either drug were

found.

3.5.1.AQ Desirudin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.AR Desvenlafaxine

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

2) Summary: Concurrent use of desvenlafaxine and a selective serotonin reuptake inhibitor (SSRI) may result in serotonin syndrome, which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea (Prod Info PRISTIQ(TM) oral extended-release tablets, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical
6) Clinical Management: Coadministration of desvenlafaxine and an SSRI may result in a life-threatening condition called serotonin syndrome. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination), especially during treatment initiation and dose increases (Prod Info PRISTIQ(TM) oral extended-release tablets, 2008).
7) Probable Mechanism: additive serotonergic effect

3.5.1.AS Dexfenfluramine

1) Interaction Effect: serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Dexfenfluramine is a nonspecific serotonin agonist that both enhances the release of serotonin and inhibits serotonin reuptake. Combination therapy with dexfenfluramine and another selective serotonin reuptake inhibitor, such as fluvoxamine, has the potential to cause serotonin syndrome (Schenck & Mahowald, 1996a). Serotonin syndrome is a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Sternbach, 1991k). Dexfenfluramine should not be used in combination with fluvoxamine (Prod Info Redux(R), 1997).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of dexfenfluramine and fluvoxamine may result in an additive increase in serotonin levels in the central nervous system, and could result in serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes). Dexfenfluramine should not be used in combination with fluvoxamine or other serotonin specific reuptake inhibitors.
7) Probable Mechanism: additive serotonergic effects

3.5.1.AT Dexketoprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.AU Diazepam

1) Interaction Effect: diazepam and N-desmethyldiazepam accumulation
2) Summary: Coadministration of fluvoxamine 150 mg daily with a single oral dose of diazepam 10 mg resulted in a 65% decrease in clearance of diazepam. The clearance of diazepam's primary active metabolite, N-desmethyldiazepam, is reduced to immeasurable levels. This effect may be more pronounced with increasing doses of fluvoxamine (Prod Info Luvox(R), 1997g).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Diazepam and fluvoxamine should not be taken concurrently due to the possibility of significant diazepam accumulation. Consider switching to a benzodiazepine eliminated by glucuronidation (eg, lorazepam, oxazepam, temazepam) and monitor for signs of benzodiazepine intoxication (eg, sedation, dizziness, ataxia, weakness, decreased cognition or motor performance).
7) Probable Mechanism: reduced diazepam clearance

3.5.1.AV Diclofenac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.AW Dicumarol

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for

hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.AX Diflunisal

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.AY Dihydroergotamine

1) Interaction Effect: an increased risk of ergotism (nausea, vomiting, vasospastic ischemia)

2) Summary: Because of the potential for serious toxicity including vasospasm that can occur with increased plasma concentrations of ergot derivatives, the concurrent use of fluvoxamine and ergot derivatives is contraindicated. Fluvoxamine and ergot derivatives are both metabolized by cytochrome P450 3A4 enzymes, and the competition for metabolism could result in an increased plasma concentration of the ergot derivative (Prod Info Cafergot(R), 2002).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: The concurrent use of fluvoxamine and ergot derivatives is contraindicated.

7) Probable Mechanism: inhibition of cytochrome P450 3A4- mediated ergot metabolism by fluvoxamine

3.5.1.AZ Diltiazem

1) Interaction Effect: bradycardia

2) Summary: Fluvoxamine may inhibit the metabolism of diltiazem, causing elevated diltiazem levels and bradycardia (Prod Info Luvox(R), 1997s).

3) Severity: minor

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Monitor patients for appropriate cardiovascular response to calcium channel blockade, with dose titration as required to achieve desired effect.

7) Probable Mechanism: decreased diltiazem metabolism

3.5.1.BA Dipyridamole

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis,

hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.BB Dipyrone
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BC 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 antidepressants that prolong the QT interval (Prod Info Inapsine(R), 2002).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Droperidol should be administered with extreme caution in the presence of risk factors for development of prolonged QT syndrome, such as treatment with antidepressants.
7) Probable Mechanism: additive cardiac effects

3.5.1.BD Droxicam
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined

use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BE Duloxetine
1) Interaction Effect: increased duloxetine bioavailability and an increased risk of serotonin syndrome
2) Summary: Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) that is primarily metabolized by the CYP1A2 and CYP2D6 isozymes. The concomitant use of duloxetine with fluvoxamine, a SSRI, is not recommended due to the potential for serotonin syndrome. In addition, coadministration of fluvoxamine 100 mg (a CYP1A2 inhibitor) with duloxetine 40 mg twice a day in 14 CYP2D6 poor metabolizer subjects resulted in a 6-fold increase in duloxetine AUC and Cmax. Also, when 14 male patients were given duloxetine 60 mg together with fluvoxamine 100 mg, duloxetine AUC, Cmax, and half-life increased by 6-fold, about 2.5-fold, and 3-fold, respectively (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: established
6) Clinical Management: The concomitant use of duloxetine and fluvoxamine is not recommended due to the potential for development of serotonin syndrome. Additionally, concomitant use has resulted in significantly increased duloxetine exposure and serum levels (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: inhibition of CYP1A2-mediated duloxetine metabolism; additive serotonergic effects

3.5.1.BF Eletriptan
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concomitant use of sumatriptan, a 5-hydroxytryptamine-1 (5HT-1) agonist, and a serotonin specific reuptake inhibitor (SSRI) (Prod Info Imitrex(R) Nasal Spray, 2003). Because eletriptan is a 5HT 1B/1D agonist, a similar interaction between SSRIs and eletriptan may occur (Prod Info Relpax(R), 2003). Concurrent use of a triptan and an SSRI may result in serotonin syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndrome with patients who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administration, 2006).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as eletriptan, and an SSRI may result in a life-threatening condition called serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.BG Eltrombopag
1) Interaction Effect: increased eltrombopag plasma concentrations
2) Summary: Concomitant use of eltrombopag and fluvoxamine, a strong CYP1A2 inhibitor, may result in elevated eltrombopag plasma concentrations due to inhibition of CYP1A2-mediated eltrombopag metabolism. The patient should be monitored for excessive eltrombopag exposure when eltrombopag and fluvoxamine are coadministered (Prod Info PROMACTA(R) oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of eltrombopag and fluvoxamine, a strong CYP1A2 inhibitor, may result in elevated eltrombopag plasma concentrations. Monitor the patient for excessive eltrombopag exposure when eltrombopag and fluvoxamine are coadministered (Prod Info PROMACTA(R) oral tablets, 2008).
7) Probable Mechanism: inhibition of CYP1A2-mediated eltrombopag metabolism by fluvoxamine

3.5.1.BH Enoxaparin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control

and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.BI Epoprostenol

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.BJ Eptifibatide

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.BK Ergoloid Mesylates

1) Interaction Effect: an increased risk of ergotism (nausea, vomiting, vasospastic ischemia)
2) Summary: Because of the potential for serious toxicity including vasospasm that can occur with increased plasma concentrations of ergot derivatives, the concurrent use of fluvoxamine and ergot derivatives is contraindicated. Fluvoxamine and ergot derivatives are both metabolized by cytochrome P450 3A4 enzymes, and the competition for metabolism could result in an increased plasma concentration of the ergot derivative (Prod Info Cafergot(R), 2002).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The concurrent use of fluvoxamine and ergot derivatives is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A4- mediated ergot metabolism by fluvoxamine

3.5.1.BL Ergonovine

1) Interaction Effect: an increased risk of ergotism (nausea, vomiting, vasospastic ischemia)
2) Summary: Because of the potential for serious toxicity including vasospasm that can occur with increased plasma concentrations of ergot derivatives, the concurrent use of fluvoxamine and ergot derivatives is contraindicated. Fluvoxamine and ergot derivatives are both metabolized by cytochrome P450 3A4 enzymes, and the competition for metabolism could result in an increased plasma concentration of the ergot derivative (Prod Info Cafergot(R), 2002).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The concurrent use of fluvoxamine and ergot derivatives is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A4- mediated ergot metabolism by fluvoxamine

3.5.1.BM Ergotamine

1) Interaction Effect: an increased risk of ergotism (nausea, vomiting, vasospastic ischemia)
2) Summary: Because of the potential for serious toxicity including vasospasm that can occur with increased plasma concentrations of ergot derivatives, the concurrent use of fluvoxamine and ergot derivatives is contraindicated. Fluvoxamine and ergot derivatives are both metabolized by cytochrome P450 3A4 enzymes, and the competition for metabolism could result in an increased plasma concentration of the ergot derivative (Prod Info Cafergot(R), 2002).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The concurrent use of fluvoxamine and ergot derivatives is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A4- mediated ergot metabolism by fluvoxamine

3.5.1.BN Estazolam

1) Interaction Effect: increased estazolam plasma concentrations and risk of estazolam toxicity
2) Summary: Fluvoxamine is a inhibitor of CYP3A and estazolam metabolism is catalyzed by CYP3A, therefore fluvoxamine is expected to increase plasma estazolam concentration resulting in an increased risk of estazolam toxicity and associated adverse effects (Prod Info ProSom(TM), 2004).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Monitor for signs of benzodiazepine intoxication (eg, sedation, dizziness, ataxia, weakness, decreased cognition or motor performance). If symptoms are present, reduce estazolam dose or consider switching to a benzodiazepine eliminated by glucuronidation (eg, lorazepam, oxazepam, temazepam).
7) Probable Mechanism: fluvoxamine inhibition of P450-3A isoform-mediated estazolam metabolism

3.5.1.BO Etodolac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BP Etofenamate

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BQ Etoricoxib

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched

among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BR Felbinac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BS Fenbufen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BT Fenfluramine

1) Interaction Effect: serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Fenfluramine is a nonspecific serotonin agonist that both enhances the release of serotonin and inhibits serotonin reuptake. Combination therapy with fenfluramine and another selective serotonin reuptake inhibitor, such as fluvoxamine, has the potential to cause serotonin syndrome (Schenck & Mahowald, 1996). Serotonin syndrome is a hyperserotonergic state characterized by symptoms such as

restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Sternbach, 1991j). Until more data are available, fenfluramine should not be used in combination with fluvoxamine.
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of fenfluramine and fluvoxamine may result in an additive increase in serotonin levels in the central nervous system, and could result in serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes). Fenfluramine should not be used in combination with fluvoxamine or other serotonin specific reuptake inhibitors.
7) Probable Mechanism: additive serotonergic effects

3.5.1.BU Fenoprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BV Fentiazac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BW Floctafenine
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an

increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BX Flufenamic Acid
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BY Flurbiprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1

to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BZ Fondaparinux

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.CA Fosphenytoin

1) Interaction Effect: an increased risk of phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremors)

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). Fluvoxamine inhibits several of the isoenzymes of the cytochrome P450 enzyme system (oxidative metabolism); IA2, IIC9, and IIIA4. Since phenytoin is eliminated at least partially via the CYP450 IIC9 pathway, it is possible that coadministration

with fluvoxamine may cause elevations in phenytoin plasma levels (Prod Info Luvox(R), 1997t). During an in vitro study, the inhibitory effects of fluvoxamine on cytochrome P450 2C9 were evaluated using p-hydroxylation of phenytoin as an established index reaction reflecting CYP2C9 activity. In vivo, p-hydroxylation of phenytoin depends on the formation of 5-(p-hydroxy-phenyl)-5-phenylhydantoin (HPPH). Fluvoxamine, a strong inhibitor of HPPH, impaired the formation of HPPH, which can lead to an increase in steady-state phenytoin levels (Schmider et al, 1997a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Consideration should be given to monitoring of phenytoin serum levels when fluvoxamine is added or withdrawn from therapy and dosage adjustments made accordingly. Patients should be counseled to be aware of the potential side effects of phenytoin toxicity such as drowsiness, ataxia, and nystagmus, and to notify their physician if such side effects occur.
7) Probable Mechanism: decreased oxidative metabolism

3.5.1.CB Frovatriptan
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concomitant use of sumatriptan, a 5-hydroxytryptamine-1 (5HT-1) agonist, and a serotonin specific reuptake inhibitor (SSRI) (Prod Info Imitrex(R) Nasal Spray, 2003). Because frovatriptan is a 5HT 1B/1D agonist, a similar interaction between SSRIs and frovatriptan may occur (Prod Info Frova(R), 2004). Concurrent use of frovatriptan and an SSRI may result in serotonin syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndrome with patients who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administration, 2006).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as frovatriptan, and an SSRI may result in a life-threatening condition called serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.CC Furazolidone
1) Interaction Effect: weakness, hyperreflexia, and incoordination
2) Summary: Although not its primary mechanism of action, furazolidone has monoamine oxidase inhibitor activity. Cases of serious sometimes fatal reactions have been reported in patients receiving selective serotonin reuptake inhibitors (SSRI) in combination with monoamine oxidase inhibitors (MAOIs). Hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma have been reported. Furazolidone should not be used in combination with an SSRI, or within a minimum of 14 days of discontinuing therapy with a MAOI (Prod Info Furoxone(R), 1999).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If concurrent therapy with furazolidone and a selective serotonin reuptake inhibitor (SSRI) is deemed to be necessary, closely monitor the patient for signs of serotonergic excess (mental status changes, diaphoresis, fever, weakness, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.CD Galantamine
1) Interaction Effect: increased galantamine plasma concentrations
2) Summary: Based upon in vitro studies, the major enzymes involved in galantamine metabolism are CYP3A4 and CYP2D6. Fluvoxamine is a known inhibitor of CYP2D6. In a population pharmacokinetic analysis using a database of 852 Alzheimer's disease patients, several drugs which inhibit CYP2D6, including fluvoxamine (N=14), demonstrated a 25-33% decrease in galantamine clearance. The resulting plasma concentration increase of galantamine may warrant caution when it is coadministered with fluvoxamine. Monitor for galantamine toxicity including anorexia, nausea, vomiting, dizziness, arrhythmias or gastrointestinal bleeding (Prod Info RAZADYNE(R) ER extended release oral capsules, oral tablets, oral solution, 2007).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable

6) Clinical Management: Increased galantamine plasma concentrations may result from fluvoxamine inhibition of galantamine CYP2D6-mediated metabolism. Monitor for galantamine toxicity including anorexia, nausea, vomiting, dizziness, arrhythmias, or gastrointestinal bleeding (Prod Info RAZADYNE(R) ER extended release oral capsules, oral tablets, oral solution, 2007).
7) Probable Mechanism: inhibition of cytochrome CYP2D6-mediated galantamine metabolism

3.5.1.CE Ginkgo

1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: The addition of Ginkgo biloba and/or St. John's Wort to therapy with buspirone and fluoxetine may have precipitated a hypomanic episode in a case report (Spinella & Eaton, 2002a). It is unclear if Ginkgo or St. John's Wort, the combination of both, or other patient factors, contributed to the effect. Theoretically, Ginkgo may increase the risk of serotonin syndrome when taken with selective serotonin reuptake inhibitors (SSRIs). Caution is advised, especially when ginkgo is taken to counteract sexual dysfunction associated with SSRIs. Ginkgo may inhibit monoamine oxidase (Sloley et al, 2000; White et al, 1996), and has demonstrated serotonergic activity in animals (Ramassamy et al, 1992) which might increase the risk of serotonin syndrome when ginkgo is combined with SSRIs. The potential MAO inhibitory activity of ginkgo is questionable. A human study did not show MAO inhibition in the brain following oral consumption (Fowler et al, 2000). Ginkgo biloba extract inhibited MAO-A/MAO-B in the rat brain in vitro (Sloley et al, 2000; White et al, 1996) and MAO-B in human platelets in vitro (White et al, 1996). No significant MAO inhibition was found in mice following oral consumption (Porsolt et al, 2000).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients closely for symptoms of serotonin syndrome if ginkgo is combined with selective serotonin reuptake inhibitors (SSRIs).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) A 42-year-old female experienced symptoms consistent with a mixed hypomanic episode following concomitant use of fluoxetine, buspirone, Ginkgo biloba, and St. John's Wort. The symptoms resolved following discontinuation of Ginkgo and St. John's Wort. The patient was being treated for depression following a mild traumatic brain injury with fluoxetine 20 milligrams (mg) twice daily and buspirone 15 mg twice daily. Several weeks prior to presentation, buspirone was increased to 20 mg twice daily for persistent anxiety and the patient began taking Ginkgo biloba, melatonin, and St. John's Wort in unspecified doses. Melatonin was considered unlikely to have contributed to her symptoms. Ginkgo and St. John's Wort were considered possible contributors since they may potentiate antidepressants, and considering the temporal relationship between the use of the herbs and onset of symptoms and discontinuation of the herbs and resolution of symptoms. However, the brain injury was considered a possible contributor (Spinella & Eaton, 2002).

3.5.1.CF Glimepiride

1) Interaction Effect: an increase in plasma concentrations of glimepiride
2) Summary: Caution is advised when fluvoxamine is coadministered with glimepiride. An increase in plasma concentrations of glimepiride has been documented in healthy patients when used concomitantly with fluvoxamine without a significant effect on blood glucose concentrations (Niemi et al, 2001).
3) Severity: minor
4) Onset: rapid
5) Substantiation: established
6) Clinical Management: Use glimepiride and fluvoxamine concomitantly with caution or use therapeutic alternative. Monitor the patient for hypoglycemia if used concurrently.
7) Probable Mechanism: inhibition of the metabolism of glimepiride through the cytochrome P450 2C9 enzyme
8) Literature Reports
a) Plasma concentrations of glimepiride were moderately increased when used concomitantly with fluvoxamine. A double-blind, randomized, crossover study with three phases including a 4-week washout period between the phases was conducted in twelve healthy volunteers. The aim of the study is to investigate the effects of fluvoxamine on the pharmacokinetics and pharmacodynamics of glimepiride. Subjects received fluvoxamine 100 mg or placebo orally once daily for 4 days. On day 4, a single oral dose of 0.5 mg of glimepiride was administered after the patients fasted overnight. Meals were served 15 minutes after, 3 hours after, and 7 hours after glimepiride administration. For the fluvoxamine phase, the peak concentration (Cmax) was 143% (p less than 0.05) of the respective placebo value, and the half-life was increased from 2 to 2.3 hours (p less than 0.01). The increase in the area under the concentration-time curve (AUC) was not significant, and differences in blood glucose levels were not statistically significant (Niemi et al, 2001).

3.5.1.CG Guarana

1) Interaction Effect: symptoms of excessive caffeine (insomnia, headache, restlessness, nervousness, palpitations, and arrhythmias)

2) Summary: The primary pharmacologically-active ingredient of guarana is caffeine. Fluvoxamine inhibits CYP1A2 and CYP2D6 which are responsible for caffeine metabolism. Decreased caffeine clearance and increased half-life have been demonstrated in humans. Signs and symptoms of caffeine excess may result if the compounds are taken together. Patients should avoid guarana use during therapy with fluvoxamine in order to avoid complications (Jeppesen et al, 1996c).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Patients should be advised of the caffeine content of guarana, and of symptoms of excess if taken with fluvoxamine (insomnia, headache, restlessness, nervousness, palpitations, and arrhythmias) as well as symptoms of caffeine withdrawal which may accompany abrupt discontinuation of guarana (headache, fatigue, depression, anxiety, and insomnia). Patients should avoid guarana use during therapy with fluvoxamine in order to avoid complications.
7) Probable Mechanism: fluvoxamine may inhibit the metabolism of the caffeine content of guarana
8) Literature Reports
a) In an open, randomized, cross-over study of 8 volunteers, fluvoxamine significantly decreased caffeine total clearance and increased caffeine half-life. Fluvoxamine was administered as 50 milligrams (mg) for 4 days, then 100 mg for 8 days while subjects abstained from all caffeine intake. Caffeine 200 mg was then administered orally. Total clearance of caffeine decreased from 107 milliliters/minute (ml/min) to 21 ml/min, and half-life increased from 5 hours to 31 hours. Patients taking fluvoxamine should restrict caffeine intake (Jeppesen et al, 1996b).
b) In vitro, fluvoxamine was found to be a very potent inhibitor of the formation of N-demethylated caffeine metabolites with K1 values of 0.08 micromoles (mcmol) to 0.28 mcmol. The formation of 1,7-dimethylxanthine was abolished by 10 mcmol of fluvoxamine, implying the N3-demethylation of caffeine is almost entirely catalyzed by CYP1A2 (Rasmussen et al, 1998a).
c) At least 14 metabolites are formed from caffeine whose main route of elimination is N3-demethylation to paraxanthine (1,7-methylxanthine) which accounts for greater than 80% of caffeine elimination (Lelo et al, 1986a).
d) CYP1A2 is the major enzyme metabolizing caffeine to 1,7-dimethylxanthine (Berthou et al, 1991a; Sesardic et al, 1990a; Butler et al, 1989a). CYP1A2 is also a major enzyme in the formation of 3,7-dimethylxanthine and 1,3-dimethylxantihine from caffeine (Gu et al, 1992a; Berthou et al, 1991a; Grant et al, 1987a).

3.5.1.CH Haloperidol
1) Interaction Effect: an increased risk of haloperidol toxicity
2) Summary: Haloperidol serum concentrations were increased by the coadministration of fluvoxamine in a small double blind, randomized, placebo controlled, crossover study (Daniel et al, 1994a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Caution should be used when fluvoxamine is administered with haloperidol. Monitor serum concentrations of haloperidol and adjust the dose accordingly. Also monitor the patient for signs and symptoms of worsening clinical and cognitive assessments.
7) Probable Mechanism: inhibition of cytochrome P450-mediated metabolism of haloperidol
8) Literature Reports
a) Four inpatient males with chronic schizophrenia were stabilized on haloperidol and benztropine orally. In randomized order, the patients were then placed on fluvoxamine for six weeks or identically appearing placebo. Results showed that the addition of fluvoxamine to haloperidol therapy significantly elevated serum concentrations of haloperidol. In addition, haloperidol concentrations did not plateau during the six-week period of fluvoxamine treatment, indicating that the haloperidol concentrations may have continued to increase at a constant dose of fluvoxamine. The coadministration of haloperidol and fluvoxamine also worsened all measures of clinical and cognitive function assessments, including delayed recall memory and attentional function. It is possible that haloperidol may require the cytochrome P450 1A2 system for metabolism, and fluvoxamine is known to be a potent inhibitor of this enzyme pathway (Daniel et al, 1994).

3.5.1.CI Heparin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
7) Probable Mechanism: unknown
8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.CJ Hydroxytryptophan

1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Hydroxytryptophan (5-HTP) may potentiate the serotonergic effect of selective serotonin reuptake inhibitors (SSRIs) (Meltzer et al, 1997a). Since 5-HTP increases serotonin levels, when combined with an SSRI, the serotonin level may be increased sufficiently to produce serotonin syndrome. Caution is advised with concomitant use of 5-HTP and SSRIs.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: No cases have been reported of serotonin syndrome resulting from this combination. Caution is advised if hydroxytryptophan (5-HTP) and a selective serotonin reuptake inhibitor (SSRI) are used concomitantly. Monitor the patient for early signs of serotonin syndrome such as anxiety, confusion, and disorientation.
7) Probable Mechanism: additive serotonergic effect
8) Literature Reports

a) Hydroxytryptophan (5-HTP) (200 milligrams (mg) orally) as a single dose increased plasma cortisol and prolactin levels in both medicated and unmedicated patients with major depression or obsessive compulsive disorder (OCD). These responses were greater if the patient was also taking fluoxetine (n = 16) (p less than 0.0001). Mean fluoxetine dose for depressed patients was 44 mg/day,and for OCD patients it was 60 mg/day. Cortisol or prolactin (PRL) levels in patients taking 5-HTP with tricyclic antidepressants (n = 14) or those receiving no medication (n = 83) were not significantly different from each other. A measurement of serotonergic effects of antidepressants can be evaluated by measuring hypothalamic-pituitary-adrenal (HPA) axis or PRL response. No clinical manifestations of serotonin

syndrome were reported in patients taking 5-HTP concomitantly with fluoxetine (Meltzer et al, 1997).

3.5.1.CK Ibuprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.CL Iloprost

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.CM Imipramine

1) Interaction Effect: imipramine toxicity (dry mouth, urinary retention, sedation)

2) Summary: Addition of fluvoxamine to imipramine or desipramine therapy can result in significantly increased tricyclic antidepressant plasma levels and signs of tricyclic toxicity (Spina et al, 1992c; Spina et al, 1993ac; Spina et al, 1993c). Fluvoxamine significantly increases imipramine half-life and reduces clearance (Spina et al, 1993c). The addition of fluvoxamine to imipramine or desipramine therapy may result in greatly increased tricyclic antidepressant plasma levels and tricyclic toxicity (Spina et al, 1992c; Spina et al, 1993ac). A bidirectional effect is suggested, in which fluvoxamine increases imipramine concentrations (by interfering with N-demethylation), and imipramine increases fluvoxamine levels (Hartter et al, 1993e).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients for signs of imipramine and fluvoxamine toxicity; lower doses of one or both agents may be required with concomitant therapy.

7) Probable Mechanism: decreased imipramine metabolism

8) Literature Reports

a) The pharmacokinetics of combined imipramine and fluvoxamine were studied in healthy volunteers (Spina et al, 1993b). After a 7-day course of fluvoxamine, imipramine half-life was significantly increased (from 23 to 41 hours) and clearance decreased (from 1.02 to 0.28 L/h/kg).

b) The addition of fluvoxamine to imipramine or desipramine in four patients was reported to result in greatly increased tricyclic antidepressant plasma levels (Spina et al, 1992b). Three of four patients showed signs of tricyclic toxicity. The effect of fluvoxamine 100 mg daily for 10 days on plasma concentrations of imipramine was studied in seven depressed patients on maintenance therapy (Spina et al, 1993ab). Imipramine plasma levels were three to four times higher during fluvoxamine coadministration. One patient complained of anticholinergic effects, along with tremor and confusion.

The mechanism of this drug interaction was inhibition of demethylation of imipramine. A pharmacokinetic study in healthy volunteers demonstrated a significantly increased imipramine half-life and reduced clearance (Spina et al, 1993b).

c) Metabolism of tricyclic antidepressants coadministered with fluvoxamine was studied in eight depressed patients (two patients received imipramine) (Hartter et al, 1993d). Fluvoxamine was found to interfere with N-demethylation of imipramine. The combination of fluvoxamine and imipramine led to increased plasma levels of imipramine and decreased concentrations of the N-demethylated imipramine metabolite desimipramine. In addition, TCA-fluvoxamine coadministration apparently raised plasma levels of fluvoxamine.

3.5.1.CN Indomethacin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.CO Indoprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.CP Iproniazid

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concurrent administration or overlapping therapy with fluvoxamine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis,

shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of selective serotonin reuptake inhibitors and MAO inhibitors (Prod Info Luvox(R), 1997f; Lappin & Auchincloss, 1994c; Graber et al, 1994c; Suchowersky & de Vries, 1990c). Concomitant use is not recommended.
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of fluvoxamine and a MAO inhibitor should be avoided. Wait at least two weeks after discontinuing an MAO inhibitor before initiating therapy with fluvoxamine. Wait at least two weeks after discontinuing fluvoxamine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: serotonin reuptake inhibition
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991c). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement in symptoms after the second dose (Lappin & Auchincloss, 1994b).
c) A drug interaction occurred in a 61-year old woman whose regimen of sertraline 100 mg twice daily was added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites (Graber et al, 1994b).
d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990b). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.CQ Isocarboxazid
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with fluvoxamine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Luvox(R), 1997z; Lappin & Auchincloss, 1994s; Graber et al, 1994s; Suchowersky & de Vries, 1990s). Concomitant use is contraindicated (Prod Info Marplan(R), 1998).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of fluvoxamine and isocarboxazid is contraindicated. Wait at least two weeks after discontinuing isocarboxazid before initiating therapy with fluvoxamine. Wait at least two weeks after discontinuing fluvoxamine before initiating therapy with isocarboxazid.
7) Probable Mechanism: serotonin reuptake inhibition
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991m). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment

with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement in symptoms after the second dose (Lappin & Auchincloss, 1994r).

c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least 5 half-lives of the parent drug and any active metabolites (Graber et al, 1994r).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990r). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.CR Isoxicam

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.CS Ketoprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate

an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.CT Ketorolac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.CU Lamifiban
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.CV Levomethadyl
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 with levomethadyl. Possible pharmacodynamic interactions can occur between levomethadyl and potentially arrhythmogenic agents such as fluvoxamine that prolong the QT interval (Prod Info Orlaam(R), 2001).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Levomethadyl is contraindicated in patients being treated with fluvoxamine as it may precipitate QT prolongation and interact with levomethadyl.
7) Probable Mechanism: unknown

3.5.1.CW Lexipafant
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified

5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.CX Linezolid

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Linezolid is a reversible, nonselective inhibitor of monoamine oxidase. Concurrent administration or overlapping therapy with fluvoxamine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. There have been spontaneous reports of serotonin syndrome associated with concomitant use of linezolid and serotonergic agents (Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension, 2008; Prod Info Luvox (R), 2000). If fluvoxamine and linezolid are used concomitantly, monitor closely for symptoms of serotonin syndrome. Serotonin syndrome can be life-threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care and other therapy as necessary (Boyer & Shannon, 2005).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: If fluoxamine and linezolid are used concomitantly, monitor closely for symptoms of serotonin syndrome such as neuromuscular abnormalities (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including tachycardia, mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and delirium). Serotonin syndrome can be life-threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care and other therapy as necessary (Boyer & Shannon, 2005)
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase

3.5.1.CY Lithium

1) Interaction Effect: possible increased lithium concentrations and/or an increased risk of SSRI-related serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concomitant use of lithium and various SSRIs has been associated with enhanced side effects of either or both drugs, and with or without elevated lithium levels. The combination has resulted in neurotoxicity and increased lithium levels in one case report (Salama & Shafey, 1989a). Signs and symptoms of lithium toxicity and serotonin syndrome have also been reported in patients who demonstrated therapeutic serum lithium levels while on concurrent fluoxetine and lithium (Muly et al, 1993a; Noveske et al, 1989a). Two studies have failed to identify a pharmacokinetic interaction between lithium and citalopram (Gram et al, 1993a; Baumann et al, 1996a). Combined administration of citalopram (40 mg daily for 10 days) and lithium (30 mmol/day for 5 days) had no significant effect on the pharmacokinetics of citalopram or lithium. However, plasma lithium levels should be monitored with appropriate adjustment to the lithium dose in accordance with standard clinical practice. Lithium may enhance the serotonergic effects of citalopram, therefore caution should be exercised when citalopram and lithium are coadministered (Prod Info Celexa(R), 2004). Concurrent use of fluvoxamine and lithium has led to case reports of increased lithium levels and neurotoxicity, serotonin syndrome, somnolence, and mania (Salama & Shafey, 1989a; Ohman & Spigset, 1993a; Evans & Marwick, 1990; Burrai et al, 1991a). No pharmacokinetic interference was apparent during a multiple-dose study of coadministered lithium and paroxetine (Prod Info Paxil CR(TM), 2003). If these two agents are to be given concomitantly, the manufacturer suggests that caution be used until more clinical experience is available. Drug interactions leading to lithium toxicity have been reported when lithium was coadministered with fluoxetine and fluvoxamine (both in the same pharmacological class as paroxetine, eg, selective serotonin reuptake inhibitors) (Ohman & Spigset, 1993a; Salama & Shafey, 1989a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Monitor patients on concurrent lithium and selective serotonin reuptake inhibitor therapy for increased plasma concentrations of lithium. In addition, monitor patients for signs and symptoms associated with serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes).
7) Probable Mechanism: unknown
8) Literature Reports
a) Concomitant administration of oral lithium carbonate and oral fluoxetine resulted in increased lithium serum levels with lithium toxicity in a 44-year-old woman with a bipolar affective disorder (Salama & Shafey, 1989). Fluoxetine 20 mg daily was added to a regimen of lithium 1200 mg daily following patient complaints of weakness, tiredness, decreased concentration, and early morning awakening. Lithium serum levels increased to 1.7 mEq/L from a range of 0.75 to 1.15 mEq/L prior to fluoxetine. Fluoxetine was discontinued and the dose of lithium decreased; this resulted in a decrease in the lithium serum level within 48 hours to 1.2 mEq/L. The neurologic symptoms subsided within seven days as the lithium serum level decreased to 0.9 mEq/L. The contribution of fluoxetine to lithium toxicity in this patient was

obscured by the fact that the lithium was reduced at the time of fluoxetine withdrawal.
b) A 53-year old woman who had been taking fluoxetine 20 mg daily and lorazepam 0.5 mg four times daily for a major depressive disorder had lithium 900 mg per day added to her regimen in order to augment her response to fluoxetine. Within 48 hours, the patient became confused, ataxic, and developed a coarse tremor in her right arm. Vital signs showed a rectal temperature of 101 degrees F, and laboratory values were normal except for an elevated leukocyte count and slightly elevated bilirubin level. After discontinuation of lithium and fluoxetine, the patient's symptoms resolved over the next four days. At no point did the lithium levels reach a toxic level, suggesting that the patient's symptoms were due to a toxic reaction between fluoxetine and lithium (Noveske et al, 1989).
c) Serotonin syndrome was precipitated when lithium 300 mg twice daily was added to a three-month regimen of fluoxetine 40 mg per day. Five days later, the patient's lithium level was measured at 0.65 mEq/L and the dose was increased to 300 mg three times daily. Two days after this dosage change, the patient experienced akathisia, myoclonus, hyperreflexia, shivering, tremor, diarrhea, and incoordination. After discontinuation of lithium and initiation of cyproheptadine therapy, the patient's symptoms began to improve. The patient was discharged on a regimen of fluoxetine 40 mg per day without further symptoms of serotonin syndrome (Muly et al, 1993).
d) Eight healthy male volunteers completed three phases of an interaction study to determine the effects of coadministered lithium and citalopram. All subjects were extensive metabolizers of sparteine, indicating normal cytochrome P450 2D6 enzyme activity. Although lithium is not influenced by drug oxidation, citalopram metabolites are excreted by the kidney, as is lithium. Each subject received citalopram 40 mg alone as a single daily dose for 10 days, lithium 30 mmol (1980 mg) alone daily for five days, and lithium coadministered with citalopram on days 3-7. At least two weeks separated each treatment phase. Results showed that the concurrent administration of citalopram and lithium did not significantly alter the pharmacokinetics of lithium (Gram et al, 1993).
e) Twenty-four patients experiencing depression (DSM III criteria) were randomized under double-blind conditions to receive citalopram (40 mg to 60 mg daily) and lithium carbonate (800 mg daily) or placebo. All of the subjects had failed to respond to four weeks of citalopram monotherapy. Lithium was coadministered on days 29 to 42. No evidence of a pharmacokinetic interaction between lithium and citalopram was noted, and cotherapy was well tolerated (Baumann et al, 1996).
f) Serotonin syndrome was described in a 53-year-old patient who was stabilized on lithium 1400 mg daily (serum level 0.71 mmol/L) and was given fluvoxamine 50 mg daily. Over a 10-day period the fluvoxamine dose was increased to 200 mg daily; tremor and difficulty with fine hand movements developed. After two weeks, tremor, impaired motor function coordination, marked bilateral hyperreflexia of biceps and knee jerks, and clonus in both ankles were seen. After 12 weeks of continued therapy, during which time no further deterioration occurred, nortriptyline 100 mg daily replaced fluvoxamine, and the neuromuscular symptoms abated over a 2-week period. After four weeks the patient's neurological exam was normal (Ohman & Spigset, 1993).
g) Three cases of mania were reported in patients who were treated with lithium and fluvoxamine. The mania appeared 10 days, four weeks, and five weeks, respectively, after cotherapy was begun. Fluvoxamine was discontinued and, in two of the three patients, the mania resolved, and successful treatment of depression occurred with lithium alone. The third patient improved, but depression reappeared within a month of fluvoxamine discontinuation (Burrai et al, 1991).
h) In an open-labeled, placebo-controlled study, lithium 600 mg was administered to 16 subjects orally twice daily on days one through eight and once in the morning on day nine. In addition, oral sertraline 100 mg or placebo was given twice, ten hours and two hours prior to lithium dosing on day nine. The steady-state lithium level was only decreased by 1.4% (0.01 mEq/L) and the lithium renal clearance increased by 6.9% (0.11 L/hour) when sertraline was coadministered. Seven subjects experienced side effects, mainly tremors, after receiving lithium and sertraline, whereas no subjects who ingested placebo and lithium experienced side effects (Wilner et al, 1991).

3.5.1.CZ Lornoxicam

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI

bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DA Maprotiline

1) Interaction Effect: maprotiline toxicity (dry mouth, urinary retention, sedation)

2) Summary: An interaction of fluvoxamine with tricyclic antidepressants (TCAs) was reported (Hartter et al, 1993g). Plasma concentrations of TCAs were increased when combined with fluvoxamine. This effect was less prominent with maprotiline compared with imipramine, clomipramine, or amitriptyline. In addition, TCAs appeared to increase fluvoxamine levels.

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients for excess tricyclic antidepressant side effects such as dry mouth and lethargy. Maprotiline doses may need to be reduced in some clinical situations.

7) Probable Mechanism: decreased maprotiline metabolism

8) Literature Reports

a) Metabolism of tricyclic antidepressants coadministered with fluvoxamine was studied in eight depressed patients (one patient received maprotiline) (Hartter et al, 1993f). Fluvoxamine was found to interfere with N-demethylation of maprotiline. The combination of fluvoxamine and maprotiline led to increased plasma levels of maprotiline and decreased concentrations of maprotiline's N-demethylated metabolite, desmethylmaprotiline. Also, plasma levels of fluvoxamine were increased.

3.5.1.DB Mate

1) Interaction Effect: increased caffeine levels (insomnia, headache, restlessness, nervousness, palpitations, and arrhythmias)

2) Summary: The primary pharmacologically-active ingredient of mate is caffeine. Fluvoxamine inhibits CYP1A2 and CYP2D6 which are responsible for caffeine metabolism. Decreased caffeine clearance and increased half-life have been demonstrated in humans (Jeppesen et al, 1996a). Signs and symptoms of caffeine excess may result if the compounds are taken together. Patients should avoid mate use during therapy with fluvoxamine in order to avoid possible complications.

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Patients should be advised of the caffeine content of mate, and of symptoms of excess if taken with fluvoxamine (insomnia, headache, restlessness, nervousness, palpitations, and arrhythmias), as well as symptoms of caffeine withdrawal which may accompany abrupt discontinuation of mate (e.g., headache, fatigue, depression, anxiety, and insomnia). Patients should avoid mate use during therapy with fluvoxamine in order to avoid possible complications.

7) Probable Mechanism: inhibition of caffeine metabolism

8) Literature Reports

a) In an open, randomized, cross-over study of 8 volunteers, fluvoxamine significantly decreased caffeine total clearance and increased caffeine half-life. Fluvoxamine was administered as 50 milligrams (mg) for 4 days, then 100 mg for 8 days while subjects abstained from all caffeine intake. Caffeine 200 mg was then administered orally. Total clearance of caffeine decreased from 107 milliliters/minute (mL/min) to 21 mL/min, and half-life increased from 5 hours to 31 hours. Patients taking fluvoxamine should restrict caffeine intake (Jeppesen et al, 1996).

b) In vitro, fluvoxamine was found to be a very potent inhibitor of the formation of N-demethylated caffeine metabolites with K1 values of 0.08 micromoles (mcmol) to 0.28 mcmol. The formation of 1,7-dimethylxanthine was abolished by 10 mcmol of fluvoxamine, implying the N3-demethylation of caffeine is almost entirely catalyzed by CYP1A2 (Rasmussen et al, 1998).

c) At least 14 metabolites are formed from caffeine whose main route of elimination is N3-demethylation to paraxanthine (1,7-methylxanthine) which accounts for greater than 80% of caffeine elimination (Lelo et al, 1986). CYP1A2 is the major enzyme metabolizing caffeine to 1,7-dimethylxanthine (Berthou et al, 1991; Sesardic et al, 1990; Butler et al, 1989). CYP1A2 is also a major enzyme in the formation of 3,7-dimethylxanthine and 1,3-dimethylxantihine from caffeine (Gu et al, 1992; Berthou et al, 1991; Grant et al, 1987).

3.5.1.DC Meclofenamate

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM),

2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DD Mefenamic Acid
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DE Melatonin
1) Interaction Effect: increased central nervous system depression
2) Summary: Fluvoxamine significantly increased melatonin levels and increased drowsiness when given with melatonin in a study of 5 healthy volunteers (Hartter et al, 2000a). Endogenous melatonin levels increased following fluvoxamine administration in 7 healthy subjects (Von Bahr et al, 2000). Fluvoxamine may inhibit melatonin elimination (Hartter et al, 2000a), or metabolism via cytochrome P450 1A2 or 2C19 (Von Bahr et al, 2000). Patients taking fluvoxamine with or without melatonin supplementation should be monitored for changes in sleep and central nervous system depression.
3) Severity: minor
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Monitor patients taking fluvoxamine with melatonin supplementation for changes in sleep patterns and signs of excessive central nervous system depression. Downward titration of melatonin dosages may be required during concomitant administration with fluvoxamine.
7) Probable Mechanism: inhibition of cytochrome P450 enzymes, possibly CYP1A2 and CYP2C19, responsible for melatonin metabolism
8) Literature Reports
a) The bioavailability of oral melatonin was significantly increased after coadministration of fluvoxamine. Five volunteers (one CYP2D6 poor metabolizer) were included in a study that was designed to evaluate the effects of fluvoxamine on the pharmacokinetics of melatonin. A single dose of melatonin 5 mg was administered to all subjects. One week later a single oral dose of fluvoxamine 50 mg was administered to all subjects. Blood samples were evaluated at certain time points after

administration of each agent. An increase in melatonin serum concentrations occurred in all subjects with a 23-fold increase in area under the concentration-time curve (AUC) (6.2 to 141.3 mcg h/L) and a twelve-fold increase in maximum serum concentration (Cmax) (2.18 to 25.1 ng/ml) of melatonin. The effects of fluvoxamine on melatonin pharmacokinetics were effectively greater in the poor CYP2D6 metabolizer. The author suggests that this is most likely due to inhibition of the elimination of melatonin rather than an increased production of melatonin (Hartter et al, 2000).

3.5.1.DF Meloxicam

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DG Methadone

1) Interaction Effect: increased plasma methadone levels

2) Summary: When fluvoxamine is added to patients receiving maintenance methadone therapy, significantly increased methadone plasma level:dose ratios are seen. Symptoms of opioid toxicity were observed in one patient. In another patient, opioid withdrawal symptoms were observed following discontinuation of fluvoxamine (Prod Info Luvox(R), 1997w).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor closely if adding or withdrawing fluvoxamine in patients on chronic methadone.

7) Probable Mechanism: inhibition by fluvoxamine of cytochrome P450 3A4-mediated methadone metabolism

8) Literature Reports

a) A 28-year-old female who was admitted to a hospital for the management of an acute exacerbation of asthma had a stabilized medication regimen which included methadone 70 mg daily, diazepam 2 mg twice daily, albuterol, ipratropium, ranitidine, and spironolactone. Three weeks before admission, she had started fluvoxamine 100 mg daily. The patient's asthma was not considered to be in a significant exacerbation upon further testing, although hypoxemia and hypercapnia indicating hypoventilation was present. Methadone was decreased to 50 mg daily and diazepam was discontinued. Analysis of a blood sample taken at admission showed that the serum methadone concentration was 262 ng/mL. Twelve days later, oxygenation had improved and the methadone concentration was measured at 202 ng/mL. The reduction in serum methadone concentration and clinical improvement observed after methadone was decreased suggest that fluvoxamine may have inhibited the cytochrome P450 3A4-mediated metabolism of methadone, although diazepam may have compounded this interaction (Alderman & Frith, 1999).

3.5.1.DH Methylergonovine

1) Interaction Effect: an increased risk of ergotism (nausea, vomiting, vasospastic ischemia)

2) Summary: Because of the potential for serious toxicity including vasospasm that can occur with increased plasma concentrations of ergot derivatives, the concurrent use of fluvoxamine and ergot derivatives is contraindicated. Fluvoxamine and ergot derivatives are both metabolized by cytochrome P450 3A4 enzymes, and the competition for metabolism could result in an increased plasma concentration of the ergot derivative (Prod Info Cafergot(R), 2002).

3) Severity: contraindicated

4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The concurrent use of fluvoxamine and ergot derivatives is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A4- mediated ergot metabolism by fluvoxamine

3.5.1.DI Methylphenidate

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. Additionally, when initiating or 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 selective serotonin reuptake inhibitor (SSRI). Concomitant use of methylphenidate and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease in the dose of SSRI when these agents are coadministered. Additionally, consider adjusting the SSRI dose if necessary when initiating or discontinuing methylphenidate therapy (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.DJ Metoprolol

1) Interaction Effect: bradycardia and hypotension
2) Summary: Fluvoxamine may inhibit the metabolism of metoprolol, which resulted in bradycardia and/or hypotension in one case (Prod Info Luvox(R), 1997o).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: If metoprolol is coadministered with fluvoxamine, it is recommended that the initial dose be reduced and that dose titration proceed more cautiously than usual. No dose change is required for fluvoxamine. Monitor heart rate and blood pressure carefully.
7) Probable Mechanism: decreased metoprolol metabolism

3.5.1.DK Mexiletine

1) Interaction Effect: decreased mexiletine metabolism
2) Summary: In a single-dose study, concurrent administration of fluvoxamine and mexiletine reduced the clearance of mexiletine by 37%, significantly increasing the mean serum peak concentration and area under the concentration-time curve (Kusumoto et al, 2001a; Prod Info Mexitil(R), 2003).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Monitor patients for signs and symptoms of mexiletine toxicity (nausea, dizziness, cardiac arrhythmias). Monitor liver function, complete blood count, and electrocardiogram if mexiletine toxicity is suspected, and reduce mexiletine dose as required.
7) Probable Mechanism: fluvoxamine-induced inhibition of CYP1A2-mediated mexiletine metabolism
8) Literature Reports
a) Co-administration of fluvoxamine with mexiletine significantly reduced the metabolism and clearance of mexiletine. In a randomized, cross-over study, healthy Japanese men (n=6) received either a single oral dose of mexiletine 200 milligrams (mg) or a 7-day regimen of oral fluvoxamine 50 mg twice daily followed by fluvoxamine plus a single dose of mexiletine 200 mg on day 8. Serial blood samples were measured over the 24 hours following each mexiletine dose. Thereafter, each subject crossed over to the opposing study arm following a 7-day wash-out period. Compared with control values, concurrent administration of fluvoxamine with mexiletine provoked a significant increase in the mean maximum serum concentration (0.536 versus 0.623 micrograms/milliliter (mcg/mL), p=0.0074) and area under the concentration-time curve (5.71 versus 7.46 mcg x hour/mL, p=0.0028). Co-administration significantly decreased mean oral clearance by 37% (0.551 versus 0.341 L/hour/kilogram, p=0.015). The study authors proposed fluvoxamine-induced inhibition of CYP1A2 metabolism as the mechanism of action (Kusumoto et al, 2001).

3.5.1.DL Midazolam

1) Interaction Effect: elevated serum midazolam concentrations
2) Summary: Fluvoxamine coadministration (100 mg daily) with alprazolam 1 mg four times daily resulted in a 2-fold increase in alprazolam steady-state plasma concentrations, AUC, Cmax, and half-life. Elevated plasma levels of alprazolam were associated with impaired psychomotor performance and memory. This suggests that fluvoxamine is a potent inhibitor of cytochrome P450 3A4 enzymes, which are responsible for alprazolam metabolism. Because midazolam also relies on CYP3A4 for metabolism, a similar interaction with fluvoxamine seems likely (Prod Info Luvox(R), 1997aa).

3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When midazolam and fluvoxamine are coadministered, monitor patients for benzodiazepine toxicity (sedation, lethargy, slurred speech). Midazolam doses may need to be reduced, or consider switching to a benzodiazepine eliminated by glucuronidation (eg, lorazepam, oxazepam, temazepam).
7) Probable Mechanism: inhibition of midazolam metabolism due to cytochrome P450 3A4 enzyme inhibition

3.5.1.DM Milnacipran

1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent use of milnacipran and an SSRI may result in hypertension, coronary artery vasoconstriction or serotonin syndrome, which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea (Prod Info SAVELLA(R) oral tablets, 2009).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of milnacipran and an SSRI may result in hypertension and coronary artery vasoconstriction, through the additive serotonergic effects. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination), especially during treatment initiation and dose increases (Prod Info SAVELLA(R) oral tablets, 2009).
7) Probable Mechanism: additive serotonergic effect

3.5.1.DN Mirtazapine

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Mirtazapine increases serotonin release and fluvoxamine inhibits the CYP450 1A2, 2C9, 2D6, and 3A3/4-mediated mirtazapine metabolism. Concurrent use of fluvoxamine and mirtazapine resulted in symptoms of serotonin syndrome in a 26-year-old female (Demers & Malone, 2001). If fluvoxamine and mirtazapine are used together, monitor closely for symptoms of serotonin syndrome. Serotonin syndrome can be life-threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care and other therapy as necessary (Boyer & Shannon, 2005).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: A case of serotonin syndrome was reported with concomitant use of fluvoxamine and mirtazapine and therefore, concomitant use is discouraged(Demers & Malone, 2001). If fluvoxamine and mirtazapine are used together, monitor closely for symptoms of serotonin syndrome such as neuromuscular abnormalities (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including tachycardia, mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and delirium). Serotonin syndrome can be life-threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care and other therapy as necessary (Boyer & Shannon, 2005).
7) Probable Mechanism: additive pharmacologic effects and inhibition of CYP1A2, 2C9, 2D6, and 3A3/4-mediated metabolism of mirtazapine by fluvoxamine
8) Literature Reports
a) A 26-year-old woman with anorexia nervosa on fluvoxamine for a total of 4 months developed symptoms of serotonin syndrome after mirtazapine was added. She was on fluvoxamine 150 mg/day for 2 months with a subsequent increase to 200 mg/day for 2 months before starting mirtazapine. The symptoms of twitching, tremors, agitation, restlessness, and "feeling like she could crawl out of her skin" developed over a period of 4 days after starting mirtazapine 30 mg/day. Symptoms rapidly progressed to twitching, tremors, and restlessness. She was hospitalized with further symptoms of diaphoresis, flushing, fasciculations, and nausea and treated with cyproheptadine 4 mg every 6 hours, acetaminophen, and intravenous fluids. She remained afebrile throughout the event. Symptoms completely resolved within 24 hours. She was discharged on 50 mg/day of fluvoxamine and no recurrence the following day. The interaction was attributed to multiple mechanisms. Mirtazapine increases the release of serotonin via the 5-hydroxytryptamine (serotonin) (5-HT) 1 receptors but it is also a 5-HT2 and 5-HT3 receptors blocker. Fluvoxamine decreases mirtazapine metabolism by inhibiting cytochrome P-450 1A2, 2C9, 2D6, and 3A3/4 enzymes, and may have increased the mirtazapine serum levels resulting in increased mirtazapine adverse effects (Demers & Malone, 2001).
b) A letter to the editor (Isbister et al, 2001) disagreed with the case report that fluvoxamine and mirtazapine resulted in serotonin syndrome (Demers & Malone, 2001). Their argument is that the diagnostic criteria used was unreliable; mirtazapine, a 5-hydroxytryptamine 2A receptor blocker, is unlikely to cause serotonin syndrome and may actually offer benefit in treating it; and the symptoms

were adverse effects related to increased concentrations of mirtazapine from inhibition of metabolism by fluvoxamine (Isbister et al, 2001).

3.5.1.DO Moclobemide

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concurrent administration or overlapping therapy with fluvoxamine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Luvox(R), 1997e; Neuvonen et al, 1993a). Although not reported specifically with moclobemide in therapeutic doses, a similar reaction may occur. Concomitant use is not recommended.

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: In general, concurrent use of a serotonin specific reuptake inhibitor and a MAO inhibitor should be avoided. Wait at least 14 days after discontinuing a MAO inhibitor before initiating therapy with fluvoxamine. Wait at least 14 days after discontinuing fluvoxamine before initiating therapy with a MAO inhibitor.

7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase

8) Literature Reports

a) Concomitant use of selective serotonin reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991a). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.

b) A study reported five fatal overdose cases due to serotonin syndrome. In three of the five cases, the drug combination that induced the fatal syndrome was moclobemide, a selective monoamine oxidase inhibitor, and citalopram. Of the three patients, blood concentrations of moclobemide ranged from five times the therapeutic level to 50 times the therapeutic level, and citalopram concentrations ranged from normal therapeutic levels to five times the therapeutic level (Neuvonen et al, 1993).

3.5.1.DP Morniflumate

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DQ Nabumetone

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DR Nadroparin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was

11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.DS Naproxen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DT Naratriptan

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Rare incidences of weakness, hyperreflexia, and incoordination have been reported with the concurrent use of a selective serotonin reuptake inhibitor (SSRI) and a 5-hydroxytryptamine-1 (5HT-1) agonist (Prod Info Amerge(TM), 2002). Concurrent use of a triptan and an SSRI may result in serotonin syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndrome with patients who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administration, 2006).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as naratriptan, and an SSRI may result in a life-threatening condition called serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.DU Nialamide

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with fluvoxamine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of selective serotonin reuptake inhibitors and MAO inhibitors (Prod Info Luvox(R), 1997y; Lappin & Auchincloss, 1994q; Graber et al, 1994q; Suchowersky & de Vries, 1990q). Concomitant use is not recommended.
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of fluvoxamine and a MAO inhibitor should be avoided. Wait at least two weeks after discontinuing an MAO inhibitor before initiating therapy with fluvoxamine. Wait at least two weeks after discontinuing fluvoxamine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: serotonin reuptake inhibition

8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991l). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.

b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement in symptoms after the second dose (Lappin & Auchincloss, 1994p).

c) A drug interaction occurred in a 61-year old woman whose regimen of sertraline 100 mg twice daily was added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites (Graber et al, 1994p).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990p). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.DV Niflumic Acid

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DW Nimesulide

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of

increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DX Olanzapine
1) Interaction Effect: an increased risk of olanzapine adverse effects
2) Summary: Fluvoxamine inhibits cytochrome P450 1A2 enzymes and may inhibit olanzapine elimination (Prod Info Zyprexa(R), 1999). The clinical significance of this interaction is unknown since olanzapine is metabolized by multiple enzyme systems.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients for excessive olanzapine adverse effects (orthostatic hypotension, tachycardia, transaminase elevations, seizures).
7) Probable Mechanism: inhibition of olanzapine elimination
8) Literature Reports
a) A patient experienced elevated olanzapine plasma levels during coadministration of fluvoxamine. The patient was taking fluvoxamine and olanzapine for several months for schizophrenia and secondary depression. She appeared to move rigidly, had a slight tremor of both hands and mydriasis. Olanzapine concentration was 120 mcg/L and fluvoxamine concentration was 70 mcg/L. Olanzapine was decreased in increments from 15 mg/day to 5 mg/day. Fourteen days after the last decrease in dose, olanzapine plasma levels were 38 mcg/L. Tremor and rigidity disappeared, however, mydriasis persisted. Fluvoxamine was replaced by paroxetine which resulted in paroxetine concentration of 0.027 mg/L and olanzapine concentration of 22 mcg/L (de Jong et al, 2001).
b) Addition of fluvoxamine to olanzapine therapy may result in olanzapine-induced side effects or intoxication. Eight chronic schizophrenic patients were being treated for not less than 3 months with 10-20 mg/day of olanzapine. The dose of olanzapine was unchanged for not less than 8 weeks prior to the study and remained stable throughout the study period. Fluvoxamine 100 mg/day was added to olanzapine treatment at the start of the study (week 0) and continued for 8 weeks. Olanzapine concentrations increased during fluvoxamine treatment 1.58-fold from week 0 to week 1, 1.42-fold from week 0 to week 4, and 1.81-fold from week 0 to week 8. Percentage change from week 0 to week 8 ranged from 12% to 112%. Mean concentrations of the N-demethylated metabolite were not significantly changed. Even though all eight patients had higher olanzapine blood serum concentrations on week 8 than on week 1, the ratio of increase of olanzapine blood serum concentrations from week 0 to week 8 did not correlate significantly with fluvoxamine serum levels (p greater than 0.05). This study confirmed that the addition of fluvoxamine to a stable dose of olanzapine increased olanzapine concentrations in the blood serum. Combined olanzapine and fluvoxamine should be used cautiously and controlled clinically and by therapeutic drug monitoring to avoid olanzapine-induced side effects or intoxication (Hiemke et al, 2002).

3.5.1.DY Oxaprozin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations

in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DZ Oxycodone

1) Interaction Effect: an increased risk of serotonin syndrome (tachycardia, hyperthermia, myoclonus, mental status changes)

2) Summary: Coadministration of oxycodone and fluvoxamine has resulted in the development of serotonin syndrome in a 70-year-old woman. Presenting symptoms included confusion, nausea, fever, clonus, hyperreflexia, and tachycardia. Caution is advised if fluvoxamine and oxycodone are coadministered. Monitor patients for signs and symptoms of serotonin syndrome (tachycardia, hyperthermia, myoclonus, mental status changes) (Karunatilake & Buckley, 2006).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concomitant administration of fluvoxamine and oxycodone may increase the risk of developing serotonin syndrome. If these agents are coadministered, monitor patients for symptoms of serotonin syndrome (tachycardia, hyperthermia, myoclonus, mental status changes).

7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

8) Literature Reports

a) Concurrent administration of oxycodone and fluvoxamine resulted in a serotonin syndrome in a 70-year-old woman. The patient was receiving fluvoxamine 200 mg and doxepin 50 mg for several months for treatment of depression. Subsequent to a fall, the patients was started on slow-release oral oxycodone 40 mg twice daily, and 2 days later, short-acting oral oxycodone 10 mg, to be used on an "as needed" basis, was added to her regimen. After a dose of about 60 mg oxycodone taken over 24 hours, the patient presented to the emergency department in a state of confusion, with symptoms including nausea, fever, clonus, hyperreflexia, and shivering. The patient also had mydriasis, transient atrial fibrillation, tachycardia, and an elevated creatinine kinase level. Fluvoxamine, doxepin, and oxycodone were discontinued and the patient was treated with 5 doses of oral acetaminophen 1,000 mg over the next 2 days. The patient's neurologic and cardiovascular symptoms improved steadily over the next 48 hours. Prior to discharge, doxepin therapy was re-initiated with no apparent adverse effects. However, patient was not rechallenged with either fluvoxamine or oxycodone while she was in the hospital. According to the Naranjo probability scale, the interaction falls into the probable category (Karunatilake & Buckley, 2006).

3.5.1.EA Parecoxib

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.EB Pargyline

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental

status changes)
2) Summary: Concurrent administration or overlapping therapy with fluvoxamine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of selective serotonin reuptake inhibitors and MAO inhibitors (Prod Info Luvox(R), 1997l; Lappin & Auchincloss, 1994g; Graber et al, 1994g; Suchowersky & de Vries, 1990g). Concomitant use is not recommended.
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of fluvoxamine and a MAO inhibitor should be avoided. Wait at least two weeks after discontinuing an MAO inhibitor before initiating therapy with fluvoxamine. Wait at least two weeks after discontinuing fluvoxamine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: serotonin reuptake inhibition
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991e). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement in symptoms after the second dose (Lappin & Auchincloss, 1994f).
c) A drug interaction occurred in a 61-year old woman whose regimen of sertraline 100 mg twice daily was added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites (Graber et al, 1994f).
d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990f). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.EC Parnaparin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant

bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.ED Pentosan Polysulfate Sodium

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding

events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.EE Phenelzine

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concurrent administration or overlapping therapy with fluvoxamine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Luvox(R), 1997m; Lappin & Auchincloss, 1994i; Graber et al, 1994i; Suchowersky & de Vries, 1990i). Concomitant use of phenelzine and fluvoxamine is contraindicated (Prod Info Nardil(R), 1997).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of fluvoxamine and phenelzine is contraindicated . Wait at least two weeks after discontinuing an MAO inhibitor before initiating therapy with fluvoxamine. Wait at least two weeks after discontinuing fluvoxamine before initiating therapy with a MAO inhibitor.

7) Probable Mechanism: serotonin reuptake inhibition

8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991f). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.

b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement in symptoms after the second dose (Lappin & Auchincloss, 1994h).

c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least 5 half-lives of the parent drug and any active metabolites (Graber et al, 1994h).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990h). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.EF Phenindione

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.EG Phenprocoumon

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et

al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.EH Phenylbutazone
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.EI Phenytoin

1) Interaction Effect: an increased risk of phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremors)
2) Summary: Fluvoxamine inhibits several of the isoenzymes of the cytochrome P450 enzyme system (oxidative metabolism); IA2, IIC9, and IIIA4. Since phenytoin is eliminated at least partially via the CYP450 IIC9 pathway, it is possible that coadministration with fluvoxamine may cause elevations in phenytoin plasma levels (Prod Info Luvox(R), 1997).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Consideration should be given to monitoring of phenytoin serum levels when fluvoxamine is added or withdrawn from therapy and dosage adjustments made accordingly. Patients should be counseled to be aware of the potential side effects of phenytoin toxicity such as drowsiness, ataxia, and nystagmus, and to notify their physician if such side effects occur.
7) Probable Mechanism: decreased oxidative metabolism
8) Literature Reports

a) During an in vitro study, the inhibitory effects of fluvoxamine on cytochrome P450 2C9 were evaluated using p-hydroxylation of phenytoin as an established index reaction reflecting CYP2C9 activity. In vivo, p-hydroxylation of phenytoin depends on the formation of 5-(p-hydroxy-phenyl)-5-phenylhydantoin (HPPH). Fluvoxamine, a strong inhibitor of HPPH, impaired the formation of HPPH, which can lead to an increase in steady-state phenytoin levels (Schmider et al, 1997).

b) Phenytoin intoxication occurred in a patient after administration of fluvoxamine. Serum phenytoin concentration dramatically increased from 16.6 to 49.1 mcg/mL during treatment with fluvoxamine. Fluvoxamine may inhibit the metabolism of PHT, mediated by cytochrome P450 2C9 (CYP2C9) and CYP 2C19 enzymes (Mamiya et al, 2000).

3.5.1.EJ Pirazolac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.EK Piroxicam

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.EL Pirprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.EM Procarbazine

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with fluvoxamine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of selective serotonin reuptake inhibitors and MAO inhibitors (Prod Info Luvox(R), 1997p; Lappin & Auchincloss, 1994m; Graber et al, 1994m; Suchowersky & de Vries, 1990m). Concomitant use is not recommended.
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of fluvoxamine and a MAO inhibitor should be avoided. Wait at least two weeks after discontinuing an MAO inhibitor before initiating therapy with fluvoxamine. Wait at least two weeks after discontinuing fluvoxamine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: serotonin reuptake inhibition
8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991i). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement in symptoms after the second dose (Lappin & Auchincloss, 1994l).
c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was

added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites (Graber et al, 1994l).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990l). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.EN Propranolol

1) Interaction Effect: bradycardia and hypotension

2) Summary: Propranolol serum concentrations may increase significantly during concomitant therapy with fluvoxamine. Elevated propranolol serum concentrations may be associated with an increased risk of bradycardia and hypotension (Prod Info Luvox(R), 1997c).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Carefully monitor heart rate and blood pressure. The propranolol does may need to be reduced if bradycardia or hypotension develop. Alternatively, use of atenolol, a beta-blocker which does not undergo hepatic metabolism and is not affected by fluvoxamine, may be considered.

7) Probable Mechanism: reduced beta blocker metabolism

8) Literature Reports

a) Coadministration of propranolol (160 mg per day) and fluvoxamine (100 mg per day) in healthy volunteers resulted in a mean 5-fold increase in minimum propranolol serum concentrations. This was associated with a slight reduction in heart rate and blood pressure (Prod Info Luvox(R), 1997b; van Harten, 1993).

3.5.1.EO Propyphenazone

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.EP Proquazone

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.EQ Ramelteon
1) Interaction Effect: increased ramelteon plasma concentrations with increased risk of side effects
2) Summary: Concurrent administration of fluvoxamine and ramelteon is contraindicated due to significantly increased ramelteon plasma concentrations with concurrent fluvoxamine use (Prod Info ROZEREM(R) oral tablets, 2008).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concurrent administration of fluvoxamine and ramelteon is contraindicated (Prod Info ROZEREM(R) oral tablets, 2008).
7) Probable Mechanism: inhibition of CYP1A2-mediated ramelteon metabolism by fluvoxamine
8) Literature Reports
a) Fluvoxamine, a strong CYP1A2 inhibitor, significantly increases ramelteon plasma concentrations when used concurrently. When a single dose of ramelteon 16 mg was coadministered to subjects who received fluvoxamine 100 mg twice daily for 3 days prior, the ramelteon AUC and Cmax increased approximately 190-fold and 70-fold, respectively (Prod Info ROZEREM(R) oral tablets, 2008).

3.5.1.ER Rasagiline
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with selective serotonin reuptake inhibitors, including fluvoxamine, and non-selective MAOIs or the selective MAO-B inhibitor selegiline, has been reported to cause serious, sometimes fatal reactions. Signs and symptoms included hyperthermia, rigidity, myoclonus, autonomic instability with rapid vital sign fluctuations, and mental status changes progressing to extreme agitation, delirium, and coma. Similar reactions have been reported with serotonin-norepinephrine reuptake inhibitors (SNRIs) and non-selective MAOIs or selegiline. Rasagiline clinical trials did not allow concomitant use of fluvoxamine; the combination of rasagiline and fluvoxamine should be avoided. Wait at least two weeks after discontinuing rasagiline before initiating therapy with fluvoxamine (Prod Info AZILECT (R) oral tablets, 2006).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concurrent use of fluvoxamine and rasagiline should be avoided. Wait at least two weeks after discontinuing rasagiline before initiating therapy with fluvoxamine.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991g). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.

3.5.1.ES Reviparin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased

bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.ET Rizatriptan
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concomitant use of sumatriptan, a 5-hydroxytryptamine-1 (5HT-1) agonist, and a serotonin specific reuptake inhibitor (SSRI) (Prod Info Imitrex(R), 1998). Because rizatriptan is a 5HT 1B/1D receptor agonist, a similar interaction between SSRIs and rizatriptan may occur (Prod Info Maxalt(R), 1998a). Concurrent use of a triptan and an SSRI may result in serotonin syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndrome with patients who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administration, 2006).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as rizatriptan, and an SSRI may result in a life-threatening condition called serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these

agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) Twelve healthy volunteers received paroxetine 20 mg daily for two weeks and a single dose of rizatriptan 10 mg. Plasma concentrations of rizatriptan were not altered by the administration of paroxetine (Prod Info Maxalt(R), 1998).

3.5.1.EU Rofecoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.EV Ropivacaine
1) Interaction Effect: increased plasma levels of ropivacaine
2) Summary: Ropivacaine is metabolized in the liver by the cytochrome P450 1A2 (CYP1A2) enzyme system to 3-hydroxyropivacaine, the major metabolite. Drugs which inhibit CYP1A2, such as fluvoxamine, can potentially interact with the metabolism of ropivacaine. This would result in decreased renal clearance and increased plasma concentrations of ropivacaine (Jokinen et al, 2000a; Prod Info Naropin(TM), 1996).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Care must be taken to monitor the patient for signs of local anesthetic toxicity with the coadministration of ropivacaine and fluvoxamine.
7) Probable Mechanism: inhibition by fluvoxamine of cytochrome P450 1A2-mediated ropivacaine metabolism
8) Literature Reports
a) In a randomized, three-way crossover study, 12 healthy volunteers received a single dose of ropivacaine 40 mg as an intravenous infusion alone or combined with either oral fluvoxamine 25 mg or ketoconazole 100 mg twice daily for two days. The combined therapy with ropivacaine and ketoconazole demonstrated no clinically significant differences in the pharmacokinetic measurements obtained. The authors theorized that cytochrome P450 3A4 (CYP3A4) inhibition, as measured by ketoconazole, has little effect on the pharmacokinetics of ropivacaine. However, CYP1A2 inhibition, as measured by fluvoxamine, may result in a clinically relevant drug interaction with repeated administration. In the presence of fluvoxamine, ropivacaine total plasma clearance decreased by 68% (from 354 mL/min to 112 mL/min). The observed reduction in the total plasma clearance after fluvoxamine arises from a decrease in 3-hydroxyropivacaine formation, which is likely mediated by CYP1A2. Additionally, the half-life of ropivacaine increased from 1.9 hours to 3.6 hours when given with fluvoxamine. The reduction in ropivacaine clearance during fluvoxamine administration is likely to be of minor relevance when ropivacaine is given as a single dose. However, repeated administration of ropivacaine in a patient also receiving fluvoxamine may result in toxic ropivacaine plasma concentrations (Arlander et al, 1998).
b) Inhibition of cytochrome P450 1A2 (CYP1A2) by fluvoxamine considerably reduced elimination of ropivacaine. The eight patients in this randomized, double-blind, cross-over, four phase study ingested erythromycin 1500 mg daily for 6 days, fluvoxamine 100 mg for 5 days, both erythromycin and fluvoxamine, or placebo. Each subject received ropivacaine 0.6 mg/kg IV over 30 minutes as a single dose. Fluvoxamine increased both the AUC (p less than 0.001) of ropivacaine 3.7-fold, prolonged the

half-life from 2.3 to 7.4 h (p less than 0.01), and decreased clearance 77% (p less than 0.001) when compared with placebo. Fluvoxamine increased the AUC of 2,6-pipecoloxylidide (PPX), a ropivacaine metabolite, 2.5-fold (p less than 0.001) and the Cmax of PPX 2.8-fold (p less than 0.001) and decreased the plasma levels of 3-OH-ropivacaine to below the limit of quantitation. Erythromycin had minor effects on the pharmacokinetics of ropivacaine. The combination of fluvoxamine and erythromycin, however, when compared with fluvoxamine alone, further increased the AUC of ropivacaine by 50% (p less than 0.01), and prolonged the half-life from 7.4 to 11.9 h (p less than 0.01). The author concludes that fluvoxamine-induced cytochrome P450 1A2 inhibition considerably reduces elimination of ropivacaine. Coadministration of fluvoxamine and erythromycin increases plasma ropivacaine levels further by decreasing its clearance (Jokinen et al, 2000).

3.5.1.EW Selegiline

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concurrent administration or overlapping therapy with fluvoxamine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Luvox(R), 1997v; Lappin & Auchincloss, 1994o; Graber et al, 1994o; Suchowersky & de Vries, 1990o). Concomitant use is not recommended.

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of fluvoxamine and a MAO inhibitor should be avoided. Wait at least two weeks after discontinuing an MAO inhibitor before initiating therapy with fluvoxamine. Wait at least two weeks after discontinuing fluvoxamine before initiating therapy with a MAO inhibitor.

7) Probable Mechanism: serotonin reuptake inhibition

8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991g). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.

b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement in symptoms after the second dose (Lappin & Auchincloss, 1994n).

c) A drug interaction occurred in a 61-year old woman whose regimen of sertraline 100 mg twice daily was added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least 5 half-lives of the parent drug and any active metabolites (Graber et al, 1994n).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990n). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.EX Sibrafiban

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.EY Sibutramine

1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Sibutramine inhibits the reuptake of norepinephrine, dopamine, and serotonin. In addition, the two major metabolites of sibutramine, M1 and M2, also inhibit the reuptake of these neurotransmitters. A hyperserotonergic state, termed serotonin syndrome, may result if sibutramine is given concurrently with a selective serotonin reuptake inhibitor. Coadministration of sibutramine and selective serotonin reuptake inhibitors is not recommended (Prod Info Meridia(R), 1997).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Sibutramine should not be administered with serotonergic agents, including selective serotonin reuptake inhibitors, because of the increased risk of serotonin syndrome.
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result (Sternbach, 1991b).

3.5.1.EZ St John's Wort

1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Case reports describe the onset of serotonin syndrome-like symptoms, mania, and hypomania following the addition of St. John's Wort to sertraline, fluoxetine, and paroxetine therapy (Spinella & Eaton, 2002c; Barbanel et al, 2000a; Waksman et al, 2000a; Lantz et al, 1999a). A patient exhibited a syndrome resembling sedative/hypnotic intoxication after adding St. John's Wort to paroxetine therapy (Gordon, 1998a). St. John's Wort is thought to inhibit serotonin reuptake and may have mild monoamine oxidase inhibitory activity (Singer et al, 1999; Thiede & Walper, 1994), which when added to selective serotonin reuptake inhibitors may result in serotonin syndrome.
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Patients should be advised to wait two weeks after stopping St. John's Wort before restarting selective serotonin reuptake inhibitor therapy. If a patient plans to replace selective serotonin reuptake inhibitor (SSRI) therapy with St. John's Wort, the half-life of the specific SSRI should be taken into consideration, waiting at least 5 half-lives for the SSRI to be metabolized out of the body.
7) Probable Mechanism: additive serotonergic effect
8) Literature Reports
a) Five cases have been reported of serotonin syndrome in the elderly after combining prescription antidepressants and St. John's Wort. Case 1 developed dizziness, nausea, vomiting and a headache 4 days after starting St. John's Wort 300 milligrams (mg) three times daily combined with sertraline 50 mg daily. Her symptoms resolved 2 to 3 days after stopping all medications. Case 2 developed nausea, epigastric pain and anxiety 3 days after starting St. John's Wort 300 mg twice daily combined with sertraline 75 mg daily. His symptoms resolved in one week after discontinuing both medications, and he resumed sertraline use without complications. The third case developed nausea, vomiting, anxiety, and confusion 2 days after starting St. John's Wort 300 mg twice daily combined with sertraline 50 mg daily. His symptoms improved in 4 to 5 days after stopping both medications and taking cyproheptadine 4 mg three times daily. Case 4 developed nausea, anxiety, restless, and irritability 2 days after starting St. John's Wort 300 mg three times daily combined with sertraline 50 mg daily. Cyproheptadine 4 mg twice daily was administered for seven days, and his symptoms improved in 1 week after stopping the medication. Cases 1 through 4 resumed their prescriptive sertraline after symptoms subsided and had no further problems. Case 5 developed nausea, vomiting and restlessness 3 days after starting St. John's Wort 300 mg three times daily combined with nefazodone 100 mg twice daily. She continued to take St. John's Wort but discontinued the nefazodone and over 1 week her symptoms Improved. She refused to resume therapy with nefazodone, but continued therapy with St. John's Wort and mild to moderate symptoms of depression and anxiety returned (Lantz et al, 1999).
b) A 50-year-old female taking St. John's Wort 600 mg daily experienced symptoms of sedative intoxication when she ingested a single dose of paroxetine 20 mg. She was incoherent, groggy, slow-moving, and complained of nausea and weakness. Prior to starting St. John's Wort, she had been receiving paroxetine 40 mg daily for eight months without adverse effects. After a night of sleep, she returned to her baseline mental status (Gordon, 1998).
c) A 61-year-old female experienced restlessness and involuntary movements of her extremities after beginning paroxetine 20 milligrams (mg) two days after discontinuing St. John's Wort 600 mg daily. The

patient reported agitation and akathisia 8 hours after taking the first dose of paroxetine. She presented with diaphoresis and involuntary movement of all extremities with hyperreflexia and rigidity. Blood pressure, heart rate, and temperature were normal. After admission, blood pressure increased to 200/116 mmHg and heart rate increased to 145 beats per minute. Creatine kinase increased from 212 units/liter (U/L) initially to 1024 U/L. The patient was managed with supportive care and lorazepam and discharged after two days (Waksman et al, 2000).

d) A 28-year-old male developed a manic syndrome following comedication with St. John's Wort and sertraline. The patient was also on testosterone replacement therapy following bilateral orchidectomy 2 years earlier, but testosterone levels were subtherapeutic. The patient was prescribed sertraline 50 milligrams daily for depression following a 2 week trial of St. John's Wort per patient preference (dose not specified). Before sertraline was started, the patient was instructed to discontinue St. John'sWort, but continued it despite this advice. The patient experienced improved mood so did not see his physician, believing that he did not need further treatment. Over 2 months, the patient had elated mood, was irritable, and overspent, buying a car he could not afford, and was ultimately arrested for stealing fuel for the car. On arrest, he was referred to psychiatric services due to irritability and disinhibition. He was observed to be over-aroused, distractible, have flight of ideas, and grandiose delusions, leading to a diagnosis of a manic episode. The authors state the possibility of the manic state resulting from sertraline therapy alone, and that St. John's Wort may have increased the risk as a result of monoamine oxidase inhibition. Since the patient's testosterone level was subnormal, the possibility of its contribution to the manic state was considered low. However, the patient had elevated gonadotropin levels (luteinizing hormone and follicle-stimulating hormone) which may have predisposed the patient to mania (Barbanel et al, 2000).

e) A 42-year-old female experienced symptoms consistent with a mixed hypomanic episode following concomitant use of fluoxetine, buspirone, Ginkgo biloba, and St. John's Wort. The symptoms resolved following discontinuation of Ginkgo and St. John's Wort. The patient was being treated for depression following a mild traumatic brain injury with fluoxetine 20 milligrams (mg) twice daily and buspirone 15 mg twice daily. Several weeks prior to presentation, buspirone was increased to 20 mg twice daily for persistent anxiety and the patient began taking Ginkgo biloba, melatonin, and St. John's Wort in unspecified doses. Melatonin was considered unlikely to have contributed to her symptoms. Ginkgo and St. John's Wort were considered possible contributors since they may potentiate antidepressants, and considering the temporal relationship between the use of the herbs and onset of symptoms and discontinuation of the herbs and resolution of symptoms. However, the brain injury was considered a possible contributor (Spinella & Eaton, 2002b).

3.5.1.FA Sulfinpyrazone

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.FB Sulindac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined

use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.FC Sulodexide

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.FD Sumatriptan

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concomitant use of a triptan, such as sumatriptan, and a serotonin specific reuptake inhibitor (SSRI), such as fluvoxamine (Prod Info Imitrex(R), 2002). Concurrent use of a triptan and an SSRI may result in serotonin syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndrome with patients who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administration, 2006).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Coadministration of a triptan, such as sumatriptan, and an SSRI, such as fluvoxamine, may result in a life-threatening condition called serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination).

7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.FE Suprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.FF Tacrine

1) Interaction Effect: an increase in the plasma concentration of tacrine

2) Summary: Two studies involving healthy volunteers and single doses of tacrine found that fluvoxamine inhibited the metabolism of tacrine, causing an increase in the area under the concentration-time curve (AUC) of tacrine and three of its metabolites. Fluvoxamine inhibits cytochrome P450 1A2 enzymes, and these same enzymes are responsible for tacrine metabolism. Whether this interaction would be present in Alzheimer's patients receiving multiple tacrine doses is not known (Becquemont et al, 1997a; Teilmann Larsen et al, 1999a).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: While the exact clinical implication of this drug interaction is uncertain, monitor patients receiving tacrine and fluvoxamine concurrently for excessive tacrine adverse effects, including cholinergic effects. Also monitor liver function for increased hepatotoxicity.

7) Probable Mechanism: inhibition of cytochrome P450 1A2 enzymes by fluvoxamine

8) Literature Reports

a) A randomized, double-blind, two-period cross-over study involving 14 healthy male volunteers investigated the influence of fluvoxamine on the pharmacokinetics of a single-dose of tacrine. Study subjects received either fluvoxamine 100 mg or placebo once daily for six days, and a single dose of tacrine 40 mg was coadministered on day 6. The tacrine area under the concentration-time curve (AUC) increased from 27 ng/hr/mL to 224 ng/hr/mL in the presence of fluvoxamine. Maximum concentration (Cmax) of tacrine also increased from 7 ng/mL to 39 ng/mL during the fluvoxamine period. No significant changes in the time to reach Cmax (tmax) and the half-life of tacrine were observed. The AUC values of three tacrine metabolites were also significantly increased, but to a lesser extent than the AUC of tacrine. Whether these same results are seen in Alzheimer's patients receiving multiple doses of tacrine is not known (Becquemont et al, 1997).

b) Eighteen healthy male volunteers participated in an open, randomized crossover study to establish whether fluvoxamine in clinically relevant doses was able to inhibit the formation of tacrine metabolites. Volunteers received tacrine 40 mg as a single dose and fluvoxamine 50 mg or 100 mg once daily for five days, followed by a dose of tacrine 20 mg. Fluvoxamine reduced the apparent oral clearance of tacrine by 85%. Specifically, fluvoxamine reduced the formation of 1- and 2-hydroxytacrine, but the formation of 4-hydroxytacrine was not affected. Whether the inhibition of these metabolites reduced tacrine-induced hepatotoxicity requires further investigation (Teilmann Larsen et al, 1999).

3.5.1.FG Tapentadol

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

2) Summary: Concurrent use of tapentadol and a selective serotonin reuptake inhibitor (SSRI) may result in serotonin syndrome, which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea (Prod Info tapentadol immediate release oral tablets, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of tapentadol and an SSRI may result in a life-threatening condition called serotonin syndrome. If these agents are used together, monitor the patient closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination), especially during treatment initiation and dose increases (Prod Info tapentadol immediate release oral tablets, 2008).

7) Probable Mechanism: additive serotonergic effect

3.5.1.FH Tenidap

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent

use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.FI Tenoxicam

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.FJ Terfenadine

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Fluvoxamine should not be used in combination with terfenadine. Although there is no direct experience with this combination, fluvoxamine appears to be a potent inhibitor of the cytochrome P450IIIA4 isozyme, the enzyme primarily responsible for the metabolism of terfenadine. Inhibition of this enzyme may result in elevated terfenadine concentrations; increased plasma concentrations of terfenadine are associated with QT prolongation and torsades de pointes, which can be fatal (Prod Info Luvox(R), 1997h).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of fluvoxamine and terfenadine is contraindicated.

7) Probable Mechanism: inhibition by fluvoxamine of terfenadine metabolism

3.5.1.FK Theophylline

1) Interaction Effect: theophylline toxicity (nausea, vomiting, palpitations, seizures)

2) Summary: Fluvoxamine-theophylline combination therapy has produced toxic serum concentrations of theophylline (Sperber, 1991a; van den Brekel & Harrington, 1994; Perucca et al, 1994; Lorenz et al, 1996a). The reported mechanism of action is fluvoxamine's inhibitory effect on the hepatic cytochrome P4501A2 (CYP1A2), the microsome responsible for catalyzing theophylline metabolism (Prod Info Luvox(R), 1997r).

3) Severity: major

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: Careful monitoring of theophylline serum concentration is required. Theophylline doses should be reduced to one-third of the usual daily maintenance dose if fluvoxamine is coadministered. No dose adjustment is necessary for fluvoxamine.

7) Probable Mechanism: decreased theophylline metabolism

8) Literature Reports

a) Fluvoxamine appeared to be responsible for substantially increased serum theophylline levels and symptoms of theophylline toxicity in an 11-year-old boy taking sustained-release theophylline 300 mg twice daily (Sperber, 1991). Both drugs were discontinued, and theophylline was later reinstated (dose not specified) with no further evidence of toxicity.

b) An increase in theophylline plasma concentrations from 13 mg/L to 40 mg/L was found after fluvoxamine was added to therapy. The patient was an 83-year-old man who was receiving sustained release theophylline 600 mg per day (Diot et al, 1991).
c) Fluvoxamine 50 mg twice a day given concurrently with theophylline 1000 mg daily resulted in a theophylline plasma concentration of 32 mcg/mL and nausea and tachycardia in a 75-year-old male with normal liver function (Lorenz et al, 1996). Theophylline clearance was calculated to be 43 mL/h before the addition of fluvoxamine and 22 mL/h after four doses.
d) In 12 healthy nonsmoking volunteers with steady-state fluvoxamine levels, the pharmacokinetics of a single dose of theophylline 375 mg were evaluated. Theophylline clearance decreased three-fold. Therefore, it is recommended that the daily maintenance dose of theophylline be reduced by two-thirds in a patient also receiving fluvoxamine (Prod Info Luvox(R), 1997q).

3.5.1.FL Thioridazine

1) Interaction Effect: an increased risk of thioridazine toxicity, cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Fluvoxamine inhibits the metabolism of thioridazine, possibly through the inhibition of cytochrome P450 2D6 (CYP2D6) resulting in toxicity. The resulting elevated levels of thioridazine would be expected to enhance the prolongation of the QT interval associated with thioridazine and may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as torsade de pointes-type arrhythmias (Prod Info Mellaril(R), 2000a).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Due to the potential for significant, possibly life-threatening, proarrhythmic effects, concurrent administration of thioridazine and fluvoxamine is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated thioridazine metabolism
8) Literature Reports
a) The serum concentrations of thioridazine and its two metabolites, mesoridazine and sulforidazine, were evaluated in ten male schizophrenic patients aged 36 to 78 years at three separate time points. All patients were receiving thioridazine monotherapy for the management of schizophrenia at a mean dose of 88 mg daily. Fluvoxamine 50 mg daily was coadministered for one week. Plasma levels of thioridazine and its metabolites were measured during monotherapy with thioridazine, after one week of concurrent therapy with thioridazine and fluvoxamine, and two weeks after fluvoxamine was discontinued. Following one week of combination therapy with fluvoxamine and thioridazine, thioridazine levels increased 225%, mesoridazine levels increased 219%, and sulforidazine concentrations rose 258%. Even two weeks after the discontinuation of fluvoxamine, three patients continued to show elevated thioridazine and metabolite levels. No clinical symptoms were attributed to the interaction between these two agents (Carrillo et al, 1999).
b) The metabolism of thioridazine is inhibited by drugs such as fluvoxamine due to reduced cytochrome P450 2D6 and 1A2 isozyme activity. The elevated levels of thioridazine would be expected to enhance the prolongation of the QT interval associated with thioridazine. This, in turn, may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as torsade de pointes-type arrhythmias (Prod Info Mellaril(R), 2000).

3.5.1.FM Tiaprofenic Acid

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.FN Ticlopidine

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.FO Tinzaparin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
7) Probable Mechanism: unknown
8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was

11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.FP Tirofiban

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.FQ Tizanidine

1) Interaction Effect: increased tizanidine plasma concentrations
2) Summary: Concomitant use of fluvoxamine and tizanidine is contraindicated. Use of these drugs together has resulted in increased plasma concentrations and half-life of tizanidine (Prod Info tizanidine hcl tablets, 2006).(Prod Info Zanaflex (R) Tablets, 2004). Concurrent administration of fluvoxamine, a potent CYP1A2 inhibitor, and tizanidine induced a profound increase in tizanidine bioavailability. The inhibition of CYP1A2-mediated tizanidine metabolism provokes clinically significant hypotension and alteration of consciousness (Granfors et al, 2004). In a retrospective case series, tizanidine-associated adverse events occurred significantly more often in patients treated concomitantly with fluvoxamine and tizanidine compared with tizanidine monotherapy (Momo et al, 2004).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: established
6) Clinical Management: The concomitant use of fluvoxamine and tizanidine is contraindicated. Use of tizanidine with fluvoxamine can increase the plasma concentrations of tizanidine (Prod Info tizanidine hcl tablets, 2006) which may lead to decreased blood pressure, psychomotor impairment, and excessive drowsiness (Granfors et al, 2004).
7) Probable Mechanism: inhibition of CYP1A2-mediated tizanidine metabolism by fluvoxamine
8) Literature Reports

a) In a study of 10 healthy volunteers treated with fluvoxamine and tizanidine, the half-life, Cmax, and AUC of tizanidine increased by 12-fold, 33-fold, and 3-fold, respectively (Prod Info tizanidine hcl tablets, 2006).

b) Coadministration of fluvoxamine with tizanidine resulted in profound increases in tizanidine bioavailability due to P450 CYP1A2-mediated inhibition of tizanidine metabolism and was associated with multiple adverse clinical effects. In a randomized, double-blind, crossover study (4-week wash out period), healthy subjects (n=10) received a 4-day regimen of fluvoxamine 100 milligrams (mg) or placebo once daily. On day 4, each subject received a single oral dose of tizanidine 4 mg. Serial blood pharmacokinetic analysis was performed over the next 24 hours, in conjunction with measurement of pharmacodynamic response. When compared with placebo, the presence of fluvoxamine dramatically increased tizanidine mean maximum serum concentration (by 1210% (from 2.2 to 26.6 nanograms/milliliter), p=0.000001), mean area under the concentration-time curve (AUC 0-infinity; by 3260%, p=0.000002), and mean elimination half-life from 1.5 hours to 4.3 hours (by 290%, p=0.00004). Pharmacodynamic responses to fluvoxamine-enhanced tizanidine exposure were also dramatic: mean systolic blood pressure declined by 35 millimeters mercury (mmHg; from 115 to 79 mmHg), mean diastolic blood pressure decreased by 20 mmHg (from 66 to 46 mmHg), heart rate decreased by 4 beats per minute, and subjectively perceived drowsiness (0-100 visual analogue scale) increased by a mean of 42 points compared with the placebo-tizanidine phase (p=0.000009, p=0.00002, p=0.007, and p=0.0002, respectively). During the fluvoxamine-tizanidine phase, all subjects experienced somnolence and dizziness for between 3 and 6 hours after the dose of tizanidine. There was no compensatory tachycardic response to the treatment-associated hypotension (Granfors et al, 2004).

c) In a retrospective case series review of patients treated with tizanidine (n=913), tizanidine-related adverse events occurred with significantly greater frequency in patients treated concurrently with fluvoxamine and tizanidine (n=23) when compared with tizanidine monotherapy (26.1% (6/23) versus 5.3%, respectively; p less than 0.0001). Bradycardia occurred in the 6 affected patients, with dizziness, hypothermia, drowsiness, hypotension, and impaired speech occurring in order of descending frequency (Momo et al, 2004).

3.5.1.FR Tolmetin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.FS Toloxatone

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with fluvoxamine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of selective serotonin reuptake inhibitors and MAO inhibitors (Prod Info Luvox(R), 1997n; Lappin & Auchincloss, 1994k; Graber et al, 1994k; Suchowersky & de Vries, 1990k). As a reversible and selective monoamine oxidase inhibitor, toloxatone may not potentiate the effects of selective serotonin reuptake inhibitors to the same frequency, extent, and duration observed with other MAOIs. However, until further studies confirm the safety and efficacy of this combined therapy, caution should be used.
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of fluvoxamine and a MAO inhibitor should be avoided. Wait at least two weeks after discontinuing an MAO inhibitor before initiating therapy with fluvoxamine. Wait at least two weeks after discontinuing fluvoxamine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: serotonin reuptake inhibition
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991h). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement in symptoms after the second dose (Lappin & Auchincloss, 1994j).
c) A drug interaction occurred in a 61-year old woman whose regimen of sertraline 100 mg twice daily was added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites (Graber et al, 1994j).
d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky

& de Vries, 1990j). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.FT Tramadol

1) Interaction Effect: an increased risk of seizures and serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Seizures and serotonin syndrome have been reported in patients using tramadol. The risk of seizures and serotonin syndrome may be enhanced when fluvoxamine and tramadol therapy are combined (Prod Info Ultram(R), 2001).
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 concomitant fluvoxamine therapy. If possible, avoid this combination, especially in patients with underlying conditions that might predispose to seizures. Observe the patient closely for signs and symptoms of serotonin syndrome.
7) Probable Mechanism: increased concentration of serotonin in the nervous system and periphery

3.5.1.FU Tranylcypromine

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with fluvoxamine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Luvox(R), 1997a; Lappin & Auchincloss, 1994a; Graber et al, 1994a; Suchowersky & de Vries, 1990a). Concomitant use is not recommended.
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of a selective serotonin reuptake inhibitors, such as fluvoxamine, and tranylcypromine is contraindicated. Wait at least two weeks after discontinuing an MAO inhibitor before initiating therapy with fluvoxamine. Wait at least two weeks after discontinuing fluvoxamine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: serotonin reuptake inhibition
8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.

b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement in symptoms after the second dose (Lappin & Auchincloss, 1994).

c) A drug interaction occurred in a 61-year old woman whose regimen of sertraline 100 mg twice daily was added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least 5 half-lives of the parent drug and any active metabolites (Graber et al, 1994).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms.

Rechallenge with fluoxetine alone occurred without incident.

3.5.1.FV Triazolam

1) Interaction Effect: elevated serum triazolam concentrations
2) Summary: Fluvoxamine coadministration (100 mg daily) with alprazolam 1 mg four times daily resulted in a 2-fold increase in alprazolam steady-state plasma concentrations, AUC, Cmax, and half-life. Elevated plasma levels of alprazolam were associated with impaired psychomotor performance and memory. This suggests that fluvoxamine is a potent inhibitor of cytochrome P450 3A4 enzymes, which are responsible for alprazolam metabolism. Because triazolam also relies on CYP3A4 for metabolism, a similar interaction with fluvoxamine seems likely (Prod Info Luvox(R), 1997d).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When triazolam and fluvoxamine are coadministered, monitor patients for benzodiazepine toxicity (sedation, lethargy, slurred speech). Triazolam doses may need to be reduced, or consider switching to a benzodiazepine eliminated by glucuronidation (eg, lorazepam, oxazepam, temazepam).
7) Probable Mechanism: inhibition of triazolam metabolism and clearance due to cytochrome P450 3A4 enzyme inhibition

3.5.1.FW Tryptophan

1) Interaction Effect: severe vomiting
2) Summary: Tryptophan enhances the serotonergic effect of fluvoxamine and has been reported to cause severe vomiting. Use the combination cautiously (Prod Info Luvox(R), 1997i).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of fluvoxamine and tryptophan should be avoided.
7) Probable Mechanism: enhanced serotonergic effects

3.5.1.FX Valdecoxib

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.FY Warfarin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin. In patients receiving warfarin and fluvoxamine concomitantly for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Fluvoxamine appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for warfarin metabolism (Schalekamp et al, 2008; Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluvoxamine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluvoxamine therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving fluvoxamine and anticoagulant therapy (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
7) Probable Mechanism: unknown
8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) A hospitalized 80-year-old female was started on intravenous heparin and oral warfarin therapy due to an embolic stroke secondary to atrial fibrillation and mitral stenosis. Her warfarin dose was maintained at 1 mg daily, with her INR between 2.5 and 3. Fluvoxamine 25 mg daily was started for depression, and her warfarin dose was increased to 1.5 mg daily 3 days later due to worsening of the left hemiparesis. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. Warfarin was discontinued, fresh frozen plasma was given, and fluvoxamine was discontinued. Six days later, warfarin was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of fluvoxamine. She was eventually stabilized on warfarin 1 mg daily with INR values between 2 and 2.5 (Yap & Low, 1999).

3.5.1.FZ Xemilofiban

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.GA Zolmitriptan

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concomitant use of sumatriptan, a 5-hydroxytryptamine-1 (5HT-1) agonist, and a serotonin specific reuptake inhibitor (SSRI) (Prod Info Imitrex(R), 1998a; Prod Info Zomig(TM), 1997). Because zolmitriptan is a 5HT 1B/1D agonist, a similar interaction between SSRIs and zolmitriptan may occur (Prod Info Zomig(TM), 1997). Concurrent use of zolmitriptan and an SSRI may result in serotonin syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes,

nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndrome with patients who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administration, 2006).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as zolmitriptan, and an SSRI may result in a life-threatening condition called serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) The pharmacokinetics of a single 10 mg dose of zolmitriptan were not altered by four weeks of fluoxetine 20 mg daily pretreatment in healthy volunteers. The effects of zolmitriptan on blood pressure were also not changed by fluoxetine therapy (Prod Info Zomig(R), 2002).

3.5.1.GB Zomepirac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.2 Drug-Food Combinations

3.5.2.A Grapefruit Juice
1) Interaction Effect: increased fluvoxamine exposure
2) Summary: Grapefruit juice significantly increased fluvoxamine exposure when co-administered to healthy volunteers (n=10), in a randomized, placebo-controlled crossover study. Compared with baseline, grapefruit juice produced a 1.3-fold increase in the serum mean concentration of fluvoxamine, by 33 nanograms/milliliter (ng/mL; plus/minus 10 to 44 ng/mL) (p=0.049) and increased the fluvoxamine mean area under the concentration-time curve from 550 ng hours/mL to 881 ng hours/mL (p=0.014) (Hori et al, 2003a).
3) Severity: minor
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Counsel patients to avoid grapefruit juice while taking fluvoxamine. Orange juice may be substituted as it provides the same basic nutrients but is not known to inhibit drug metabolism.
7) Probable Mechanism: inhibition of intestinal CYP3A4 and P-glycoprotein-mediated fluvoxamine metabolism
8) Literature Reports
a) Grapefruit juice significantly increased exposure to fluvoxamine, when co-administered to healthy volunteers. In a randomized, crossover study, healthy men (n=10) received 250 milliliters of either regular-strength grapefruit juice or water 3 times daily for 5 days. On day 6, oral fluvoxamine 75 milligrams was given to each subject along with the grapefruit juice or water regimen. Serial blood sampling then occurred over the next 24 hours. After 2 weeks, subjects crossed over to the opposing study arm. Compared with baseline, grapefruit juice produced a 1.3-fold increase in the mean serum

concentration of fluvoxamine, by 33 nanograms/milliliter (ng/mL; plus/minus 10 to 44 ng/mL) (p=0.049). In 8 subjects, the fluvoxamine mean area under the concentration-time curve increased from 550 ng hours/mL to 881 ng hours/mL (p=0.014); additionally, 2 subjects showed a rebound increase in fluvoxamine plasma concentration at 24 hours after fluvoxamine administration (Hori et al, 2003).

3.5.4 Drug-Tobacco Combinations

3.5.4.A Tobacco

1) Interaction Effect: increased fluvoxamine metabolism
2) Summary: In comparison to nonsmokers, fluvoxamine metabolism is increased by 25% in smokers (Prod Info Luvox(R), 1997ab).
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor fluvoxamine efficacy in patients who smoke. Larger doses of fluvoxamine may be required.
7) Probable Mechanism: hepatic enzyme induction

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) Fluvoxamine Maleate

1) Therapeutic

a) Decreases in depressive or obsessive-compulsive behavior by both subjective and objective assessments.

2) Toxic

a) Laboratory Parameters

1) Regularly monitor serum electrolytes, especially sodium, blood urea nitrogen, and serum creatinine in the following patients or disease states (Prod Info fluvoxamine maleate oral tablets, 2005):

elderly
concomitant diuretics
syndrome of inappropriate secretion of antidiuretic hormone
displacement syndromes
edematous states
adrenal disease
fluid depleted patients

b) Physical Findings

1) Monitor patients receiving antidepressants for worsening of depression, suicidality, or unusual changes in behavior, especially at the initiation of therapy or when the dose increases or decreases. Such monitoring should include at least weekly face-to-face contact with patients or their family members or caregivers during the initial 4 weeks of treatment, then visits every other week for the next 4 weeks, then at 12 weeks, and then as clinically indicated beyond 12 weeks. Families and caregivers should be advised of the need for close observation (i.e., daily observation) of patients and communication with the prescriber (Prod Info fluvoxamine maleate oral tablets, 2005).

2) Patients who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, or mania may be at an increased risk for worsening depression or suicidality. If these symptoms are observed, therapy should be re-evaluated and it may be necessary to discontinue medications when symptoms are severe, sudden in onset, or were not part of the patient's initial symptoms (Prod Info fluvoxamine maleate oral tablets, 2005).

3) Nausea and/or vomiting seen early during fluvoxamine therapy may be alleviated by reducing the dose and then gradually increasing the dose to therapeutic effect.

4.2 Patient Instructions

A) Fluvoxamine (By mouth)

Fluvoxamine

Treats symptoms of obsessive compulsive disorder (OCD) and social anxiety disorder (social phobia).

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to fluvoxamine. You should not use fluvoxamine if you are also using alosetron (Lotronex®), thioridazine (Mellaril®), terfenadine (Seldane®), astemizole (Hismanal®), cisapride (Propulsid®), pimozide (Orap®), or tizanidine (Zanaflex®). Make sure your doctor knows if you have taken an MAO inhibitor (such as isocarboxazid, phenelzine, selegiline, tranylcypromine, Eldepryl®, Nardil®, Marplan®, or Parnate®) within the past 2 weeks.

How to Use This Medicine:
Long Acting Capsule, 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.
Take this medicine at bedtime, unless your doctor tells you otherwise.
Do not use this medicine for longer than 10 weeks unless your doctor tells you otherwise.
Swallow the extended-release capsule whole. Do not crush, break, or chew it.
This medicine should come with a Medication Guide. Read and follow these instructions carefully. Ask your doctor or pharmacist if you have any questions. Ask your pharmacist for the Medication Guide if you do not have one. Your doctor might ask you to sign some forms to show that you understand this information.

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.

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 outdated medicine or medicine no longer needed.
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 fluvoxamine. Make sure your doctor knows about ALL other medicines you are using, especially medicines to treat depression or mental illness.
Tell your your doctor if you are using blood thinners (warfarin or Coumadin®), diuretics (water pills), or pain or arthritis medicine (sometimes called “NSAIDs”) such as aspirin, ibuprofen, Aleve®, or Motrin®. Tell your doctor if you use a tranquilizer or sedative such as alprazolam (Xanax®), diazepam (Valium®), midazolam (Versed®), ramelteon (Rozerem®), or triazolam (Halcion®).
Your doctor should know if you use blood pressure medicine (such as atenolol, metoprolol, propranolol, Corgard®, Inderal®, Lopressor®, Toprol®, or Tenormin®) or medicine to treat headaches (such as eletriptan, sumatriptan, Imitrex®, or Relpax®).
Tell your doctor if you also use carbamazepine (Tegretol®), clozapine (Clozaril®), diltiazem (Cardizem®), linezolid (Zyvox®), lithium (Eskalith®), methadone (Dolophine®), mexiletine (Mexitil®), quinidine, omeprazole (Prilosec®), phenytoin (Dilantin®), St. John's wort, Tacrine (Cognex®), theophylline (Theo-Dur®), tramadol (Ultram®), or tryptophan supplements.
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 have diabetes, liver disease, heart disease or a recent heart attack, epilepsy or seizures, bleeding problems, or a history of mania. Tell your doctor if you smoke.
For some children, teenagers, and young adults, this medicine can increase thoughts of suicide. Tell your doctor or your child's doctor right away if you or your child start to feel more depressed and have thoughts about hurting yourselves. Report any unusual thoughts or behaviors that trouble you or your child, especially if they are new or are getting worse quickly. Make sure the doctor knows if you or your child have trouble sleeping, get upset easily, have a big increase in energy, or start to act reckless. Also tell the doctor if you or your child have sudden or strong feelings, such as feeling nervous, angry, restless, violent, or scared. Let the doctor know if you, your child, or anyone in your family has bipolar disorder (manic-depressive) or has tried to commit suicide.
While you are using this medicine, be sure to keep all appointments with your caregiver or mental health

counselor. It is very important that your caregivers observe you for changes in your mental status or behavior.
Fluvoxamine should not be used to treat depression. It should not be given to a child unless that child has been diagnosed with OCD.
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert.
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:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing.
Anxiety, agitation, aggression, trouble sleeping, or panic attack.
Blurred vision, shallow breathing, trouble standing or walking.
Change in how much or how often you urinate.
Chest pain.
Confusion, extreme weakness, muscle twitching.
Fast, slow, or uneven heartbeat.
Feeling irritable, nervous, or shaky.
Fever, chills, cough, sore throat, and body aches.
Lightheadedness or fainting.
Numbness, tingling, or burning pain in your hands, arms, legs, or feet.
Seizures or tremors.
Sudden and severe stomach pain, nausea, or vomiting.
Swelling in your hands, feet, or ankles.
Unusual behavior, thoughts of hurting yourself or others.
Unusual bleeding or bruising.
Yellowing of your skin or the whites of your eyes.

If you notice these less serious side effects, talk with your doctor:
Diarrhea, constipation, stomach upset, or loss of appetite.
Dry mouth.
Headache or dizziness.
Mood or behavior changes after you stop using the medicine.
Muscle pain.
Pain during monthly periods.
Problems having sex.
Prolonged erection of the penis.
Skin rash.
Sleepiness.
Sweating more than usual.
Weakness.

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

4.3 Place In Therapy

A) Fluvoxamine Maleate

1) Obsessive-compulsive Disorder

a) The extended-release formulation of fluvoxamine maleate is indicated for the treatment of obsessions and compulsions in adult patients with obsessive compulsive disorder (OCD) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008), and the immediate-release formulation of fluvoxamine maleate is indicated for the treatment of obsessions and compulsions in patients with OCD aged 8 years and older (Prod Info LUVOX(R) oral tablets, 2007).

b) Treatment with extended-release fluvoxamine maleate at once-daily doses of 100 to 300 milligrams was safe and led to clinical improvement in adult patients with obsessive-compulsive disorder compared to placebo in a 12-week, multicenter, randomized, double-blind study (n=253) (Hollander et al, 2003).

c) A 10-week study demonstrated that immediate-release fluvoxamine and behavior therapy were more efficacious for treating obsessive compulsive disorder (OCD) compared to placebo and behavior therapy (Hohagen et al, 1998).

d) Immediate-release fluvoxamine was significantly more effective than placebo in children (8 years or older) and adolescents with obsessive compulsive disorder (OCD) in a 10-week, double-blind study in 120 children with at least a 6-month history of OCD (Riddle, 1996).

2) Social Anxiety Disorder

a) Extended-release fluvoxamine maleate is indicated for social anxiety disorder, also known as social phobia (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).

b) In a randomized, double-blind, multicenter, placebo-controlled study (n=300), patients with generalized social anxiety disorder (GSAD) who received fluvoxamine extended-release (ER) demonstrated a

significantly greater reduction in the mean Liebowitz Social Anxiety Scale (LSAS) total score from baseline compared with patients who received placebo (Westenberg et al, 2004), with a trend towards continued clinical benefit with fluvoxamine ER compared to placebo in a 12-week double-blind extension phase of this study (Stein et al, 2003).

3) Depression

a) All of the selective serotonin reuptake inhibitors (SSRIs) are effective for treating depression, although selected characteristics of each agent may offer greater benefit in some patients. Fluvoxamine does not have any major therapeutic benefits over other SSRIs; however, discontinuation of therapy among patients treated with fluvoxamine appeared higher than for other SSRIs during clinical trials. Gastrointestinal symptoms and drowsiness/sedation were more common especially early in therapy than with other SSRIs. Ultimately, the selection of an SSRI is dependent on clinical judgement and response of patients to previous therapy (Edwards & Anderson, 1999).

b) Data suggest that a trial of a second serotonin reuptake inhibitor (SSRI) is a viable clinical alternative in depressed patients who have failed to respond to an adequate trial of the first SSRI used. In a retrospective review of 55 patients who had failed to respond to at least five weeks of therapy with either fluoxetine, sertraline, fluvoxamine, or paroxetine (all at therapeutic dosages), 51% responded to a trial of an alternative agent. The choice of the second agent was based on clinician preference; no difference between response rates of the different drugs was noted (Joffe et al, 1996).

4.4 Mechanism of Action / Pharmacology

A) Fluvoxamine Maleate

1) Mechanism of Action

a) Fluvoxamine maleate is a potent selective serotonin (5-HT) reuptake inhibitor (SSRI) belonging to the 2-aminoethyl oxime ethers of aralkylketones series and is unrelated to other SSRIs and clomipramine. In obsessive compulsive disorder the clinical effect is presumed to be from its specific inhibition of serotonin reuptake in brain neurons. In-vitro studies have shown that fluvoxamine maleate has no significant affinity for histaminergic, alpha or beta adrenergic, muscarinic, or dopaminergic receptors (Prod Info LUVOX(R) CR extended-release oral capsules, 2008; Prod Info LUVOX(R) oral tablets, 2007).

2) Review Articles

a) Fluvoxamine is a compound in the series of 2-aminoethyloxime ethers of aralkylketones. The drug acts as an antidepressant and has no structural similarities to tricyclic antidepressants. Fluvoxamine is a potent selective inhibitor of presynaptic serotonin (5-hydroxytryptamine or 5-HT) reuptake (Claassen et al, 1977). Following a single dose of fluvoxamine, the serotonin turnover in the rat forebrain was reduced (Claassen et al, 1977). Also, in the raphe nuclei the intraneuronal and extraneuronal concentrations of serotonin decreased and increased, respectively (Constantinidis et al, 1981). In vitro and in vivo experiments demonstrated that fluvoxamine fails to facilitate noradrenergic neurotransmission, similar to other specific inhibitors of serotonin uptake (Bradford, 1983; Claassen, 1983). Unlike the tricyclic antidepressants, fluvoxamine demonstrates a very low in vitro affinity for alpha-1, alpha-2, beta-1, dopamine-2, histamine-1, serotonin-1, serotonin-2 or muscarinic receptors (Richelson & Nelson, 1984; Benfield & Ward, 1986). In vitro and in vivo studies have not demonstrated any monoamine oxidase inhibitor activity (Lapierre et al, 1983; Benfield & Ward, 1986).

b) The exact relationship of serotonin uptake inhibition and its effects on depression are not known. It is proposed that fluvoxamine's antidepressant activity is initiated by enhanced serotoninergic input to other neuronal systems in the brain. This may lead to primary and secondary changes in receptors and rates of firing and rates of release of neurotransmitters which may result in remission of depressive symptoms (Fuller & Wong, 1987).

c) The effects of treatment with fluvoxamine on platelet and plasma serotonin were studied in 11 drug-free patients with major depression (Celeda et al, 1992). Single-dose fluvoxamine (50 mg) was without effect on serotonin, whereas treatment with 100 to 150 mg/day for 12 weeks reduced both platelet (-89%) and plasma (-60%) serotonin. Patients who responded to the treatment at 6 weeks had significantly lower pretreatment values of platelet serotonin than the rest. This suggests that "low serotonin" patients may respond more rapidly to fluvoxamine. Platelet serotonin and Hamilton Depression Scale scores correlated significantly during treatment. These data demonstrate a marked action of fluvoxamine as a serotonin reuptake inhibitor at therapeutic doses and confirm that this mechanism is relevant for its efficacy as an antidepressant.

d) Fluvoxamine does not have significant effects on central norepinephrine function in human depressed patients, as determined by measurement of MHPG, VMA, NMN, and HVA in urine and NE in plasma (Johnson et al, 1993).

e) The possible relationship between plasma tryptophan (Trp) to large neutral amino acid (LNAA) ratio, thought to reflect brain serotonin (5-HT) formation, was estimated in 47 patients with major depression (unipolar and bipolar) before and after 6 weeks of fluvoxamine. The authors found a significant difference between responders (n=39) and nonresponders (n=8) for Trp/LNAA ratio, whereas no difference emerged between the two groups for the mean plasma steady-state fluvoxamine levels. These data suggest that a specific plasma amino acid profile may be a useful indicator of good clinical response to fluvoxamine (Lucca et al, 1994).

4.5 Therapeutic Uses

4.5.A Fluvoxamine Maleate

Alcoholism

Asperger's disorder

Autistic disorder

Body dysmorphic disorder

Compulsive buying

Compulsive exhibitionism

Compulsive gambling

Depression

Eating disorder

Fibromyalgia

Hypochondriasis

Mixed anxiety and depressive disorder

Myocardial infarction; Prophylaxis

Obsessive-compulsive disorder

Panic disorder

Posttraumatic stress disorder

Premenstrual dysphoric disorder

Prostatic pain

Repetitive self-excoriation

Severe major depression with psychotic features

Social phobia

Stereotypy habit disorder

Trichotillomania

Wernicke-Korsakoff syndrome

4.5.A.1 Alcoholism

a) 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

b) Summary:

Adverse effects limit the usefulness of fluvoxamine for treating alcoholism (Kranzler et al, 1993).

c) Adult:

1) Adverse effects limit the usefulness of fluvoxamine for treating alcoholism. Results of open-label and placebo-controlled trials of fluvoxamine as an adjunct to relapse prevention psychotherapy in alcoholics were reported (Kranzler et al, 1993). In the open trial, 16 inpatient alcoholics began a 12-week treatment program, with 10 patients dropping out during the first 4 weeks of treatment. In the controlled trial, 8 of 10 patients on fluvoxamine dropped out during the first 4 weeks of treatment, compared with only 1 of 9 patients on placebo. Baseline patient characteristics did not explain the baseline differential attrition in the controlled trial, although the placebo-treated patients are more alcohol-dependent. In both trials, patients taking fluvoxamine complained of a variety of adverse effects, which they identified as the basis for early termination of treatment. The most commonly reported adverse effects were nausea, headache, and sedation. More severe effects included hepatitis (1), depigmenting dermatitis (1), and focal seizures (1).

4.5.A.2 Asperger's 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:

Fluvoxamine treatment improved sleep and reduced excessive fears and interests in a case report of a boy with Asperger's syndrome (Furusho et al, 2001).

c) Pediatric:

1) Fluvoxamine treatment improved sleep and reduced excessive fears and interests of an 8-year-old boy with Asperger's syndrome, a pervasive developmental disorder with similarities to autism. In addition to poor sleep, the boy showed an inability to communicate with school classmates and teachers and displayed anxiety about remembered unpleasant occurrences. Although language development was normal, he sometimes spoke in a peculiar voice. He was given fluvoxamine 25 milligrams twice daily (after breakfast and supper). Within 4 weeks, his excessive fears and interests were reduced, his sleep improved, hyperactivity declined, and he gained control over unusual behaviors, such as using the peculiar voice. After 7 months of treatment, he continued to have some difficulty communicating with others. No adverse effects were observed (Furusho et al, 2001).

4.5.A.3 Autistic disorder

a) 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

b) Summary:

In adults, fluvoxamine was more effective than placebo for improving symptoms of autism (McDougle et al, 1996).

c) Adult:

1) In a 12-week, placebo-controlled trial (n=30), fluvoxamine was more effective than placebo for reducing repetitive thoughts/behavior and aggression and for improving some aspects of social interaction and language usage. Patients assigned to fluvoxamine were initially treated with 50 milligrams (mg) per day which was adjusted to a maximum of 300 mg daily over 3 weeks; the dosage was 276 mg versus 283 mg in patients treated with fluvoxamine versus placebo, respectively, at the conclusion of the study. Using the Clinical Global Impression Scale, fluvoxamine was statistically superior to placebo (p less than 0.001); statistically significant differences were also noted for other assessment scales. In addition, 4 of 15 patients treated with fluvoxamine showed clinically significant improvements in social functioning, including full-time employment (n=1), participation in a wedding (n=1), and a move from a group home to a supervised apartment (n=2). Adverse effects were mild and did NOT require treatment discontinuation. Based on the positive results obtained in these adult patients with autism, further study is required in children and adolescents with autism (McDougle et al, 1996).

4.5.A.4 Body dysmorphic disorder

a) 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

b) Summary:

Fluvoxamine produced a significant response in patients with body dysmorphic disorder in an open-

label study (n=30) (Phillips et al, 2001).

c) Adult:

1) In a 16-week, open-label study, fluvoxamine appeared effective in the treatment of body dysmorphic disorder (BDD). After establishing the diagnosis of BDD, patients (n=30, 21 females) were treated with fluvoxamine 50 milligrams (mg) daily with increases to 150 mg twice daily by day 9, if tolerated. Using an intent-to-treat analysis, it was found that there were statistically significant (p less than 0.001) decreases in the Brown Assessment of Beliefs Scale (BABS), 66%; the Yale-Brown Obsessive Compulsive Scale modified for BDD (BDD-YBOCS), 46.6%; the Hamilton Rating Scale for Depression (HAM-D), 38%; and the Montgomery-Asberg Depression Rating Scale (MADRS), 38%; at study end-point. Additionally, the Clinical Global Impressions Scale (CGI) rated 63% of patients as responders. Five of 7 delusional patients were responders; and response was not related to initial severity of illness. The mean dose of fluvoxamine was 238.3 mg/day (range 50-300 mg/day) and the mean response time was 6.1 weeks (range, 1 to 16 weeks). Only 60% of the patients completed the study (reasons for drop-outs not stated). This preliminary study suggests that fluvoxamine is effective for BDD, but blinded, placebo-controlled studies are needed to determine efficacy (Phillips et al, 2001).

4.5.A.5 Compulsive buying

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Ineffective
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Treatment with fluvoxamine did not alter the buying behavior of subjects prone to compulsive buying in a randomized, placebo-controlled trial (n=37) (Ninan et al, 2000).

c) Adult:

1) Results of a prospective, randomized, double-blind, placebo- controlled study demonstrated no benefit with fluvoxamine therapy in the number of shopping episodes, amount of time spent shopping, amount of money spent, or number of items purchased in 37 subjects with compulsive buying disorder. Forty-two subjects entered the study beginning with a 1-week single-blind placebo lead-in. Five subjects who experienced more than a 50% improvement in the Yale-Brown Obsessive Compulsive Scale modified for compulsive buying (YBOCS-CB) scores after this first week were excluded. Seventy-four percent of the 42 enrolled patients were diagnosed with comorbid psychiatric disorders. Subjects were randomized to placebo or daily fluvoxamine 50 milligrams (mg) increased weekly up to 300 mg according to subject response and tolerance. The average dose of fluvoxamine was 215 mg. The most commonly reported adverse events with fluvoxamine therapy were gastrointestinal distress (25%) and insomnia (20%), compared with headache (29%) and sedation (18%) with placebo. Each of the efficacy variables, YBOCS-CB, Global Assessment of Functioning (GAF), and Hamilton Rating Scale for Depression (HAM-D) improved with time for both treatment groups, yet no difference between treatment groups was observed (Ninan et al, 2000).

4.5.A.6 Compulsive exhibitionism

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:

Fluvoxamine was effective in one case of compulsive exhibitionist behavior (Zohar et al, 1994).

c) Adult:

1) Fluvoxamine was effective in extinguishing inappropriate compulsive exhibitionist behavior in a 36-year-old patient who was persistently masturbating in front of women in public. After 2 weeks of fluvoxamine at a dose of 300 milligrams daily, the behavior and impulses had disappeared completely (Zohar et al, 1994).

4.5.A.7 Compulsive gambling

a) 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

b) Summary:

In a small, open study, fluvoxamine reduced pathological gambling (Hollander et al, 1998).

c) Adult:

1) Of 10 patients who completed 8 weeks of fluvoxamine therapy, total abstinence of gambling was

achieved in 7. Sixteen patients began treatment with placebo for 8 weeks but 4 and 2 were terminated due to noncompliance and lack of efficacy, respectively. The remaining patients received fluvoxamine; the mean fluvoxamine dose was 220 milligrams/day at study endpoint. The Yale-Brown scale gambling behavior scores were reduced by 25%, and 7 of 10 patients were considered treatment responders by the clinician-rated Clinical Global Impression scores. While fluvoxamine appeared effective, this study was small, non-blinded, and of short duration; therefore, a randomized, controlled trial is needed to verify the results (Hollander et al, 1998).

4.5.A.8 Depression

a) Overview

FDA Approval: Adult, no; 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

b) Summary:

Fluvoxamine was more effective than placebo during double-blind trials for the treatment of depression (Ottevanger, 1994; Martin et al, 1987a) (Porro et al, 1988).

A single night time dose of fluvoxamine appears to be best tolerated (Siddigui et al, 1985).

c) Adult:

1) Fluvoxamine is effective in the treatment of DELUSIONAL DEPRESSION (Gatti et al, 1996). In a group of 59 patients, 84.2% responded favorably within the six-week study period. The dose of fluvoxamine used was 100 mg daily days 1 through 3; 200 mg daily days 4 through 7; and 300 mg daily from day 8. No other psychotropic drugs were used, except for eight patients who continued to receive maintenance therapy with lithium.

2) Fluvoxamine was effective in the treatment of severely depressed patients in a re-evaluation of a double-blind study of fluvoxamine, imipramine, and placebo in 308 patients (Ottevanger, 1994). Improvement was superior in severely depressed patients to that of moderately depressed patients, which in turn was superior to mildly depressed patients. Anticholinergic side effects were more common for imipramine, while gastrointestinal effects were more frequent with fluvoxamine.

3) Fluvoxamine was safe and effective for treating depression during a 6-week, large-scale, open trial of 5625 depressed patients (Martin et al, 1987a). All patients were started on fluvoxamine 50 to 100 milligrams at night, increasing after the first week, if necessary, to a maximum of 300 milligrams per day. Of the original 5625 patients admitted, 73% completed the study. In 6.4% (358 patients), withdrawal was not considered to be drug related. Other reasons for withdrawal included adverse effects in 16.2% (912 patients) and lack of efficacy in 2.1% (117 patients). The most commonly reported adverse effect was nausea (12.7%), followed by headache (5%), dizziness (4.5%), and somnolence (3.8%).

4) Fluvoxamine produced a more significant reduction in the global score of the Hamilton Rating Scale of Depression than placebo during a 4-week, double-blind study of 41 patients with depression (Porro et al, 1988). Patients randomized to receive fluvoxamine started at doses of 100 milligrams/day and were increased to 150 milligrams/day after 3 days. A significant reduction in the partial scores connected with anxiety and depression was observed in the fluvoxamine-treated patients after 7 days of therapy when compared with baseline scores. This trend became greater during the course of the treatment. Placebo-treated patients demonstrated a reduction in anxiety-related scores during the first 7 days; however, this disappeared over the course of treatment. The most commonly reported adverse effects associated with fluvoxamine therapy were nausea, vomiting, tremor, dry mouth, and increased salivation; however, they were only slightly-to-moderately severe and usually resolved by the end of the study.

5) An uncontrolled, non-randomized study of fluvoxamine 100 milligrams/day in 16 depressed HIV-1-infected patients revealed that fluvoxamine should not be used as first line treatment in this clinical setting. Good efficacy was reported in 6 patients, whereas the other 10 discontinued the drug due to severe adverse effects (acute total insomnia, gastrointestinal disturbance, aggressive and impulsive behavior, and excessive sedation) (Grassi et al, 1995).

4.5.A.9 Eating disorder

a) Overview

FDA Approval: Adult, no; 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

b) Summary:

In small open-label and larger double-blind, placebo-controlled trials, fluvoxamine has been effective for reducing the number of binge-eating episodes and for bulimia nervosa (Aynso-Gutierrez et al, 1994), (Brambilla et al, 1995a; Hudson et al, 1998).

c) Adult:

1) In a 9-week study, fluvoxamine effectively reduced the frequency of binges in patients with binge-eating disorder. In this double-blind, flexible-dose study (n=85), patients were randomly assigned to

placebo or fluvoxamine 50 milligrams (mg) daily titrated to a maximum dose of 300 mg daily. Fluvoxamine compared to placebo resulted in a significant reduction in frequency of binges (p=0.006), Clinical Global Impression severity scale score (p=0.002), and body mass index (p=0.04). Of the 67 patients who completed 9 weeks of treatment, 15 and 12 were in remission (no binges) or markedly improved (75% or greater improvement) in the fluvoxamine and placebo groups, respectively (p=0.04). Significantly more patients treated with fluvoxamine than placebo discontinued treatment due to adverse effects (p=0.03); however, none of the adverse effects were serious. Of interest, the placebo response was between 42% and 44% which suggests that a conservative approach should be used in offering drug therapy for this disorder (Hudson et al, 1998).

2) A review article discussing BINGE EATING DISORDER found that fluvoxamine was effective in isolated cases and a few small trials (Hudson et al, 1996). A significant reduction in the frequency of binge eating was noted by one investigator in 10 patients who did not self-induce vomiting. This was conducted over an 8 week course. Another investigator found similar reductions in the frequency of binge eating episodes, in addition to a significant overall improvement compared to placebo over a 9-week course. In a case report, fluvoxamine was effective for binge-eating disorder. A 58-year-old female sought treatment for binge-eating 4 episodes per week. She suffered from chronic binges for 18 years. Previous unsuccessful therapy included psychotherapy, and over-the-counter appetite suppressants. Randomized to fluvoxamine 100 milligrams daily, she reported no binge eating episodes by the second week of therapy. She reported only 1 binge episode during the following seven weeks of treatment. Her binge eating relapsed after 2 weeks without fluvoxamine. She was unable to restart fluvoxamine however, as it was not commercially available at the time.

3) Fluvoxamine was effective in the treatment of 20 patients with bulimia nervosa when used in doses of 50 to 150 mg per day for eight weeks (Aynso-Gutierrez et al, 1994). Four patients showed drowsiness and 3 insomnia.

4) In an uncontrolled, non-randomized study, 15 women with bulimia nervosa were administered 4 months of combined cognitive-behavioral and nutritional therapy along with either fluvoxamine 300 milligrams (mg) per day or amineptine 300 mg/day. Bulimic Investigation Test symptoms and gravity improved significantly and equally in both groups, whereas Eating Disorders Inventory scores and depression and anxiety according to the Hamilton Rating Scale for Depression and Anxiety decreased, but not significantly. Body mass index was normal before therapy and did not change during treatment. These preliminary results need to be validated in larger and better designed studies (Brambilla et al, 1995a).

4.5.A.10 Fibromyalgia

a) 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

b) Summary:

Fluvoxamine may be helpful for patients with fibromyalgia (Nishikai & Akiya, 2003).

c) Adult:

1) Fluvoxamine was equally effective to amitriptyline in reducing pain associated with fibromyalgia. In an open-label, uncontrolled study, 68 Japanese patients with fibromyalgia received either amitriptyline at a mean dose of 20 milligrams (mg)/day or fluvoxamine at a mean dose of 25 mg/day for 4 weeks. Patients evaluated pain relief by means of a visual analog scale and efficacy was defined as a decrease in pain by at least 50%. At 4 weeks, 50% of patients in the amitriptyline group and 41% of patients in the fluvoxamine group reported effective relief of pain (p=NS). Drowsiness was the most commonly reported adverse event with amitriptyline treatment and nausea was most frequently reported with fluvoxamine. The authors hypothesize that because the efficacy of amitriptyline for the treatment of fibromyalgia-related pain has been established in previous, controlled trials and because fluvoxamine showed similar efficacy to amitriptyline in this open-label study; fluvoxamine may be helpful for patients with fibromyalgia (Nishikai & Akiya, 2003).

4.5.A.11 Hypochondriasis

a) 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

b) Summary:

Fluvoxamine may be beneficial in the treatment of hypochondriasis (Fallon et al, 2003).

c) Adult:

1) The results of one study suggest that fluvoxamine may be a beneficial treatment in reducing symptoms of patients with hypochondriasis. In a small, 12-week, open-label study, patients with at least a moderate hypochondriasis rating on the Heightened Illness Concern Severity Scale (HICSS) received

daily divided doses of fluvoxamine (50 milligrams (mg) initially, increased every 7 days to a maximum dose of 300 mg by the sixth week) for 10 weeks following a 2-week placebo run-in phase. Response was defined as a clinician-rated change in score of "much improved" or "very much improved" on the Clinical Global Impressions (CGI) scale. In the intent-to-treat analysis, 57.1% of patients responded to fluvoxamine treatment. In patients who completed 6 or more weeks of treatment, 72.7% were responders and mean scores on the HICSS were significantly reduced from baseline to endpoint (5 vs 3.64, p=0.001). Fluvoxamine was generally well tolerated. Further, well- controlled studies are needed to substantiate these findings (Fallon et al, 2003).

4.5.A.12 Mixed anxiety and depressive disorder

a) 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

b) Summary:

Fluvoxamine was effective for treating depression accompanied by an anxiety disorder in a small, open-label study (n=30) (Sonawalla et al, 1999).

c) Adult:

1) Eighteen (60%) of 30 patients achieved a score of 2 or less on the Clinical Global Impressions-Improvement (CGI-I) scale for both anxiety and depression. All patients had major depression with at least 1 co-morbid anxiety disorder. Fluvoxamine was initiated at 50 milligrams (mg)/day and was titrated to 200 mg/day as needed and tolerated; the mean dose was 143 mg/day at 12 weeks (study endpoint). Twenty (67%) and 23 (77%) patients showed a response on the CGI-I depression and CGI-I anxiety scales at endpoint, respectively. Twelve patients withdrew from the study before 12 weeks. This small open study suggests that fluvoxamine is effective for treating depression accompanied by an anxiety disorder, but these results must be confirmed in a controlled clinical trial (Sonawalla et al, 1999).

4.5.A.13 Myocardial infarction; Prophylaxis

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:

SSRIs, including fluvoxamine, may confer a protective effect against first MI (Sauer et al, 2001).

c) Adult:

1) In a case-control study comprised of 653 cases of first myocardial infarction (MI) and 2990 control subjects, results indicated that selective serotonin reuptake inhibitors (SSRIs) may confer a protective effect against first MI. The subjects in this study were smokers, between the ages of 30 to 65 years, with a first MI hospitalized between September 1995 and December 1997. The four SSRIs investigated in this study were fluoxetine, fluvoxamine, paroxetine, and sertraline; doses taken by participants were not stated. The odds ratio of patients who were taking SSRIs having a first MI compared to controls (after adjustment for potential confounders) was 0.35 (95% CI 0.18, 0.68; p less than 0.01). The authors suggested that this effect was possibly attributable to an inhibitory effect on serotonin-medicated platelet activation or amelioration of other factors associated with increased risk for MI in depression (Sauer et al, 2001).

4.5.A.14 Obsessive-compulsive disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (8 years and older (immediate-release formulation 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:

The extended-release formulation of fluvoxamine maleate is indicated for the treatment of obsessions and compulsions in adult patients with obsessive compulsive disorder (OCD) (Prod Info LUVOX(R) CR extended-release oral capsules, 2008), and the immediate-release formulation of fluvoxamine maleate is indicated for the treatment of obsessions and compulsions in patients with OCD aged 8 years and older (Prod Info LUVOX(R) oral tablets, 2007).

A 10-week study demonstrated that immediate-release fluvoxamine and behavior therapy were more efficacious for treating obsessive compulsive disorder compared to placebo and behavior therapy (Hohagen et al, 1998).

Immediate-release fluvoxamine was significantly more effective than placebo in children (8 years or

older) and adolescents with obsessive compulsive disorder (OCD) in a 10-week, double-blind study in 120 children with at least a 6-month history of OCD (Riddle, 1996).
Treatment with extended-release fluvoxamine maleate at once-daily doses of 100 to 300 milligrams was safe and led to clinical improvement in adult patients with obsessive-compulsive disorder compared to placebo in a 12-week, multicenter, randomized, double-blind study (n=253) (Hollander et al, 2003).

c) Adult:

1) General Information

a) Of the selective serotonin reuptake inhibitors (SSRIs) (ie, fluoxetine, sertraline, paroxetine, fluvoxamine) with U.S. Food and Drug Administration approval for treating OCD, all are effective. Limited clinical studies also suggest that the SSRIs are comparable to clomipramine; however, results of a meta-analysis found that clomipramine may be more effective than the SSRIs (Flament & Bisserbe, 1997; Leonard, 1997). Selection of initial treatment is often based on the side effect profile of the individual drug; in general, the SSRIs are tolerated better than clomipramine (Leonard, 1997). Early studies used near maximal doses of an SSRI which resulted in a high incidence of adverse effects; however, initial low doses with gradual dose adjustment result in a good response in some patients and better tolerance in most (Leonard, 1997). While the optimal duration of treatment has NOT been defined, most patients require long-term treatment. A few small studies have shown relapse rates between 65% and 90% when pharmacologic treatment was stopped (Rasmussen & Eisen, 1997). Patients who do NOT respond to 10 to 12 weeks of maximum doses of an SSRI and/or behavioral therapy are considered refractory to treatment. In about 20% of this group, a trial of a second SSRI will be effective. In the remaining patients, augmentation therapy with haloperidol or clonazepam may be beneficial (Rasmussen & Eisen, 1997).

2) Clinical Trials

a) Immediate-release Formulation

1) Fluvoxamine and behavior therapy are efficacious for treating obsessive compulsive disorder (OCD). Patients were randomized to receive fluvoxamine 300 milligrams (mg) daily, initiated at doses of 50 mg daily and titrated as tolerated in 50 mg increments weekly, and behavior therapy (n=24) or placebo and behavior therapy (n=25). After 10 weeks of treatment, both groups showed significant improvements in scores on the Structured Clinical Interview (SCID), Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), Hamilton Depression Scale (HAM-D), Clinical Anxiety Scale (CAS), Global Assessment Scale (GAS), and the Clinical Global Improvement Scale (CGIS). Fluvoxamine and behavioral therapy were significantly more effective in treating obsessions than placebo and behavior therapy, as defined by improvements in total Y-BOCS scores and Y-BOCS obsession scores. Treatment with fluvoxamine and behavior therapy also showed a significantly greater improvement than placebo and behavior therapy in patients with secondary depression. Treatment with fluvoxamine and behavior therapy may be advantageous in patients whose obsessions, not compulsions, dictate their clinical profile and for patients that have depression secondary to OCD (Hohagen et al, 1998).

2) Data from small, short-term or non-blinded studies indicate that patients with obsessive-compulsive disorder (OCD) may tolerate substantial reductions in fluvoxamine dosage without a relapse (Mundo et al, 1997; Ravizza et al, 1996). In a double-blind study, patients with stable OCD tolerated reductions in the dosage of fluvoxamine or clomipramine of 33% to 67% without relapses for up to 102 days. Thirty patients were randomly assigned to group I (same dosage), group II (33% to 40% reduction in dosage), or group III (60% to 67% reduction in dosage). Five patients relapsed during the study; 3 were in the control group, and 1 each was in groups II and III. No statistical difference was identified between treatment groups for the cumulative number of patients who completed the study without a relapse. Larger studies are needed to confirm these results (Mundo et al, 1997).

3) Long-term outcome at 18 months posttreatment favored exposure therapy with or without fluvoxamine for treating OCD. Drug effects did not last while exposure therapy did. At 18 months, a smaller number of exposure therapy patients were receiving antidepressant treatment, but all three groups showed comparable improvement. Sixty outpatients with OCD treated for six months with either 1) fluvoxamine and antiexposure therapy (F), 2) fluvoxamine and exposure therapy (FE), or 3) placebo and exposure therapy (PE) (20 patients per group) were followed up one year after these treatments were stopped to determine their clinical status. Fluvoxamine dosage ranged up to 300 mg per day, and the drug was taken for 24 weeks. It was gradually tapered from week 24 to 28. Antiexposure therapy was a mild form of behavior therapy using relaxation instead of confrontation with feared situations. Thirty-three of 60 patients were rated at 18 months. FE and F produced a greater reduction in rituals at 8 weeks and in depression at 24 weeks than did PE, but this difference disappeared at 12 months (Cottraux et al, 1993).

4) OCD patients with co-morbid chronic tic disorder may require addition of a neuroleptic to fluvoxamine for effective symptom reduction (McDougle et al, 1994). A 25-year-old male patient with a history of Tourette's syndrome was treated with fluvoxamine for OCD symptoms. Fluvoxamine worsened tics, led to coprolalia (use of feces-related foul language) and did not help the OCD. The addition of pimozide dramatically reduced both the OCD and Tourette's

symptoms. Double-blind sequential discontinuation of fluvoxamine and pimozide confirmed that pimozide alone reduced only tics and the combination of fluvoxamine and pimozide was required for improvement in OCD. Tics may reflect a subtype of OCD and OCD patients unresponsive to a serotonin-reuptake inhibitor alone may benefit from the addition of a dopamine antagonist (Delgado et al, 1990).

b) Extended-release Formulation

1) In a 12-week, multicenter, randomized, double-blind, placebo-controlled study (n=253), treatment with extended-release (ER) fluvoxamine maleate was safe and led to a statistically significant and clinical relevant decrease in obsessive-compulsive disorder (OCD) severity in adult patients. Patients meeting the DSM-IV criteria for OCD (mean duration, approximately 16 years), and with scores of 21 or higher on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and 16 or lower on the 17-item Hamilton Rating Scale for Depression randomly received either fluvoxamine ER (n=127; mean age, 38.1 years) or placebo (n=126; mean age, 36.7 years) orally once daily for 12 weeks. Fluvoxamine ER was initiated at a nightly dose of 100 milligrams (mg) and titrated in weekly 50-mg increments over 6 weeks to a target dose of 100 to 300 mg/day. The dose remained constant during the remaining 6 weeks of the study (mean daily dose at endpoint, 271 mg). Patients were assessed every 2 weeks using the Y-BOCS (primary efficacy measure) and the Clinical Global Impressions-Severity of Illness (CGI-S) and -Improvement (CGI-I) scales. At baseline, the Y-BOCS scores were 26.6 and 26.3 in the fluvoxamine ER and placebo groups, respectively. A modified intent-to-treat (including patients with at least 1 postbaseline efficacy measurement) analysis of Y-BOCS total score revealed a mean +/- standard error (SE) decrease from baseline to week 12 of 8.5 +/- 0.7 (31.7% change) in the fluvoxamine ER group compared to 5.6 +/- 0.7 (21.2% change) in the placebo group (F=10.48; df=1218; p=0.001). There were significant treatment differences in favor of fluvoxamine ER group for both the obsession (39.6% change vs 24.4% change; p less than 0.001) and compulsion (34.3% vs 24.8%; p=0.048) subtotals of the Y-BOCS. Notably, treatment differences were evident at week 2 and were sustained throughout the 12-week study. Among secondary efficacy measures, compared to placebo, significant improvements occurred in fluvoxamine ER-treated patients for both the CGI-S (-1 +/- 0.1 vs -0.6 +/- 0.1; p=0.002) and the CGI-I (endpoint, 2.7 +/- 0.1 (range, 1 to 5) vs 3.2 +/- 0.1 (range, 1-6); p less than 0.001) scores. More patients discontinued treatment due to adverse events in the fluvoxamine ER versus placebo group (19% vs 6%). The most common adverse events occurring with fluvoxamine ER at a higher frequency than placebo included nausea (34% vs 13%), insomnia (35% vs 20%), somnolence (27% vs 11), asthenia (25% vs 8%), diarrhea (18% vs 8%), and anorexia (13% vs 5%). Abnormal ejaculation and anorgasmia (8% and 5%, respectively) only occurred in the fluvoxamine ER group, and decreased libido was also reported more frequently in the fluvoxamine ER group (7% vs 3%) (Hollander et al, 2003).

d) Pediatric:

1) Fluvoxamine maleate was significantly more effective than placebo in children (8 years or older) and adolescents with obsessive compulsive disorder (OCD). In this 10-week, double-blind study, 120 children with at least a 6-month history of OCD were randomized to receive fluvoxamine or placebo. During the first 4 weeks, the dose was titrated to patient response; the dose at 4 weeks was continued for the last 6 weeks of the study. Efficacy was assessed via the Children's Yale-Brown Obsessive Compulsive Scale which showed significant improvement at weeks 1 to 4, 6, and 10. No serious adverse effects were reported. Fluvoxamine was safe and effective in children with OCD (Riddle, 1996).

2) Fluvoxamine maleate was effective in decreasing depression and bulimic symptoms, but its impact on impulsive, suicidal, and anorectic symptoms was less clear. The safety and efficacy of fluvoxamine were evaluated in the treatment of adolescent patients with obsessive compulsive disorder (n=14) and major depression (n=6). Patients were age 13 to 18 and were treated for 8 weeks in an open-label trial. They were rated at 2-week intervals using Y-BOCS (Yale-Brown Obsessive Compulsive Scale) and other rating scales. Fluvoxamine maleate was more effective in OCD patients than in depressed patients, as evidenced by significant decreases in Y-BOCS scores. The most common side effects were dermatitis, insomnia, hyperactivity, excitement, anxiety, tremor and nausea. The drug was discontinued in 4 patients because of more severe side effects (delirium, hallucinations) (Apter et al, 1994).

4.5.A.15 Panic disorder

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:

In uncontrolled or placebo-controlled studies, fluvoxamine was effective for treating panic disorder in patients with and without depression (Spiegel et al, 1996; Black et al, 1993a).

c) Adult:

1) Fluvoxamine was effective for treating panic disorder complicated by depression. In an 8-week, open-label, flexible-dose trial, fluvoxamine was administered to 17 patients. Thirteen patients had panic

disorder with agoraphobia; 14 patients had an additional anxiety disorder; 15 patients had a major depressive disorder; and 5 patients also had obsessive-compulsive disorder. Fluvoxamine was initiated at 40 milligrams per day, increased to 100 milligrams on day 5 and to 150 milligrams on day 9. The dose was increased at 50 milligram intervals each week until side effects occurred; the maximum dose of 300 milligrams was reached; or panic attack and depression resolved. Fifteen patients completed the study. One patient dropped out due to side effects and one for unknown reasons. The most common adverse events were nausea, insomnia, anxiety/restlessness, headache, drowsiness and dry mouth. At the study's end (at a mean fluvoxamine dose of 213 milligrams), there was a statistically significant difference from baseline in the number of panic attacks, anticipatory anxiety, general anxiety, depression and a self-rating of disability; however, fluvoxamine did NOT affect agoraphobia avoidance (Spiegel et al, 1996).

2) Fluvoxamine was superior to cognitive therapy (CT) and placebo (PL) in the treatment of seventy-five outpatients with moderate-to-severe panic disorder. CT subjects also showed improvement but the degree of improvement was not different from that of PL patients. Fluvoxamine also produced improvement earlier than CT; at week 4, 57% of fluvoxamine patients were rated moderately improved or better compared to 40% for the CT group and 22% for the PL group. At the same time point, 43% of fluvoxamine patients were free of panic attacks compared with 25% of CT and 4% of PL patients (Black et al, 1993a).

3) In a case report, fluvoxamine 150 milligrams/day for 6 weeks prevented panic attacks and decreased obsessive-compulsive symptoms in a 36-year-old woman (Servant et al, 1988). The patient had a 12-year history of recurrent panic attacks. The patient had most recently been treated with imipramine 150 mg/day and lorazepam 2.5 mg/day without improvement.

4) In a placebo-controlled, double-blind study, fluvoxamine significantly reduced the number of panic attacks compared to placebo. The severity of attacks was not affected by fluvoxamine. There was no difference between drug and placebo until 6 weeks of treatment when placebo lost its effect on anxiety, depressive mood, and disability (Hoehn-Saric, 1993).

4.5.A.16 Posttraumatic stress disorder

a) 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

b) Summary:

Open trials suggest that fluvoxamine may be useful for treating post-traumatic stress disorder (Escalona et al, 2002; Davidson et al, 1998; Marmar et al, 1996).

c) Adult:

1) Some symptoms of combat-related post-traumatic stress disorder (PTSD) improved during treatment with fluovoxamine; however, there was a high drop-out rate from the study due to side effects and lack of perceived therapeutic benefit. Fifteen Vietnam combat veterans with no other psychiatric diagnosis than PTSD and depression were treated with fluvoxamine, starting at a dose of 50 milligrams (mg) twice daily and increasing to a maximum of 300 mg/day, in an open-label, 14- week study. The study was preceded by a 30-day washout period. The mean daily dose of fluvoxamine at week 14 was 150 mg. Only 8 patients completed 8 weeks of the study and 5 completed the entire study. In intent-to-treat analysis, scores on intrusion and avoidance scales of the Clinician PTSD Scale (CAPS) showed significant improvement (p less than 0.001), as did scores on the Hamilton Anxiety Scale (p less than 0.001). However, measures of depression showed no significant changes. Hyperarousal scores also were unchanged. Gastrointestinal side effects and dizziness were the most common adverse effects reported (Escalona et al, 2002).

2) In an open, 8-week trial, fluvoxamine resulted in symptom improvement in 64.2% of civilian patients with post-traumatic stress disorder (PTSD). Fifteen patients with confirmed PTSD were treated with fluvoxamine 50 milligrams (mg) daily with adjustment of dose to a maximum of 200 mg daily depending on symptom improvement and side effects. Using assessment scales including the Structured Interview for PTSD, Treatment-Outcome PTSD Scale, and the Duke Global Rating Scale for PTSD, the symptom score improved by 40% to 50%; this difference was clinically and statistically significant. Five patients left the trial early due to adverse effects (n=2) and administrative reasons (n=3); however, 14 of 15 patients were included in the efficacy analysis. Positive results of this and an earlier trial indicate that a double-blind, placebo-controlled trial should be performed with fluvoxamine for PTSD (Davidson et al, 1998).

3) In an open-label trial, fluvoxamine improved stress-related symptoms in 10 Vietnam combat veterans with post-traumatic stress disorder. The 12-week study consisted of a drug wash out and DSM-IIIR diagnoses screening during weeks 0 to 2, followed by fluvoxamine 50 milligrams (mg) daily starting at week 2. Fluvoxamine was increased weekly by 50 mg to a therapeutic dose; the (modal) daily dose was 150 mg, (range 100 to 250 mg daily). Self-report and clinician ratings of stress-specific and general psychiatric symptomatology improved significantly over the first 6 weeks and continued at this level for the duration of the study. These included the intrusion, avoidance and hyperarousal symptoms of PTSD. The comorbid features of depression and anxiety were also significantly affected;

however, hostility was unaffected. The most commonly reported side effects were sedation, headache, nausea, and insomnia (Marmar et al, 1996).

4.5.A.17 Premenstrual dysphoric disorder

a) 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

b) Summary:

With the exception of food cravings, symptoms associated with premenstrual syndrome were significantly improved by the use of fluvoxamine in an open-label study (Freeman et al, 1996).

c) Adult:

1) With the exception of food cravings, symptoms associated with premenstrual syndrome were significantly improved by the use of fluvoxamine (Freeman et al, 1996). In an open-label, pilot study, fluvoxamine was examined for the treatment of premenstrual dysphoric disorder (PDD), commonly referred to as PREMENSTRUAL SYNDROME. Twelve women who met the DSM-IV criteria for PDD were treated with fluvoxamine for 2 menstrual cycles. Fluvoxamine was started at 50 milligrams per day on day 1 of the menstrual cycle. At 4 weeks, the mean daily dose was 85 milligrams and at 8 weeks, all women took 100 milligrams daily. Eight of the 10 women completing the study reported side effects. Commonly reported side effects included insomnia, fatigue, dry mouth, nausea and loss of libido. Most effects were transient and were only experienced early in the treatment. Improvement in the daily symptom reports (DSR) was significant at both 4 and 8 weeks. Four factors, mood, function, pain and physical changes made up the DSR. Seventeen individual items were contained within these 4 factors. Further controlled studies are needed to substantiate these findings. It would also be helpful to determine if fluvoxamine is needed on a daily basis throughout the menstrual cycle.

4.5.A.18 Prostatic pain

a) 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

b) Summary:

Fluvoxamine reduced pain and normalized urinary flow rates in patients with prostatodynia in a randomized, double-blind, placebo-controlled study (n=42) (Turkington et al, 2002).

c) Adult:

1) Fluvoxamine treatment was more likely than placebo to reduce pain and normalize urinary flow rates in patients with prostatodynia. In this randomized, double-blind, placebo-controlled study (n=42), patients with at least a one-year history of perigenital pain without local or systemic infection and without local inflammation were assigned to receive placebo or fluvoxamine for 8 weeks. Treatment medication was initiated at 50 milligrams (mg) daily, then increased by 50 mg every 2 weeks, as needed (median dose, 150 mg; range, 50-300 mg). Patients treated with fluvoxamine reported significant improvements in pain as compared with placebo-treated patients (p=0.01). Significantly more patients in the fluvoxamine group showed improvement in urinary flow rate as compared with the placebo group (7 of 8 vs 1 of 6, respectively; p=0.03). Larger studies are needed to address the efficacy of fluvoxamine for all symptoms of prostatodynia and to identify the optimal dose (Turkington et al, 2002).

4.5.A.19 Repetitive self-excoriation

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 response rate of 50% was seen in patients treated with fluvoxamine in an open-label study (Arnold et al, 1999).

c) Adult:

1) In an open, 12-week study, patients with psychogenic excoriation improved during treatment with fluvoxamine; however, 7 patients withdrew early due to adverse effects (n=4) or unrelated reasons. Response defined as a 30% or greater decrease in the total score on the modified Yale-Brown Obsessive Compulsive Scale (Y-BOCS) was achieved in 50% of enrolled patients. The modified Y-BOCS score was reduced from 17.9 at baseline to 10.9 at termination. Adverse effects were common and included those normally expected with fluvoxamine. This study suggests that fluvoxamine may be useful for psychogenic excoriation; however, controlled clinical trials are needed to confirm this (Arnold

et al, 1999).

4.5.A.20 Severe major depression with psychotic features

See Drug Consult reference: PSYCHOTIC DEPRESSION - DRUG THERAPY

4.5.A.21 Social phobia

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (extended-release formulation only); 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

b) Summary:

Extended-release fluvoxamine maleate is indicated for social anxiety disorder, also known as social phobia (Prod Info LUVOX(R) CR extended-release oral capsules, 2008).
In a randomized, double-blind, multicenter, placebo-controlled study (n=300), patients with generalized social anxiety disorder (GSAD) who received fluvoxamine controlled-release (CR) demonstrated a significantly greater reduction in the mean Liebowitz Social Anxiety Scale (LSAS) total score from baseline compared with patients who received placebo (Westenberg et al, 2004); there was a trend towards continued clinical benefit with fluvoxamine ER compared to placebo in a 12-week double-blind extension phase of this study (Stein et al, 2003).

c) Adult:

1) Fluvoxamine extended-release (ER) was an effective therapy in the treatment of patients with generalized social anxiety disorder (GSAD). In a randomized, double-blind, placebo-controlled, multicenter study, patients (n=300) with GSAD and a score of at least 60 on the Liebowitz Social Anxiety Scale (LSAS) received fluvoxamine ER (initial, 100 milligrams (mg)/day, titrated weekly in 50 mg increments, as needed, to maximum of 300 mg/day; mean dose, 209 mg/day) for 12 weeks. A significantly greater reduction in the mean LSAS total score was observed from baseline to endpoint in the fluvoxamine ER group as compared with the placebo group (37% vs 28%, respectively; p=0.02). The mean LSAS total score for patients in the fluvoxamine ER group was significantly more improved as compared with placebo at weeks 4, 8, 10, and 12 (p less than 0.05, all values), but not at week 6 (p=0.066). Reductions on the fear and avoidance subscales of the LSAS were also significantly greater for fluvoxamine ER-treated patients as compared with placebo-treated patients (p=0.015 and p=0.04, respectively). Additionally, fluvoxamine ER was superior to placebo in three of four secondary measures including the Clinical Global Impression Improvement (CGI-I) Scale, CGI-Severity (CGI-S) of Illness Scale, and the Sheehan Disability Scale (SDS) (p=0.026, p=0.022, and p=0.036, respectively). Nausea (47%), headache (35%), insomnia (32%), asthenia (28%), and somnolence (22%) were the most commonly reported adverse events. Adverse effects related to sexual dysfunction were not significantly different between treatment groups, however these effects included abnormal ejaculation, anorgasmia, impotence, and decreased libido (Westenberg et al, 2004).

a) In a 12-week double-blind extension of the aforementioned study, there was a trend towards continued clinical benefit with fluvoxamine ER (n=56) compared to placebo (n=53) among patients with generalized social anxiety disorder. Patients completing the 12-week acute phase study and achieving at least minimal improvement (ie, a CGI-I score of 3 or less) continued to receive study medications as assigned in the acute phase; the mean fluvoxamine ER dose in the extension phase was 181 milligrams/day. Notably, the extension phase was not powered to detect statistical significance due to the small number of patients expected to continue into the extension study. At the end of 24 weeks of treatment, the mean +/- standard error (SE) LSAS total scores continued to decline in the fluvoxamine ER group compared to placebo (difference from week 12, -6.3 +/- 1.6 for fluvoxamine ER versus (vs) -1.6 +/- 1.6 for placebo; p=0.109). Although not statistically significant, greater improvements were seen in the fluvoxamine ER group compared to placebo for the secondary measures of CGI-S and SDS scores during the 12-week extension. The percentage of responders (ie, score of 1 or 2 on the CGI-I; 80% vs 74%; p=0.322) and remitters (ie, score of 1 on the CGI-I; 38% vs 28%; p=0.318) was numerically higher in the fluvoxamine ER group than the placebo group. During the extension phase, 9% (5/56) and 4% (2/53) of fluvoxamine ER- and placebo-treated patients, respectively, discontinued treatment due to adverse events. Common adverse events occurring more frequently than placebo included sweating (9% vs 4%), nausea (7% vs 2%), and sexual dysfunction (16% vs 5%), with 7% of fluvoxamine ER-treated patients reporting abnormal ejaculation (0% in the placebo group) (Stein et al, 2003).

2) Fluvoxamine was superior to placebo for treating social phobia. Patients diagnosed with DSM-IV social anxiety disorder were randomly assigned to 12 weeks of double-blind treatment with placebo (n=44) or fluvoxamine 50 milligrams daily (n=42) with titration at weekly intervals to a maximum dose of 300 milligrams daily. Response was defined by a score of 1 (very much improved) or 2 (much improved) on the Clinical Global Impression scale (CGI). Of the patients (n=64) who completed the full 12 weeks of the study, 53.3% and 23.5% treated with fluvoxamine and placebo, respectively, were considered responders on the CGI scale (p=0.01). In addition, evaluation using specialized social phobia scales demonstrated significant improvement in the fluvoxamine versus placebo group (ie, Brief

Social Phobia Scale, p less than 0.01; Social Phobia Inventory, p=0.02; Liebowitz Social Anxiety Scale subscales for work and family life, p=0.006 and p=0.02). The mean fluvoxamine dose was 202 milligrams/day at study end. Treatment was withdrawn due to adverse effects in 25% and 9.1% of patients treated with fluvoxamine and placebo, respectively; nausea and insomnia were the primary adverse effects that led to treatment discontinuation. Treatment benefit was first observed at 6 weeks and continued through week 12 of the study. Comparison of fluvoxamine with other accepted treatments is needed (Stein et al, 1999).

3) Fluvoxamine was effective in a small group of patients who met DSM-III-R criteria for social phobia. Fifteen patients were treated with fluvoxamine 50 milligrams (mg)/day with titration to 150 mg/day as needed; treatment was continued for 6 weeks. Five patients discontinued treatment due to adverse effects or difficulty traveling for appointments. Assessment scales including the Hamilton Rating for Anxiety, Brief Social Phobia Scale, Marks-Sheehan Phobia Scale, Fear Questionnaire, and Sheehan Patient Rated Anxiety Scale showed a significant reduction from baseline to week 7. Patients also reported a reduction in anxiety associated with giving a speech at baseline and conclusion of the study. This small, open study suggests that fluvoxamine is effective for social anxiety disorder (DeVane et al, 1999).

4.5.A.22 Stereotypy habit disorder

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:

Three patients responded to fluvoxamine with complete cessation of stereotypic behavior in 1 patient

c) Adult:

1) Of 3 elderly women with stereotypic behavior, 2 almost completely stopped the behavior, and 1 had a partial response to fluvoxamine (Trappler & Vinuela, 1997). Pretreatment assessment with the Abnormal Involuntary Movement Scales (AIMS) yielded a score of 13 to 16. The first patient gnawed on her fingers, clothing, and towels but stopped this behavior after receiving fluvoxamine 50 milligrams (mg) daily for 4 weeks; the AIMS decreased to 1. Treatment was continued for 10 weeks; this patient remained symptom-free 6 months after stopping fluvoxamine. The second patient had almost complete resolution of chewing on her sweater and finger sucking 3 weeks after increasing fluvoxamine to 100 mg daily; her AIMS also decreased to 1. The third patient caused constant irritation and infection to her left eyelid due to constantly wiping it with her sleeve. This behavior partially abated after treatment with fluvoxamine 150 mg daily; the AIMS went from 16 to 7. Therapy was tolerated well by all patients who ranged in age from 81 to 88 years. Since 2 patients maintained a response after treatment withdrawal, this behavior was considered responsive to fluvoxamine and is likely related to a serotonergic mechanism.

4.5.A.23 Trichotillomania

a) 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

b) Summary:

Fluvoxamine may have beneficial effects in patients with trichotillomania (Stanley et al, 1997).

c) Adult:

1) In a 12-week, open trial, fluvoxamine treatment resulted in some improvement in trichotillomania. Twenty-one patients were treated with fluvoxamine 50 milligrams (mg) daily with dosage adjustment to a maximum of 300 mg daily. Of the 21 patients treated, only 13 completed the entire 12 weeks of treatment. When the data were analyzed including patients completing the study, few statistically significant differences were found in symptoms on the assessment scales; however, when all patients were included, significant differences were found in several symptoms on the assessment scales. One possible explanation for this difference includes early treatment withdrawal in patients with a good response; another possible reason is the assessment scales were NOT well validated for trichotillomania. Since some symptomatic improvement occurred in both groups (completers and non-completers), controlled clinical trials are needed to assess fluvoxamine treatment for trichotillomania (Stanley et al, 1997).

4.5.A.24 Wernicke-Korsakoff syndrome

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:

Results of studies have been mixed when fluvoxamine was used for treating alcoholic Korsakoff syndrome. Available studies have included only a few patients; therefore, larger, well-controlled studies may resolve the controversy (O'Carroll et al, 1994; Stapleton et al, 1988).

c) Adult:

1) Fluvoxamine 200 milligrams/day was ineffective in the treatment of alcoholic Korsakoff syndrome in 8 patients who were treated for 4 weeks in a double-blind, placebo-controlled, crossover trial. Fluvoxamine had no cognitive-enhancing effect as measured by a detailed neuropsychological battery on a weekly basis. There was significant impairment in verbal fluency. Two patients developed a major depressive episode in the fluvoxamine group; within 3 days of fluvoxamine discontinuation, their mood returned to normal (O'Carroll et al, 1994).

2) Fluvoxamine 100 to 200 milligrams/day improved episodic memory in 7 patients with alcohol amnestic disorder (Korsakoff's psychosis) in a 4-week, double-blind, crossover design study. These improvements were significantly correlated with reductions in cerebrospinal fluid 5-HIAA levels, suggesting that facilitation of serotonergic neurotransmission may ameliorate the episodic memory failure in patients with alcohol amnestic disorder (Martin, 1989).

3) Fluvoxamine produced a small but significant improvement in memory performance in 5 alcoholic ORGANIC BRAIN SYNDROME patients during a double-blind, crossover study. Fluvoxamine 200 milligrams/day for 4 weeks was administered to all patients. Overall improvement in performance was associated with higher levels of fluvoxamine and lower levels of 5-hydroxy-indole-acetic acid (5HIAA), a metabolite of serotonin, in the cerebrospinal fluid (Stapleton et al, 1988).

4.6 Comparative Efficacy / Evaluation With Other Therapies

Amineptine

Amitriptyline

Clomipramine

Clovoxamine

Desipramine

Dothiepin

Fluoxetine

Flupenthixol

Imipramine

Lithium

Lorazepam

Maprotiline

Mianserin

Milnacipran

Oxaprotiline

Paroxetine

Sertraline

4.6.A Amineptine

4.6.A.1 Bulimia nervosa

a) Fifteen women with bulimia nervosa were treated with a combined cognitive-behavioral, nutritional and antidepressant therapy (either amineptine 300 milligrams (mg) per day or fluvoxamine 300 mg/day) for 4 months. The combination of psychotherapeutic and pharmacologic therapy showed rapid, good effects and improvement was stable in most of the patients until the end of the observations. Prior to therapy, the patients had high global Eating Disorders Inventory (EDI) scores; these did not change during fluvoxamine therapy and decreased during amineptine administration in some patients (not statistically significant). No statistically significant improvement (p=0.4) was found in depression or anxiety in the two groups. The Bulimic Investigation Test Edinburgh (BITE) symptoms and gravity scores improved significantly (p=0.001) in both groups and gravity was more significantly (p=0.05) improved with amineptine than fluvoxamine. Optimum dosage and duration of treatment for this condition have not been determined. The data of this study are preliminary and the results need to be validated in a larger population over a longer observation period (Brambilla et al, 1995).

4.6.B Amitriptyline

Depression

Fibromyalgia

4.6.B.1 Depression

a) SUMMARY: In two clinical studies, amitriptyline and fluvoxamine were equally effective in treating patients with depression (Gasperini et al, 1992; Remick et al, 1994). A greater percentage of the amitriptyline group discontinued therapy due to side effects (Remick et al, 1994).

b) In a double-blind, randomized parallel study lasting seven weeks, fluvoxamine (mean dose 175 mg/day) was compared to amitriptyline (mean dose 135 mg/day) in 33 outpatients with moderate degrees of depression. There was no statistically significant difference between the two drugs as judged using the Hamilton Rating Scale for Depression and the Clinical Global Impression Scale. The two drugs had a comparable safety profile, although a greater percentage of the amitriptyline group discontinued therapy due to side effects (Remick et al, 1994).

c) In another study, amitriptyline was compared to fluvoxamine in a double-blind trial of 56 patients with major depressive disorders. The study lasted 6 weeks and doses of amitriptyline and fluvoxamine escalated from 50 to 300 mg and 100 to 300 mg, respectively. Patients were divided into responders and non-responders based on the Hamilton rating scale for depression and the Montgomery-Asberg depression rating scale. Overall, the drugs were found equally effective, but there was some symptom specificity which might guide the selection of one or the other drug in the clinical setting (Gasperini et al, 1992).

4.6.B.2 Fibromyalgia

a) Fluvoxamine was equally effective to amitriptyline in reducing pain associated with fibromyalgia. In an open-label, uncontrolled study, 68 Japanese patients with fibromyalgia received either amitriptyline at a mean dose of 20 milligrams (mg)/day or fluvoxamine at a mean dose of 25 mg/day for 4 weeks. Patients evaluated pain relief by means of a visual analog scale and efficacy was defined as a decrease in pain by at least 50%. At 4 weeks, 50% of patients in the amitriptyline group and 41% of patients in the fluvoxamine group reported effective relief of pain (p=NS). Drowsiness was the most commonly reported adverse event with amitriptyline treatment and nausea was most frequently reported with fluvoxamine. The authors hypothesize that because the efficacy of amitriptyline for the treatment of fibromyalgia-related pain has been established in previous, controlled trials and because fluvoxamine showed similar efficacy to amitriptyline in this open-label study; fluvoxamine may be helpful for patients with fibromyalgia (Nishikai & Akiya).

4.6.C Clomipramine

Anxiety

Cataplexy

Depression

Obsessive-compulsive disorder

Panic disorder

4.6.C.1 Anxiety

a) Fluvoxamine and clomipramine were comparable in reducing anxiety symptoms in patients with agoraphobia with panic attacks (APA), generalized anxiety disorders (GAD), and obsessive-compulsive disorders (OCD) as classified by DSM-III during a randomized, double-blind study (Westenberg et al, 1987). Of the 50 patients in this study, 39 diagnosed with APA, 5 with GAD, and 6 with OCD. Patients were randomly assigned to receive either clomipramine, up to 150 milligrams/day, or fluvoxamine, up to 100 milligrams/day, for the 6-week study. Both drugs demonstrated significant improvement in anxiety symptoms after drug therapy when compared to pretreatment.

4.6.C.2 Cataplexy

a) Both fluvoxamine and clomipramine improved cataplexy, but not narcolepsy, in 18 patients with these diseases during a cross-over study (Schachter & Parkes, 1980). It was not revealed if either the patients or researchers were blinded to drug therapy. It should be noted that 15 of the 18 patients were receiving clomipramine 25 to 100 milligrams/daily at the start of the trial, and may have been accustomed to the adverse effects of clomipramine. Also, if the patients were not blinded to drug therapy, some patients may have associated more adverse effects with a new drug, fluvoxamine. Patients were randomly allocated to receive fluvoxamine or clomipramine for a 3-week interval. After a 1-week drug-free period, the patients crossed over to the other drug. The daily dosing range for both drugs ranged from 25 to 200 milligrams/day. All patients were clinically assessed by observers on 5 occasions. The observers' impression was that fluvoxamine caused a moderate reduction in the frequency of attacks of cataplexy and sleep paralysis in most subjects. Fluvoxamine abolished cataplexy in 4 patients and sleep paralysis in 2 patients; only 12 of the 18 patients completed the fluvoxamine-treatment period. The observers felt that clomipramine was more effective than fluvoxamine in preventing both cataplexy and sleep paralysis. Clomipramine abolished cataplexy in 4 patients and sleep paralysis in 5 patients.

4.6.C.3 Depression

a) SUMMARY: Several double-blind, short-term studies have demonstrated fluvoxamine to be as effective as clomipramine in the treatment of depression (De Wilde et al, 1983; Klok et al, 1981). Anticholinergic adverse effects appear to be less common with fluvoxamine therapy.

b) Fluvoxamine and clomipramine were compared for antidepressant activity in a 6-week, randomized, double-blind study of 43 outpatients with major depression (De Wilde et al, 1983). Oral fluvoxamine 100 to 300 milligrams or oral clomipramine 50 to 150 milligrams was administered once daily in the evening. Assessments of the HAM-D (Hamilton Rating Scale for Depression) during the study and at the end failed to demonstrate any significant differences in antidepressant activity between the 2 drugs. The incidence of anticholinergic adverse effects were slightly more significant in the clomipramine-treated group.

c) Clomipramine and fluvoxamine appeared to be equally effective in the treatment of depression for 36 female inpatients during a 4-week, randomized, double-blind study (Klok et al, 1981). Patients were randomized to receive either oral clomipramine or oral fluvoxamine 50 milligrams 3 times daily. Diazepam 10 to 30 mg/day for severe agitation and/or anxiety was the only other psychotropic agent administered. Significant improvements in the Hamilton Rating Scale for Depression, the Clinical Global Impression, and the Zung Self-Rating Depression scale were seen in both treatment groups. Anticholinergic adverse effects appeared more frequently in the clomipramine-treated patients, while gastrointestinal effects were more prevalent in the fluvoxamine group.

d) Fluvoxamine and clomipramine appeared to have similar clinical efficacy in the treatment of endogenous depression for 30 unipolar and bipolar inpatients during a 4-week, randomized, double-blind study (De Wilde et al, 1983). Both drugs were administered orally in doses of 150 to 300 milligrams/day in 3 divided doses. At the end of the study, the fluvoxamine-treated patients demonstrated a 73% improvement on the Hamilton Rating Scale for Depression, while the clomipramine-treated patients had a 62% improvement. In the bipolar patients, 3 of 4 on fluvoxamine responded, while only 1 of 5 on clomipramine demonstrated a good response on the CGI Global Change Scale. Overall, the differences in efficacy between the 2 drugs were not statistically significant. Adverse anticholinergic effects were significantly more prevalent in the clomipramine-treated group.

e) Both clomipramine and fluvoxamine produced significant improvements on the Hamilton Rating Scale for Depression (HAM-D) in 32 patients with mixed depression during a 4-week, randomized, double-blind study (Dick & Ferrero, 1983). The average daily dosage was 130 milligrams and 132.8 milligrams for fluvoxamine and clomipramine, respectively. The mean percentage improvement on the HAM-D for the fluvoxamine-treated patients was 63.8%, and for the clomipramine-treated patients it was 66.3%.

4.6.C.4 Obsessive-compulsive disorder

a) Fluvoxamine (150 to 125 milligrams/day) and clomipramine (100 to 250 milligrams/day were equally effective in the treatment (10 weeks) of 66 outpatients with obsessive compulsive disorder. Both treatments were well-tolerated. Fluvoxamine produced fewer anticholinergic adverse effects and caused less sexual dysfunction than clomipramine, but caused more headache and insomnia (Freeman et al, 1994). under OBSESSIVE COMPULSIVE DISORDER add:

b) In a randomized, double-blind study of 26 patients with obsessive compulsive disorder without comorbid diseases, fluvoxamine and clomipramine, each titrated from an initial dose of 50 milligrams (mg) in the evening up to a maximum of 300 mg daily within two weeks, were equally effective (38% improvement over

baseline with fluvoxamine versus 40% for clomipramine). Efficacy was assessed according to the Yale-Brown Obsessive Compulsive Scale and Clinical Global Impression Scale. Fluvoxamine was better tolerated, with less anticholinergic adverse effects while clomipramine had a quicker onset of action. Further studies are needed to demonstrate a time-related effect that might differentiate these drugs (Milanfranchi et al, 1997).

4.6.C.5 Panic disorder

a) Clomipramine (10 milligrams (mg) for three days and 20 mg for four days) and fluvoxamine (50 mg/day for seven days) were both effective in decreasing the hypersensitivity to 35% carbon dioxide, supporting the serotonergic effect of these drugs to decrease panic attacks through modification of carbon dioxide sensitivity. Thirty-nine panic disorder patients were enrolled in a double-blind, randomized, placebo-controlled study, where each patient was given the 35% carbon dioxide challenge on days 0, 3, and 7. Patients on clomipramine and fluvoxamine showed significant reduction in sensitivity over placebo after seven days as seen by the percent change on a visual analogue for anxiety scale (p=0.027) (Perna et al, 1997).

4.6.D Clovoxamine

1) Efficacy

a) SUMMARY: Clovoxamine induces only minor electroencephalographic changes in healthy subjects; whereas, changes produced by fluvoxamine more closely resemble those of imipramine, including an increase of slow activity. Clovoxamine appears less sedating than fluvoxamine, and may possess mild alerting effects.

b) In computerized electroencephalographic studies involving healthy subjects (Saletu et al, 1980), oral clovoxamine 50 to 125 mg was primarily associated with an increase in very fast beta-activity (predominant 6 hours postdose), suggesting an activating effect of the drug. Although an increase in fast beta-activity was also observed with fluvoxamine 75 mg, this agent also produced a concomitant increase of slow activity and a decrease of alpha-activity. Imipramine 75 mg produced the most marked electroencephalographic changes, characterized by a concomitant increase of slow and fast activities and a decrease of alpha-activity. Augmentation of slow activity was, however, less with fluvoxamine than imipramine, suggesting less sedative properties of the former. Overall, pharmacodynamic data based on both electroencephalographic and psychometric parameters indicated that imipramine 75 mg produced the most central nervous system changes, followed by fluvoxamine 75 mg, clovoxamine 125 mg, clovoxamine 75 mg, and clovoxamine 50 mg. Peak effects occurred 4 to 6 hours after clovoxamine and fluvoxamine, compared to 2 to 4 hours following imipramine. Adverse effects were minimal with clovoxamine, with euphoria occurring in a few subjects; in contrast, tiredness was common after fluvoxamine (50% of subjects) and imipramine (80%).

c) The results of a further placebo-controlled study in healthy volunteers also suggested a lower propensity of clovoxamine to induce sedation in comparison with fluvoxamine. In doses of 50 mg twice daily (8 am and 6 pm), fluvoxamine was associated with changes suggestive of enhanced nighttime sedation; fluvoxamine-treated were significantly less refreshed upon awakening and had greater difficulty in achieving morning alertness compared to placebo, and there were trends toward fewer nocturnal awakenings and shorter sleep latency in the fluvoxamine group. In contrast, these effects were not observed clovoxamine 150 mg daily (100 mg at 8 am and 50 mg at 6 pm); depth of sleep was reduced significantly with clovoxamine compared to placebo (Ochs et al, 1989).

4.6.E Desipramine

4.6.E.1 Depression

a) The efficacy of fluvoxamine was compared to that of desipramine in a multicenter, double-blind, placebo-controlled six-week flexible dose trial of 90 outpatients with major depressive disorder. Dosage range for each active medication was 100 to 300 milligrams/d. The Montgomery-Asberg Depression Rating Scale, the Hamilton Rating Scale for Depression, and the Clinical Global Impression Scale were used to assess response. There was no significant difference in efficacy among the three treatments until week six, when both active drug groups continued to improve while the placebo group remained at the same level of depression. The authors concluded that 6 weeks was too short a time to identify the differences between active drug and placebo in the patient population (Roth et al, 1990).

b) An immediate increase in pain threshold (polysynaptic R-III reflex and subjective pain rating to electric shock) was seen in a single-dose, placebo-controlled study comparing desipramine, fluvoxamine, and moclobemide in healthy volunteers (n=10) (Coquoz et al, 1993).

4.6.F Dothiepin

4.6.F.1 Depression

a) Fluvoxamine and dothiepin were comparable in reducing symptoms of depression in 73 patients during a 6-week, double-blind study (Mullin et al, 1988). The patients were randomized to receive initial starting doses of either fluvoxamine 100 milligrams or dothiepin 75 milligrams daily. The doses were increased gradually, as tolerated, to a maximum of fluvoxamine 300 milligrams or dothiepin 225 milligrams/day. At the conclusion of the study, both drugs demonstrated efficacy in treating depression as measured by the Hamilton Depression Rating Scale (HAMD), Clinical Global Impression, and Clinical Global Improvement

scales. There were no significant differences in efficacy between the 2 drugs. Dothiepin was associated with more anticholinergic adverse effects, while fluvoxamine was associated with more nausea and vomiting.
b) Fluvoxamine (25 to 200 mg/d) was equivalent to dothiepin (25 to 200 mg/d) in efficacy in 52 elderly inpatients with major depressive disorder. Patients were treated for 6 weeks with weekly assessments for therapeutic response and presence of adverse effects. The mean dosage during the last 2 weeks of the study was 157 mg/d for fluvoxamine and 159 mg/d for dothiepin. Sixty-three percent of fluvoxamine patients and 60% of dothiepin patients showed marked improvement at six weeks (Rahman et al, 1991).

4.6.G Fluoxetine

4.6.G.1 Depression
a) In a randomized, double-blind study (n=100), fluvoxamine and fluoxetine demonstrated comparable efficacy and side effects in out-patients with major depression. After randomization, patients were treated initially with fluvoxamine 50 milligrams (mg) daily adjusted to a maximum of 150 mg daily or fluoxetine 20 mg daily adjusted to a maximum of 80 mg daily. Throughout the study, significant differences in efficacy were NOT detected on several depression scales including the Hamilton depression scale and clinical global impressions scale. Adverse effects were common with both drugs but the severity was mild in the majority of patients. Even though this study included 100 patients, it may NOT have detected subtle differences between the 2 treatments (Rapaport et al, 1996).

4.6.H Flupenthixol

4.6.H.1 Depression
a) Flupenthixol was as effective as fluvoxamine in the treatment of depression, and had a more favorable adverse effect profile (Hamilton et al, 1989). In a multicenter trial, 72 patients with depression were randomized to receive either flupenthixol 1 milligram/day (n=36) or fluvoxamine 100 milligram/day (n=36) for 4 weeks. Patients were evaluated objectively on days 1, 8, 15, and 29 using the Hamilton Depression Rating Scale, the Clinical Global Impressions Scale, and a self-assessment analog scale. At the end of the first week, the dose was doubled if response was judged to be insufficient. While both drugs were shown to be effective, mean improvement scores were higher at all evaluation times as measured by any of the 3 parameters in the group receiving flupenthixol. At the end of the first week, 89% of the flupenthixol group showed at least minimal improvement, compared with 75% of the fluvoxamine group. At the end of the study, all patients receiving flupenthixol had responded to treatment, compared with 83% of the fluvoxamine group. Four patients taking fluvoxamine were withdrawn due to adverse effects, but no patients receiving flupenthixol were withdrawn.

4.6.I Imipramine

4.6.I.1 Depression
a) SUMMARY: Fluvoxamine and imipramine appear to be equally efficacious in the treatment of depression (Lapierre et al, 1987; Guelfi et al, 1983; Guy et al, 1984; Itil et al, 1983); (March, 1990)(Lydiard et al, 1989).
b) Fluvoxamine demonstrated a trend toward superiority over imipramine in treating 63 patients with major depression during a 4- to 6-week, randomized, placebo-controlled, double-blind study (Lapierre et al, 1987). All drugs were started at 50 milligrams/day, and were gradually increased to a maximum of 300 mg/day. The mean daily dose of fluvoxamine at the the end of the study was 207 mg, and 192 mg for imipramine. At the end of the study, the total Hamilton Rating Scale for Depression (HAM-D) score had decreased by 75%, 55%, and 6% in the fluvoxamine-, imipramine-, and placebo-treated groups, respectively. At the end of the study there were 8, 3, and 1 responders from the fluvoxamine, imipramine, and placebo groups, respectively. Only 1 patient in each active treatment group withdrew from the study because of adverse effects.
c) Fluvoxamine was comparable to imipramine in antidepressant activity during a 4-week, double-blind, multicenter study of 151 patients (Guelfi et al, 1983). Drug therapy was administered in twice daily dosing in the range of 100 to 300 milligrams daily for fluvoxamine and 50 to 200 milligrams daily for imipramine. At the end of the study there was a mean improvement in the Hamilton Rating Scale for Depression (HAM-D) of 67.2% in the fluvoxamine-treated group and a 62.1% improvement in the imipramine-treated group. A similar improvement was detected with both drugs on the Clinical Global Impression Scale. At the end of the study, the mean daily dose of fluvoxamine was 221 mg and 112 mg for imipramine. A total of 37 patients withdrew from the study prematurely; 19 on fluvoxamine and 18 on imipramine. The reasons for early withdrawal appeared to be similar between both drugs.
d) Fluvoxamine and imipramine were comparable in efficacy for the treatment of depression in 36 patients diagnosed with unipolar or bipolar depression during a 4- to 6-week, randomized, double-blind study (Guy et al, 1984). Both medications were administered at bedtime with a maximal dosage range between 150 to 225 milligrams/day. In the unipolar depressed fluvoxamine-treated patients, 92% were judged "improved" at the end of the study compared to 81% of the imipramine group. However, the imipramine-treated group appeared to have a higher percent of patients rated as "much" or "very much" improved, 75% compared to 54% of the fluvoxamine group.
e) A double-blind comparative study of fluvoxamine and imipramine was carried out in 20 outpatients with depressive disorder. Patients received randomly-assigned medication over a 4-week period in a dosage

range of 50 of 300 mg given in 2 divided doses. There was a significant symptom severity reduction in both groups at the end of 4 weeks, and fluvoxamine was more effective than imipramine in reducing suicidal ideas and anxiety/somatic symptoms. Anticholinergic-type adverse reactions predominated for imipramine and gastrointestinal effects for fluvoxamine (Gonella et al, 1990).

f) In a 6-week, double-blind, placebo-controlled, variable-dose study assessing the comparative antidepressant efficacy of fluvoxamine (FLU), imipramine (IMI), and placebo (PBO), 45 patients with major depressive disorder were evaluated for response and side effects. Dosage ranged between 100 to 300 milligrams/day for active medications. No statistically significant differences between either the FLU (N=17) and PBO or the FLU and IMI groups were found. Side effects were present in all three groups: IMI(N=18): constipation (83%), dry mouth (55%), and sweating, dizziness, and nausea, all 39%. FLU(N=18): diarrhea, headache, dry mouth, all 41%, nausea (35%), and flatus (29%). PBO(N=18): pruritus (29%, nausea (23%), headache (18%), asthenia and somnolence, both 12%. This study revealed a high placebo response, with a 50% improvement at week 6. Thus, it is difficult to show differences from active medication unless the study is carried out for a longer time. In addition, the numbers of patients are too small to detect a true difference. Second, patients seemed to either respond or not respond to FLU, while the response to IMI appeared to be more graded. This may reflect a subgroup of depressed patients that have a serotonin-deficient type of depression (Lydiard et al, 1989).

g) Other double-blind, placebo-controlled studies comparing imipramine and fluvoxamine have only demonstrated slightly more improvement in depression with either drug when compared with placebo (Dominguez et al, 1985; Norton et al, 1984).

4.6.I.2 Adverse Effects

a) SUMMARY: Fluvoxamine produces less cardiovascular and anticholinergic adverse effects than imipramine; however, nausea and vomiting are more common with fluvoxamine therapy (Benfield & Ward, 1986a; Roos, 1983; Saletu et al, 1980a; Laird et al, 1993).

b) Adverse effects data was pooled from the results of 10 double-blind, placebo-controlled trials comparing fluvoxamine (n=222) with imipramine (n=221) (Benfield & Ward, 1986a). Anticholinergic effects such as dry mouth, dizziness/syncope, sweating, and abnormal accommodation were much more prevalent in patients receiving imipramine. Nausea/vomiting was the only adverse effect to be much more prevalent in the fluvoxamine-treated patients.

c) The cardiac effects of tricyclic antidepressants were compared with fluvoxamine. The major cardiac adverse effects observed with tricyclic antidepressants include postural hypotension, heart rate increase, and slight prolongation of the intraventricular conduction time and QT interval. The only cardiac effect observed with fluvoxamine was a statistically, but not clinically, significant slowing of heart rate (Roos, 1983).

d) Fluvoxamine produced less psychomotor impairment than imipramine. Fluvoxamine was superior to imipramine 75 milligrams in regards to concentration, reaction time, mood, psychomotor activity, and affectivity. Following the administration of fluvoxamine 75 milligrams to 10 healthy volunteers, psychometric tests demonstrated a tendency towards an improvement in psychomotor activity, concentration, attention, after-effect, and mood and a significant increase in critical flicker fusion frequency when compared to placebo (Saletu et al, 1980a).

4.6.J Lithium

4.6.J.1 Depression

a) The rate of recurrence of unipolar depressive episodes was lower for fluvoxamine 200 milligrams (mg) per day than lithium salts 600 to 900 mg/day in a randomized study of 64 unipolar patients. Follow-up continued for 24 months (Franchini et al, 1994). Further follow-up at 36 months showed no additional recurrences of depression in either the fluvoxamine or the lithium group (Franchini et al, 1996). Due to methodological limitations, further studies are needed.

4.6.K Lorazepam

4.6.K.1 Depression

a) Fluvoxamine (50 to 300 mg/d) was compared with lorazepam (1 to 6 mg/d) in a multi-center, double-blind, parallel group study in 112 general practice patients with mixed anxiety and depression. Response was assessed over a 6-week period using the Montgomery-Asberg Depression Rating Scale (MADRS) and the Clinical Anxiety Scale (CAS). There were no significant differences between treatments at any point except in an elderly subgroup where anxiety improved more rapidly with lorazepam. There were significant improvements in MADRS and CAS, and global ratings compared with baseline at all subsequent assessments. Lorazepam produced more sedation while fluvoxamine produced more nausea and vomiting (Laws et al, 1990).

4.6.L Maprotiline

4.6.L.1 Schizophrenia

a) Fluvoxamine was more effective than maprotiline for improving negative symptoms associated with schizophrenia. Patients entered in this study had schizophrenia of at least 2 years duration and received more than 1 antipsychotic with anticholinergics (stable dose maintained during study). Patients (n=38) were

randomly assigned to fluvoxamine or maprotiline 50 milligrams (mg) daily which was increased to 100 mg during the remaining 5 weeks of the study. Thirteen patients left the study within 2 weeks due to personal reasons, side effects, or worsening symptoms; these patients were NOT included in the efficacy analysis. The total score for the Scale for the Assessment of Negative Symptoms was significantly (p=0.045) lower in the fluvoxamine (65.6 to 57.1) versus maprotiline (80.3 to 78) group; similar results were obtained for the Brief Psychiatric Rating Scale for negative factors. Five (38.5%) patients in the fluvoxamine group were responders (defined by 20% improvement in total SANS score) versus none in the maprotiline group. The authors suggest that the serotonergic versus the antidepressant effect of fluvoxamine are responsible for the change in negative symptoms. Further study is needed since the sample size was small, and many patients left the study (Silver & Shmugliakov, 1998).

4.6.M Mianserin

4.6.M.1 Depression

a) Both fluvoxamine and mianserin are effective for the treatment of depressive illness (Perez & Ashford, 1990). Efficacy and CNS effects of fluvoxamine were compared with those of mianserin in depressed outpatients in a 6-week double-blind trial. The study included active treatment with 100 to 300 milligrams/d of fluvoxamine or 60 to 180 milligrams/d of mianserin. Data from 63 patients (30 fluvoxamine) showed comparable efficacy at the end of 6 weeks. MADRS scores (Montgomery-Asburg Depression Rating Scale) improved 65.6% with fluvoxamine and 60.8% with mianserin with no significant differences between treatments at any assessment. Mianserin produced more sedation during the first week of treatment but this difference resolved for the remainder of the study.

b) Fluvoxamine 50 to 200 milligrams and mianserin 20 to 80 milligrams/d were equivalent in efficacy and tolerability in a study of 57 elderly patients with major depressive episode. Seven of 25 fluvoxamine patients and 4 of 25 mianserin patients had to leave the study because of intolerable side effects (Phanjoo et al, 1991).

4.6.N Milnacipran

4.6.N.1 Depression

a) Although there was no significant difference in efficacy between groups of patients treated with fluvoxamine or milnacipran when viewed overall, among the subset of severely depressed patients, significantly more who were treated with milnacipran responded to treatment (50% or greater improvement in Hamilton Depression Rating Scale (HDRS) score) than who were treated with fluvoxamine. The groups comprised patients who had been treated with milnacipran (maximum dose 15 milligrams (mg) per day) for at least 22 months (n=102) or with fluvoxamine (maximum dose 250 mg/day) for the same period (n=90). Overall, 53% of milnacipran-treated patients and 47% of fluvoxamine-treated patients responded to treatment. Among patients with an initial HDRS score of 19 or greater, 69% of those treated with milnacipran and 46% of those treated with fluvoxamine responded (p=0.046). Scores showing improvement in insomnia and agitation significantly favored milnacipran. There were no significant differences between groups for individual or total adverse events. However, urological adverse events occurred more frequently in the milnacipran group and gastrointestinal symptoms in the fluvoxamine group. Palpitations occurred only in the milnacipran group (3%) (Fukuchi & Kanemoto, 2002).

b) Several comparative trials (mainly unpublished) have indicated no significant difference in efficacy between milnacipran 50 to 150 mg twice daily and fluvoxamine 100 mg twice daily or fluoxetine 20 mg once daily in major depression (Guelfi et al, 1998; Anon, 1997). One study reported the superiority of fluoxetine 20 mg once daily (statistically significant for most parameters) over milnacipran 100 mg once daily in major depressive outpatients (Ansseau et al, 1994); however, this study suffered from methodological problems, the most significant being once-daily dosing of milnacipran, which may not achieve therapeutic levels.

c) Meta-analyses of studies comparing milnacipran and fluoxetine/fluvoxamine have been performed by the manufacturer; greater improvements (eg, Hamilton, Montgomery-Asberg) were described for milnacipran, which were usually statistically significant (Lopez-Ibor et al, 1996; Anon, 1997; Elwood, 1997). However, only a few trials were selected for analysis, and not all patients in these trials were evaluated; the superiority of milnacipran was demonstrated only after results were subjected to multiple reanalysis (Anon, 1997).

d) Comparisons with other similar agents (eg, sertraline) are lacking.

4.6.O Oxaprotiline

4.6.O.1 Depression

a) Oxaprotiline appeared to be more efficacious than fluvoxamine in 71 depressed patients resistant to prior tricyclic antidepressants during a randomized, double-blind, partial crossover study (Nolen et al, 1988). Patients were randomized to receive either fluvoxamine or oxaprotiline at a starting dose of 50 mg BID, which was gradually increased to a maximum of 150 mg BID as tolerated. The mean daily doses of oxaprotiline and fluvoxamine at the end of 4 weeks were 260 mg and 288 mg, respectively. Only 9 of 33 (27%) patients receiving oxaprotiline demonstrated a response, while none of the fluvoxamine-treated patients responded. During the second treatment phase, 55 patients were crossed over to the other drug. The mean daily doses of oxaprotiline and fluvoxamine at the end of the second phase were 267 mg and 286 mg, respectively. Of the 31 patients completing at least 2 weeks of oxaprotiline therapy, 12 (38%)

responded; however, 6 (19%) relapsed within 6 months for a long-term response rate of only 19%. Of the 21 patients completing at least 2 weeks of fluvoxamine therapy, 2 patients (9%) responded with lasting effects.

4.6.P Paroxetine

4.6.P.1 Depression

a) Fluvoxamine and paroxetine produced similar improvements in depressive symptoms in patients with an initial or recurrent episode of major depression. Adverse effects occurred in 100% and 97% of patients treated with paroxetine and fluvoxamine, respectively. Fluvoxamine was associated with a higher incidence of asthenia, dry mouth, somnolence, and insomnia; whereas, paroxetine caused a higher incidence of headache, nausea, diarrhea, sweating, abnormal dreams, and sexual dysfunction. In this 7-week, randomized, double-blind study, 58 patients were assigned to receive fluvoxamine 50 milligrams(mg)/day or paroxetine 20 mg/day initially; the protocol allowed for dosage titration to fluvoxamine 150 mg/day or paroxetine 50 mg/day. An additional 10 fluvoxamine- and 8 paroxetine-treated patients dropped out of the study for various reasons, but all of the patients were included in the intent-to-treat efficacy analysis. Due to the small sample size of this study, only large differences between treatments would be detectable; therefore, larger studies are needed to detect differences in treatment effects between these drugs (Kiev & Feiger, 1997).

b) The pharmacology, pharmacokinetics, adverse effects, drug interactions, efficacy, and dosage and administration of fluvoxamine (FVX), sertraline (SRT) and paroxetine (PRX) were compared in a comprehensive review (Grimsley & Jann, 1992). All three agents have large volumes of distribution and are highly protein-bound. In contrast to fluoxetine, FVX, SRT, and PRX all have shorter elimination half-lives (approximately 24 hours) and are metabolized to clinically-inactive compounds. Nausea was the most commonly reported adverse effect for all three agents. Other reported adverse effects include sedation, headache, dry mouth, insomnia, sexual dysfucntion, and constipation. FVX has been found to be superior to placebo and equivalent to imipramine, clomipramine, desipramine, mianserin, and maprotiline in the treatment of depression and both FVX and SRT have been shown to be superior to placebo in the treatment of obsessive-compulsive disorder (OCD). PRX has been found to be superior to placebo and equivalent to amitriptyline, imipramine, clomipramine, and doxepin in the treatment of depression while SRT has been found to be superior to placebo and equivalent to amitriptyline. Clinical experience has demonstrated all three drugs to be effective in the treatment of depression. They may be especially useful in elderly patients, in those who cannot tolerate alternate treatments, and in those who do not respond to adequate trials of other antidepressant therapies.

4.6.Q Sertraline

4.6.Q.1 Depression

a) In a small study (n=64), the incidence of recurrent depression was similar between patients treated prophylactically with sertraline and fluvoxamine. Sixty-four patients entered the study and received either sertraline 100 milligrams(mg)/day or fluvoxamine 200 mg/day for 2 years; increases in dose were allowed if depression recurred. During the study period, 7 sertraline-treated and 6 fluvoxamine-treated patients had a new episode of depression (p=0.88). Adverse effects were minor and transient for both treatments. Results of this study suggest that sertraline and fluvoxamine were effective for preventing recurrent depression episodes, but are limited by the absence of a placebo control group(Franchini et al, 1997).

b) The pharmacology, pharmacokinetics, adverse effects, drug interactions, efficacy, and dosage of fluvoxamine (FVX), sertraline (SRT) and paroxetine (PRX) were compared in a comprehensive review (Grimsley & Jann, 1992a). All three agents have large volumes of distribution and are highly protein-bound. In comparison to fluoxetine, FVX, SRT, and PRX all have shorter elimination half-lives (approximately 24 hours) and are metabolized to clinically-inactive compounds. These agents, therefore, are less likely than fluoxetine to interact with other drugs. Nausea was the most commonly reported adverse effect for all three agents. Other reported adverse effects include sedation, headache, dry mouth, insomnia, sexual dysfunction, and constipation. FVX has been found to be superior to placebo and equivalent to imipramine, clomipramine, desipramine, mianserin, and maprotiline in the treatment of depression and both FVX and SRT have been shown to be superior to placebo in the treatment of obsessive-compulsive disorder (OCD). PRX has been found to be superior to placebo and equivalent to amitriptyline, imipramine, clomipramine, and doxepin in the treatment of depression while SRT has been found to be superior to placebo and equivalent to amitriptyline. Clinical experience has demonstrated all three drugs to be effective in the treatment of depression. They may be especially useful in elderly patients, in those who cannot tolerate alternate treatments, and in those who do not respond to adequate trials of other antidepressant therapies.

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DRUGDEX® Evaluations

THIORIDAZINE

0.0 Overview

1) Class
- **a)** This drug is a member of the following class(es):
  - Antipsychotic
  - Phenothiazine
  - Piperidine

2) Dosing Information
- **a)** Thioridazine Hydrochloride
  - **1)** Adult
    - **a)** Schizophrenia, Refractory
      - **1)** initial, 50 to 100 mg ORALLY 3 times a day; may increase gradually to a MAX of 800 mg/day in 2 to 4 divided doses (Prod Info Mellaril(R), 2000)
      - **2)** maintenance, once effective control of symptoms achieved, may gradually reduce dose to determine the minimum maintenance dose (range from 200 to 800 mg/day in 2 to 4 divided doses) (Prod Info Mellaril(R), 2000)
  - **2)** Pediatric
    - **a)** Safety and effectiveness not established in children under 2 years of age
      - **1)** Schizophrenia, Refractory
        - **a)** initial, 0.5 mg/kg/day in divided doses; may increase gradually to a MAX of 3 mg/kg/day (Prod Info Mellaril(R), 2000)

3) Contraindications
- **a)** Thioridazine Hydrochloride
  - **1)** abnormal serum potassium concentration
  - **2)** central nervous system (CNS) depression, coma, or drug-induced CNS depression
  - **3)** co-administration with other drugs that cause QTc-interval prolongation or drugs that inhibit thioridazine metabolism or clearance
  - **4)** history of cardiac arrhythmias or QTc-interval prolongation
  - **5)** hypersensitivity to thioridazine
  - **6)** patients with a QTc-interval greater than 450 milliseconds
  - **7)** patients with reduced hepatic cytochrome P450 2D6 enzyme activity
  - **8)** patients with severe hypertensive or hypotensive heart disease

4) Serious Adverse Effects
- **a)** Thioridazine Hydrochloride
  - **1)** Agranulocytosis
  - **2)** Cholestatic jaundice syndrome
  - **3)** Death
  - **4)** Disorder of hematopoietic structure
  - **5)** Drug-induced lupus erythematosus, Systemic
  - **6)** Ineffective thermoregulation, Heatstroke or hypothermia
  - **7)** Leukopenia
  - **8)** Neuroleptic malignant syndrome
  - **9)** Obstipation
  - **10)** Paralytic ileus
  - **11)** Priapism
  - **12)** Prolonged QT interval
  - **13)** Seizure
  - **14)** Sudden cardiac death
  - **15)** Thrombocytopenia
  - **16)** Torsades de pointes

5) Clinical Applications
- **a)** Thioridazine Hydrochloride
  - **1)** FDA Approved Indications
    - **a)** Schizophrenia, Refractory

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

Thioridazine
Thioridazine HCl
Thioridazine Hydrochloride

1.2 Storage and Stability

A) Thioridazine Hydrochloride

1) Oral route

a) Thioridazine tablets should be stored at 25 degrees Celsius (77 degrees Fahrenheit); excursions permitted to 15 to 30 degrees Celsius (59 to 86 degrees Fahrenheit) (Prod Info Mellaril(R), 2000ae).

b) Thioridazine oral solution should be stored below 30 degrees Celsius (86 degrees Fahrenheit) in a tightly sealed, amber bottle. The solution can be diluted in distilled water, tap water, or juices; storage of bulk dilutions is not recommended (Prod Info Mellaril(R), 2000ae).

c) Thioridazine when mixed with lithium citrate syrup (5 and 10 mL) is visually incompatible. Centrifugation of this mixture yielded two liquid phases, a clear supernatant and a viscous hydrophobic sediment. This mixture should be avoided due to the possibility that underdosing could occur (Theesen et al, 1981).

1.3 Adult Dosage

Normal Dosage

Dosage in Geriatric Patients

1.3.1 Normal Dosage

1.3.1.A Thioridazine Hydrochloride

1.3.1.A.1 Oral route

1.3.1.A.1.a Schizophrenia, Refractory

1) The usual oral starting dose of thioridazine for schizophrenia unresponsive to other agents is 50 to 100 milligrams three times daily with gradual incremental increases to a maximum of 800 milligrams/day if necessary. The dose should be reduced gradually to determine the minimum maintenance dose once effective control of symptoms has been achieved (Prod Info Mellaril(R), 2000ae).

1.3.1.A.2 IMPORTANT NOTE

a) Patients being considered for thioridazine therapy should have baseline electrocardiograms and measurement of serum potassium concentrations. Thioridazine is contraindicated in patients with a QTc-interval greater than 450 milliseconds and in patients with a history of cardiac arrhythmias. The drug should not be given until serum potassium levels are within the normal range (Prod Info Mellaril(R), 2000ae).

1.3.1.A.3 MAXIMUM DOSE

a) Thioridazine doses should not exceed 800 milligrams/day as higher doses have been associated with pigmentation retinopathy and irreversible blindness (Prod Info Mellaril(R), 2000ae).

1.3.1.A.4 ORAL SOLUTION PREPARATION

a) The oral concentrate of thioridazine may be diluted with distilled water, acidified tap water, or suitable juices. Each dose should be diluted just prior to administration. The preparation and storage of bulk dilutions is not recommended (Prod Info Mellaril(R), 2000ae).

1.3.4 Dosage in Geriatric Patients

A) Thioridazine Hydrochloride

1) Elderly patients should be treated with reduced doses of phenothiazine drugs and monitored closely for excessive parkinsonism side effects. This patient population has a higher incidence of these side effects which may be irreversible and unresponsive to conventional anti-parkinsonian drugs (Ayd, 1961; Paulson, 1968). Unless there are compelling reasons to the contrary, thioridazine use in the elderly should be avoided because of side effect-related complications.

2) Significantly higher plasma concentrations of thioridazine (1.5- to 2-fold higher) were reported in elderly patients (mean age, 76 years) as compared with young adults (mean age, 28 years). Adverse effects (postural hypotension, dry mouth) were more frequent and severe in the elderly subjects. These data suggest that dosing reductions are indicated in elderly patients receiving thioridazine (Cohen & Sommer, 1988).

1.4 Pediatric Dosage

1.4.1 Normal Dosage

1.4.1.A Thioridazine Hydrochloride

1.4.1.A.1 Oral route

1.4.1.A.1.a Schizophrenia, Refractory

1) For children who suffer from schizophrenia unresponsive to other agents, the recommended dose of oral thioridazine is 0.5 milligram/kilogram/day in divided doses. Dosage may be titrated gradually to optimum clinical response or to the maximum dose of 3 milligrams/kilogram/day (Prod Info Mellaril(R), 2000ae).

1.4.1.A.2 IMPORTANT NOTE

a) Patients being considered for thioridazine therapy should have baseline electrocardiograms and measurement of serum potassium concentrations. Thioridazine is contraindicated in patients with a QTc-interval greater than 450 milliseconds and in patients with a history of cardiac arrhythmias. The drug should not be given until serum potassium levels are within the normal range (Prod Info Mellaril(R), 2000ae).

1.4.1.A.3 MAXIMUM DOSE

a) Thioridazine doses should not exceed 3 milligrams/kilogram/day as higher doses have been associated with pigmentation retinopathy and irreversible blindness (Prod Info Mellaril(R), 2000ae).

1.4.1.A.4 ORAL SOLUTION PREPARATION

a) The oral concentrate of thioridazine may be diluted with distilled water, acidified tap water, or suitable juices. Each dose should be diluted just prior to administration. The preparation and storage of bulk dilutions is not recommended (Prod Info Mellaril(R), 2000ae).

2.0 Pharmacokinetics

Drug Concentration Levels

ADME

2.2 Drug Concentration Levels

A) Thioridazine Hydrochloride

1) Therapeutic Drug Concentration

a) Schizophrenia, not established (Smith et al, 1985; Sajadi et al, 1984; Shvartsburd et al, 1984a).

2.3 ADME

Distribution

Metabolism

Excretion

Elimination Half-life

2.3.2 Distribution

A) Distribution Sites

1) Thioridazine Hydrochloride

a) OTHER DISTRIBUTION SITES

1) CEREBROSPINAL FLUID (Nyberg et al, 1981).

B) Distribution Kinetics

1) Thioridazine Hydrochloride

a) Volume of Distribution

1) 17.8 L/kg (Axelsson, 1977).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics

1) Thioridazine Hydrochloride

a) LIVER, extensive (Sakalis, 1977; Axelsson & Martensson, 1977).

1) Thioridazine disposition was found to be influenced by debrisoquin hydroxylation phenotype (von Bahr et al, 1991).

B) Metabolites

1) Thioridazine Hydrochloride

a) MESORIDAZINE, active (Cohen et al, 1979; Aguilar, 1975).

1) MESORIDAZINE is twice as potent as THIORIDAZINE and is commercially available as Serentil (R) (Cohen et al, 1979; Aguilar, 1975).

b) Sulforidazine, (active) (Chakraborty et al, 1989).

c) 5-sulfoxide (ring), inactive (Sakalis, 1977; Axelsson & Martensson, 1977).

2.3.4 Excretion

A) Kidney

1) Thioridazine Hydrochloride

a) Renal Excretion (%)

1) small amounts (Sakalis, 1977; Axelsson & Martensson, 1977).

2.3.5 Elimination Half-life

A) Parent Compound

1) Thioridazine Hydrochloride

a) ELIMINATION HALF-LIFE

1) 21 to 24 hours (Shvartsburd et al, 1984a; Axelsson, 1977).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING

1) Thioridazine Hydrochloride

a) Oral (Tablet; Solution)

1) Thioridazine hydrochloride has been shown to prolong the QTc interval in a dose related manner, and drugs with this potential, including thioridazine hydrochloride, have been associated with torsades de pointes-type arrhythmias and sudden death. Due to its potential for significant, possibly life-threatening, proarrhythmic effects, thioridazine hydrochloride should be reserved for use in the treatment of schizophrenic patients who fail to show an acceptable response to adequate courses of treatment with other antipsychotic drugs, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs (Prod Info MELLARIL(R) oral tablet, solution, USP, MELLARIL-S(R) oral suspension, USP, 2000).

3.1 Contraindications

A) Thioridazine Hydrochloride

1) abnormal serum potassium concentration

2) central nervous system (CNS) depression, coma, or drug-induced CNS depression

3) co-administration with other drugs that cause QTc-interval prolongation or drugs that inhibit thioridazine metabolism or clearance

4) history of cardiac arrhythmias or QTc-interval prolongation

5) hypersensitivity to thioridazine

6) patients with a QTc-interval greater than 450 milliseconds

7) patients with reduced hepatic cytochrome P450 2D6 enzyme activity

8) patients with severe hypertensive or hypotensive heart disease

3.2 Precautions

A) Thioridazine Hydrochloride
1) elderly patients with dementia-related psychosis (unapproved use); increased risk of death reported with both conventional and atypical antipsychotics when used to treat behavorial and psychological symptoms associated with dementia (US Food and Drug Administration, 2008)
2) history of breast cancer (can elevate prolactin levels)
3) history of myasthenia gravis
4) history of neuroleptic malignant syndrome or tardive dyskinesia
5) leukopenia or agranulocytosis
6) patients participating in activities requiring complete mental alertness
7) seizure disorders

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Neurologic Effects

Ophthalmic Effects

Reproductive Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

3.3.1.A Thioridazine Hydrochloride

Cardiac dysrhythmia

EKG finding

Hypotension

Prolonged QT interval

Sudden cardiac death

Torsades de pointes

3.3.1.A.1 Cardiac dysrhythmia

a) Ventricular and supraventricular arrhythmias have been reported following therapeutic use of thioridazine and acute overdose. Arrhythmias have often been associated with conduction defects manifested by prolonged QRS interval and slight prolongation of the QT interval in association with either sinus bradycardia or tachycardia (Fletcher et al, 1969). Although in some cases discontinuation of the drug results in resolution of the cardiac arrhythmias and the return of a normal EKG within 2 weeks to 4 months (Fletcher et al, 1969), on occasion ventricular tachycardia may be refractory to conventional

modes of therapy including cardioversion, procainamide, and lidocaine. Electrical pacing with a transvenous electrical pacemaker has been reported to stabilize refractory arrhythmias (Annane et al, 1996) The increased cardiotoxicity of thioridazine over other neuroleptics was confirmed in a prospective study of neuroleptic overdosage (poisoning) in adult patients presenting to Newcastle (Australia) Hospitals between 1987-1993 (Buckley et al, 1996).
b) In a retrospective analysis of 141 adult thioridazine mono-intoxications, sinus tachycardia was a symptom of toxicity in 21% of the cases. The arrhythmia occurred after ingestion of 1125 mg (median; range 250 to 8000 mg) (Schuerch et al, 1996).
c) A 68-year-old male suffered central nervous, cardiovascular, and gastrointestinal adverse effects over 9 days after a severe thioridazine intoxication. During high toxic thioridazine plasma concentrations (6061 to 6480 nanograms/mL), the patient developed life-threatening ventricular arrhythmias followed by bradycardia. The electrocardiogram showed delays in all parts of the conduction system. A transitory atrial pacemaker was inserted to maintain a hemodynamically favorable rhythm (Schmidt & Lang, 1997).

3.3.1.A.2 EKG finding
a) Use of thioridazine was found to carry a significant risk for QT interval prolongation in patients on psychotropic medications, with an odds ratio of 5.4 linking thioridazine therapy with QT interval abnormalities (p less than 0.001). This conclusion was based on a study using logistic regression and backwards stepwise regression to determine risk factors for QT interval lengthening in patients enrolled in psychiatric treatment programs (n=495). Overall, 64 of 495 patients were taking thioridazine. Of the 64 thioridazine-users, 15 (almost 25%) were found to have abnormally lengthened QT intervals. QT intervals of 456 msec or greater were defined as abnormal, based on a review of electrocardiograms for 101 healthy volunteers. When dose-levels were looked at, only 4 thioridazine-treated patients were considered to be in the high-dose range (eg, 600 mg/day or greater); however, two of these 4 patients had abnormally prolonged QT intervals. It was suggested that thioridazine causes this effect by blocking the delayed rectifier potassium channel in the myocardium, resulting in abnormal repolarization. The authors concluded that thioridazine confers an increased risk of drug-induced arrhythmias (Reilly et al, 2000).
b) Some data indicate that ECG changes induced by thioridazine, particularly those involving T-waves, become more severe with increasing age. Although these changes are in most cases asymptomatic, elderly patients and particularly those with cardiac disease should be monitored (Thornton & Wendkos, 1971).
c) T-wave changes have been reported to represent a reversible benign repolarization disturbance rather than any indication of cardiotoxic effects. Administration of isosorbide dinitrate, ergotamine, potassium salts or isoproterenol have been reported to resolve T-wave abnormalities (Pietro, 1981).
d) EKG and serum thioridazine concentrations were studied in 43 patients with paranoid psychosis. Significant positive correlations were found between serum drug concentrations and type I changes (rounded, leveled, or notched T-waves) while Type II changes (diphasic waves) showed no concentration dependence (Axelsson & Asperstrom, 1982).

3.3.1.A.3 Hypotension
a) Labile hypertension occurred in a 62-year-old patient who was treated with thioridazine 200 mg per day. Within 3 weeks after stopping the thioridazine, episodes of hypertension (systolic 150 to 180, diastolic 100 to 120) lasting 4 to 8 hours were noted. After reinstituting thioridazine dosage at 300 mg per day, blood pressure was lowered to normal with no further hypertensive episodes (Thaker et al, 1985).

3.3.1.A.4 Prolonged QT interval
a) Summary
1) Prolongation of the QT interval, along with ventricular and supraventricular arrhythmias, have been reported following therapeutic use of thioridazine and acute overdose (Reilly et al, 2000; Prod Info Mellaril(R), 2000ae; Buckley et al, 1996). Due to the association between thioridazine therapy and QT interval prolongation, the US Food and Drug Administration requested a labeling change as of July 2000, such that use of thioridazine should be reserved for schizophrenic patients who have failed to respond to other antipsychotic agents (Anon, 2000). Occasionally, prolongation of the QT interval has led to the development of torsade de pointes (Kiriike et al, 1987). Rare cases of hypotension have also occurred (Prod Info Mellaril(R), 2000ae).
b) Incidence: rare
c) Thioridazine lengthens the QTc-interval in a dose-related manner, and drugs with this potential, including thioridazine, have been associated with arrhythmias of the torsade de pointes-type and sudden death. In 9 healthy males, QTc-interval increased by 23 milliseconds following a 50-mg dose of thioridazine (Prod Info Mellaril(R), 2000ae).

3.3.1.A.5 Sudden cardiac death
a) 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 thioridazine

compared to those who were not using antipsychotic drugs (incidence-rate ratio, 3.19; 95% confidence interval (CI), 2.41 to 4.21; p less than 0.001). In participants being treated with typical antidepressants (haloperidol, thioridazine), the incidence-rate ratio for sudden cardiac death increased from 1.31 (95% CI, 0.97 to 1.77) for those using low doses to 2.42 (95% CI, 1.91 to 3.06) for those using high doses (p less than 0.001) (Ray et al, 2009).

3.3.1.A.6 Torsades de pointes

a) Incidence: rare

b) Atypical ventricular tachycardia (torsade de pointes) presumably secondary to thioridazine was reported in a 53-year-old male and was successfully treated with isoproterenol infusion after unsuccessful use of other agents (Kemper et al, 1983).

c) A 56-year-old schizophrenic patient receiving thioridazine, trifluoperazine, and benztropine experienced syncope (Raehl et al, 1985). The patient experienced episodes of ventricular tachycardia with multifocal PVCs and torsade de pointes.

d) A patient had a preexisting prolonged QT interval that led to the development of potentially fatal ventricular arrhythmia (torsade de pointes) during low-dose, short-term therapy with thioridazine. The recurrent ventricular tachyarrhythmia was exacerbated by lidocaine and procainamide therapy but was effectively controlled by cardiac pacing (Kiriike et al, 1987).

e) Complete heart block and torsade de pointes was associated with thioridazine poisoning (3 grams). A 72-year-old female was semi comatose and had persistent third degree atrioventricular block, progressive hypotension and torsade de pointes. These symptoms resolved within 48 hours and no adverse sequelae persisted (Hulisz et al, 1994).

3.3.2 Dermatologic Effects

3.3.2.A Thioridazine Hydrochloride

Erythema multiforme

Pseudolymphoma

3.3.2.A.1 Erythema multiforme

a) Thioridazine 400 and 800 mg orally daily for 17 days was associated with the occurrence of erythema multiforme of the oral cavity in a 22-year-old patient with psychosis (Rees, 1985). Improvement of lesions was observed within 48 hours after the discontinuation of thioridazine and symptomatic treatment.

3.3.2.A.2 Pseudolymphoma

a) A case of pseudolymphoma, manifested by itchy, slightly infiltrated erythemato-popular lesions in the face exacerbating after sun exposure, was reported in a patient taking thioridazine for 5 1/2 years (Kardaun et al, 1988). All lesions disappeared four weeks after the drug was discontinued.

3.3.3 Endocrine/Metabolic Effects

3.3.3.A Thioridazine Hydrochloride

Body temperature above normal

Hirsutism

Hyperprolactinemia

Syndrome of inappropriate antidiuretic hormone secretion

Weight gain

3.3.3.A.1 Body temperature above normal

a) Apparent hyperpyrexia was induced by thioridazine in 43-year-old schizophrenic. The patient was taking 100 mg three times/day and was exposed to a non-air-conditioned environment during prolonged hot, humid weather (Jacknowitz, 1979).

b) Treatment with thioridazine resulted in hyperpyrexia and ventricular tachycardia in a young woman who was later shown to have thyrotoxicosis. Authors concluded that hyperthyroidism may enhance

thioridazine toxicity (Murphy & Fitzgerald, 1984).
c) In a study of hypothermia in the elderly, the effects of chlormethiazole, thioridazine, and lormetazepam were compared. Three out of 14 patients experienced postural hypotension (chlormethiazole group) while 11 of 14 developed the same reaction following thioridazine. Chlormethiazole was equal to placebo in hypothermia, while thioridazine and lormetazepam caused a fall in temperature. For behavior control in the elderly, and for use as a hypnotic, chlormethiazole seems to be safer than thioridazine or lormetazepam (McCarthy et al, 1986).

3.3.3.A.2 Hirsutism
a) A case of hirsutism associated with long-term thioridazine use (100 mg three times/day for 10 years) was reported (Phillips et al, 1979).

3.3.3.A.3 Hyperprolactinemia
a) Increased tumor size of a prolactin-secreting pituitary chromophobe adenoma occurred in a 42-year-old schizophrenic male who was receiving thioridazine. Thioridazine was discontinued and the patient started on bromocriptine 7.5 mg/day to decrease tumor size and diazepam to control anxiety. Peripheral vision improved and prolactin levels decreased over the next 6 months (Weingarten & Thompson, 1985).

3.3.3.A.4 Syndrome of inappropriate antidiuretic hormone secretion
a) Summary
1) The syndrome of inappropriate antidiuretic hormone secretion (SIADH) has been infrequently reported with phenothiazines.
b) SIADH was reported in a 42-year-old male receiving thioridazine 400 milligrams daily. The patient presented with symptoms of hyponatremia (serum sodium of 113 mEq/L), metabolic alkalosis, and coma. The sodium level returned to normal following discontinuation of thioridazine and supportive therapy, which included a normal saline infusion. The patient had similar hyponatremic episodes with other phenothiazine derivatives (Ananth & Lin, 1987).
c) A 58-year-old woman with chronic depression became acutely agitated and received 500 milligrams of thioridazine within an hour. It was noted that her water consumption increased during a 9-hour period. The patient was found unresponsive with intermittent seizure activity. Serum sodium was 114 mEq/L, while plasma and urine osmolality were 235 and 512 mOsm/kg, respectively. Fluid restriction improved the signs and symptoms of SIADH (Vincent & Emery, 1978).
d) One case of syndrome of inappropriate antidiuretic hormone secretion (SIADH) was reported in a 60-year-old schizophrenic patient who received thioridazine 150 milligrams/day for several months. The patient was comatose, possessed a serum sodium of 112 mEq/L, urine sodium of 17 mEq/L, and serum and urine osmolality of 239 and 257 mOsm/kg, respectively. A hemogram, ECG, brain scan, and roentgenograms of the skull, chest, and spine were normal. Thyroid, adrenal, liver, and kidney function tests were also within normal limits. An EEG revealed a diffuse slow-wave abnormality. The patient was treated with fluid restriction, regained consciousness, and was subsequently discharged (Matuk & Kalyanaraman, 1977).

3.3.3.A.5 Weight gain
a) Thioridazine administration was associated with weight gain in acute paranoid psychotic patients. Participants were divided into 3 subgroups: male patients (25 to 68 years old); female patients younger than 50 years old; and female patients older than 50 years old. Doses ranged from 80 to 1000 milligrams/day. Out of 8 male patients, 5 experienced a 1% to 10% increase in weight, while 3 demonstrated a 1 to 5% reduction in weight. All 9 female patients, younger than 50 years old, displayed a 1% to 20% increase in body weight. Eight of 16 female patients older than 50 years old experienced a 1% to 15% increase in weight, 4 individuals maintained their weight, and 3 subjects demonstrated a 1% to 5% reduction in weight. No specific doses were mentioned to determine if a dose response relationship existed (Ohman & Axelsson, 1980).

3.3.4 Gastrointestinal Effects

3.3.4.A Thioridazine Hydrochloride

Constipation

Dysphagia

Parotitis

Vomiting

Xerostomia

3.3.4.A.1 Constipation

a) Constipation and DIARRHEA have been reported with thioridazine therapy (Prod Info Mellaril(R), 2000ae).

3.3.4.A.2 Dysphagia

See Drug Consult reference: ANTIPSYCHOTIC-INDUCED DYSPHAGIA

3.3.4.A.3 Parotitis

a) A 21-year-old female treated with doses of up to 2 g/day of thioridazine with trifluoperazine developed an enlargement of the parotid glands. Discontinuation of thioridazine resulted in the glands returning to normal despite continued trifluoperazine administration. Readministration of thioridazine resulted in gland enlargement. The author postulated that passive congestion as a result of the atropine-like effects of the phenothiazine caused SALIVARY GLAND ENLARGEMENT (Worthington, 1965).

3.3.4.A.4 Vomiting

a) Vomiting and symptoms of irritability have been associated with abrupt withdrawal of thioridazine therapy. A 9-year-old male with minimal brain dysfunction treated with 125 mg/day of thioridazine for 18 months developed symptoms of IRRITABILITY, STOMACH PAINS, NAUSEA and vomiting 1 to 3 weeks following abrupt withdrawal of the drug. In addition, dyskinetic movements including choreoathetotic movements of the hands and fingers associated with facial grimacing also developed on the fourteenth day post-withdrawal but decreased in frequency lasting up to 90 days (Yepes & Winsburg, 1977).

3.3.4.A.5 Xerostomia

a) Dryness of the mouth has been reported with thioridazine therapy (Prod Info Mellaril(R), 2000ae).

3.3.5 Hematologic Effects

3.3.5.A Thioridazine Hydrochloride

3.3.5.A.1 Agranulocytosis

a) Summary

1) Leukopenia and agranulocytosis are the most common hematopoietic adverse drug reactions reported with thioridazine, and the phenothiazine derivatives are frequently implicated in this reaction. Estimates of the incidence of phenothiazine-induced agranulocytosis vary from 1 to 300 per 100,000 patients.

b) Incidence: rare

c) A female was treated with thioridazine and developed agranulocytosis and THROMBOCYTOPENIA and subsequently died due to cerebral hemorrhage (Ekblom & Walinder, 1965).

3.3.6 Hepatic Effects

3.3.6.A Thioridazine Hydrochloride

3.3.6.A.1 Hepatotoxicity

a) Summary

1) Nearly all the phenothiazines have been associated with the picture of cholestatic jaundice or mixed cholestatic-hepatocellular jaundice. Onset of clinical jaundice usually occurs during the second to fourth week of therapy, but the reaction is not necessarily related to either dose or duration of therapy.

b) Possible thioridazine-induced hepatic dysfunction was reported in a 38-year-old female who received thioridazine 300 milligrams/day. Six days following the initiation of thioridazine the patient became delusional, edematous, and serum AST (aspartate aminotransferase) was 104 units/L (normal 0 to 41 units/L), while ALT (alanine aminotransferase) was 48 units/L (normal 0 to 45 units/L), and LDH (lactate dehydrogenase) was 376 units/L (normal 100 to 225 units/L). Thioridazine was discontinued and the serum levels of AST and ALT normalized within 7 days, however the LDH remained elevated (305 units/L). It is difficult to assess the relationship of thioridazine to the development of transient hepatic dysfunction, as amitriptyline was administered concurrently (Pies, 1982).

c) Hepatic dysfunction associated with thioridazine which presented with normal bilirubin and normal liver enzyme levels was reported in a 34-year-old male schizophrenic (Urberg, 1990).

3.3.9 Neurologic Effects

3.3.9.A Thioridazine Hydrochloride

Central nervous system finding

Confusion

Extrapyramidal sign

Neuroleptic malignant syndrome

Parkinsonism

Seizure

Tardive dyskinesia

3.3.9.A.1 Central nervous system finding

a) Summary

1) Drowsiness is common, especially with large doses, but tends to diminish with continued therapy (Prod Info Mellaril(R), 2000ae). Extrapyramidal symptoms, tardive dyskinesia, and confusion occur less frequently; however, these side effects are more serious and may require a reduction in dosage (Theofilopolous et al, 1984; Jeste et al, 1982; Meyer et al, 1983).

b) In a retrospective analysis of 141 adult thioridazine mono-intoxications, the most frequent symptoms of toxicity, were DROWSINESS and sinus tachycardia (Schuerch et al, 1996). Drowsiness occurred after ingestion of 1225 mg (median; range 100 to 5000 mg) and sinus tachycardia occurred after ingestion of 1125 mg (median; range 250 to 8000 mg). The most frequent symptom of intoxication in 61 pediatric cases was drowsiness, which occurred after a median thioridazine ingestion of 4 mg/kg (range 2.2 to 27 mg/kg).

c) A 10-year-old boy treated concurrently with thioridazine and methylphenidate developed persistent TICS of the head and shoulders. Clonidine did not reduce the tics, suggesting the site of dysfunction is not within the noradrenergic system (Casat & Wilson, 1986).

d) Two hyperactive boys, who had developed motor and phonic tics during stimulant treatment, reacted similarly to low doses of haloperidol and thioridazine. Neuroleptic-induced tics may be a consequence of presynaptic dopamine blockade (Gualtieri & Patterson, 1986).

3.3.9.A.2 Confusion

a) A case of a 35-year-old female treated with thioridazine 25 mg orally 3 times/day developed a toxic confusion state. Discontinuation of thioridazine and institution of chlordiazepoxide resulted in clearing of the symptoms (De Hart, 1969).

b) A 67-year-old male treated with thioridazine for chronic brain syndrome developed, at higher dosages (25 to 50 mg twice a day), a toxic confusional state characterized as hyperactivity, startle reaction, coma, and Cheyne-Stokes respiration. Lowering of the dosage of the drug to 25 mg/day resulted in the patient becoming less comatose and less stuporous (Hader & Schulman, 1965).

c) The influence of thioridazine (1 and 1.5 mg/kg) on human cognitive, psychomotor, and reaction performance as well as subjective feelings was studied. Equivalent doses ranged from 65 to 80 mg and 97 to 120 mg. Performance was reduced in all areas and the most pronounced effects occurred in the subjective state of well-being. Reaction performance was impaired only at the higher dose. Effects on cognitive performance varied and showed least correlation with dose (Meyer et al, 1983).

d) Confusion, memory impairment, and cognitive deficits were reported in a 17-year-old female schizophrenic patient who was treated with thioridazine 200 mg per day and lithium carbonate 1200 mg/day. Lithium levels were nontoxic (0.8 to 0.9 mEq/L) (Bailine & Doft, 1986).

3.3.9.A.3 Extrapyramidal sign

a) Thioridazine has been shown to cause significant impairment of psychomotor performance as measured by pencil-and-paper tests, critical flicker fusion frequency, wire-maze tracing and tapping. Doses of 50 mg were evaluated in healthy volunteers (Theofilopolous et al, 1984).

3.3.9.A.4 Neuroleptic malignant syndrome

a) Incidence: rare

b) A case of neuroleptic malignant syndrome (NMS) was reported in a 70-year-old psychiatric patient who had taken 100 to 300 mg of thioridazine per day for 18 months (Twemlow & Bair, 1983).

c) A neuroleptic malignant syndrome was described in a 22-year-old woman with psychosis following an increase of her dose of thioridazine to 75 mg daily (Zammit & Sullivan, 1987). The patient responded

initially to withdrawal of thioridazine, however haloperidol administration for 1 day was followed by return of symptoms. Withdrawal of haloperidol resulted in stabilization; however, the patient remained psychotic and was eventually treated successfully with chlorpromazine without adverse sequelae. These data suggest that thioridazine may also cause the neuroleptic malignant syndrome.

3.3.9.A.5 Parkinsonism

a) Summary

1) Contrary to common belief, the results of a retrospective cohort study suggest that atypical antipsychotics may not be safer than typical antipsychotics when dose and potency are considered (Rochon et al, 2005).

b) LITERATURE REPORTS

1) The results of a cohort study indicate that high-dose atypical antipsychotic therapy carries a similar risk for the development of parkinsonism as does typical antipsychotic therapy. In a population-based, retrospective cohort study, adults (aged 66 years and older) with evidence of dementia were followed for up to 1 year for the development of parkinsonism symptoms associated with typical or atypical antipsychotic use. As compared with older adults receiving atypical antipsychotic therapy (ie, olanzapine, risperidone, quetiapine), incident parkinsonism was 30% more likely to occur in those taking typical antipsychotics (ie, chlorpromazine, haloperidol, perphenazine) (adjusted HR, 1.3; 95% CI, 1.04 to 1.58), and 60% less likely to occur in patient who did not receive either therapy (HR, 0.4; 95% CI, 0.29 to 0.43). Older adults using higher potency typical antipsychotics had almost a 50% greater risk of experiencing parkinsonism as compared with patients prescribed atypical antipsychotics (all were considered lower potency) (HR, 1.44; 95% CI, 1.13 to 1.84); however, in patients receiving lower potency typical antipsychotics, the risk of developing parkinsonism was no different from that in adults taking atypical antipsychotics (HR, 0.75; 95% CI. 0.48 to 1.15). In addition, a positive dose-related relationship was observed between the occurrence of incident parkinsonism and the use of atypical antipsychotics. The risk for developing parkinsonism was more than twice as great in patients using a high-dose atypical antipsychotic agent as compared with those prescribed a low-dose atypical antipsychotic agent (HR, 2.07; 95% CI, 1.42 to 3.02). Furthermore, patients taking a typical antipsychotic were found to have a similar risk for the development of parkinsonism as patients receiving high-dose atypical antipsychotic therapy (p=ns). The authors conclude that atypical antipsychotics may not be safer than typical antipsychotics when dose and potency are considered (Rochon et al, 2005).

3.3.9.A.6 Seizure

See Drug Consult reference: ANTIPSYCHOTICS - EFFECT ON SEIZURE THRESHOLD

3.3.9.A.7 Tardive dyskinesia

a) The risk of developing tardive dyskinesia and the likelihood it will become irreversible are thought to be associated with the duration of therapy and the cumulative dose; the elderly, especially elderly women, appear to be more prone to this syndrome (Prod Info Mellaril(R), 2000ae).

b) A 17-year-old female treated with 100 to 800 mg/day of thioridazine over a 2-year period developed tardive dyskinesia. Discontinuation of thioridazine and initiation of Deanol(R) therapy in doses of up to 1200 mg/day resulted in gradual improvement of the condition. After 3 months of deanol therapy the drug was discontinued, and the symptoms did not return (Kumar, 1976).

c) There was no correlation between serum concentrations of thioridazine and its major metabolites, THD-2-sulfoxide, THD-2-sulfone, and THD-5-oxide and presence of symptoms of tardive dyskinesia (TD) in elderly chronic schizophrenic patients (Widerlov et al, 1982). However, another study reported higher serum concentration-to-dose ratios in 16 middle aged or elderly female patients. Sulforidazine was significantly elevated in serum of TD patients compared to control (Jeste et al, 1982).

3.3.10 Ophthalmic Effects

3.3.10.A Thioridazine Hydrochloride

Oculogyric crisis

Retinopathy

3.3.10.A.1 Oculogyric crisis

a) Oculogyric crisis has been reported following the use of thioridazine 10 milligrams (Fitzgerald & Jankovic, 1989).

3.3.10.A.2 Retinopathy

a) Thioridazine has produced pigmentary retinopathy with visual impairment. This effect appears to be dose related. Patients develop pigmentary changes within 2 to 8 weeks after initiation of therapy with

acute symptoms including blurred vision, night blindness, and partial color blindness. After thioridazine is discontinued, pigmentary changes may still progress, however, visual function usually improves. Thioridazine appears to bind to the melanin granules in the retinal pigment epithelium which alters retinal enzyme kinetics (Shah et al, 1998). The manufacturer cautions not to exceed a maximum daily dose of 800 mg/day to avoid this adverse effect (Prod Info Mellaril(R), 2000ae).
b) A 28-year-old woman experienced decreased vision in both eyes for 2 weeks after receiving thioridazine 800 milligrams 4 times daily for 8 weeks. Her dilated fundus revealed a diffuse pigmentary retinopathy of the entire post-equatorial fundus. With fluorescein angiography, confluent areas of punctate hyperfluorescence consistent with diffuse retinal pigment epithelial alterations were seen (Shah et al, 1998).
c) Yellow vision occurred in a patient after receiving thioridazine 25 mg three times/day for 4 days (Giannini & Mahar, 1980, 1981).
d) Measurement of the oscillatory potentials of the electroretinogram (ERG) and the O2 wavelet may be necessary to detect early changes of the retina caused by thioridazine therapy. The investigators feel a daily dosage of 160 mg over the long term or 400 mg for shorter periods are critical levels of drug administration (Miyata et al, 1980).
e) Two of 18 mentally retarded institutionalized subjects who had received long-term, high dose treatment with thioridazine or chlorpromazine developed corneal and ventricular opacities (Gualtieri et al, 1982).
f) PIGMENTARY RETINOPATHY was reported in a 57-year-old woman receiving low doses of thioridazine (400 mg daily for approximately 15 years) (Lam & Remick, 1985).
g) Three cases of NUMMULAR RETINOPATHY caused by thioridazine were reported. This retinopathy is a clinical subset of classic thioridazine pigmentation retinopathy. Nummular areas of retinal pigment epithelial atrophy separated by relatively intact pigment epithelium are found in the midretinal periphery with sparing of central vision. This can occur with doses of thioridazine previously considered safe (Kozy et al, 1984). Severe nummular retinopathy and visual dysfunction were reported in a 52-year-old male with paranoid schizophrenia taking thioridazine 200 milligrams or less, over the past 13 years (Tekell et al, 1996).
h) A 51-year-old female patient developed pigmentation retinopathy after taking 400 to 800 mg thioridazine for 2 months. This is below the 800 mg ceiling dose recommended by the manufacturer and suggests that clinicians should carefully investigate visual complaints of patients taking thioridazine in the upper end of the approved dosage range (Hamilton, 1985).
i) Thioridazine toxicity to the eye has been described as "progressive chorioretinopathy", but this designation can be misleading. During the first year after TDZ exposure, retinal pigmentation evolves from a granular to a patchy or nummular appearance. However, visual function and the electroretinogram typically improve during this period. Some cases may show chorioretinal atrophy and functional loss many years later, but there is little evidence for drug-related progression. Late atrophy may represent degeneration of cells that were injured subclinically during the time of initial drug exposure. Although TDZ toxicity produces an evolving pigmentary disturbance, functional changes must be monitored independently of fundus appearance (Marmor, 1990).

3.3.14 Reproductive Effects

3.3.14.A Thioridazine Hydrochloride

Breast cancer

Sexual dysfunction

3.3.14.A.1 Breast cancer

a) Benign INTRADUCTAL PAPILLOMA occurred in a 71-year-old male following approximately 10 years of treatment of thioridazine for a chronic psychiatric disorder (Sara & Gottfried, 1987). Examination revealed a subareolar mass distending the left nipple with no discharge; the right breast was unaffected. Six months later, recurrence of a mass in the same breast was observed without pain or discharge, presumably during continued thioridazine therapy. No data were presented regarding effects of withdrawal of Mellaril(R) or substitution therapy with other non-phenothiazine psychotropic agents, and it is impossible to definitely attribute the papilloma to phenothiazine therapy.

3.3.14.A.2 Sexual dysfunction

a) INHIBITION OF EJACULATION related to thioridazine occurred in a 32-year-old patient 1 week after starting the drug at a dose of 200 mg/day (Yassa, 1983).
b) Four cases of male patients, age range 20 to 40 years, treated with oral thioridazine 100 mg four times/day developed histories of prolonged PAINFUL ERECTIONS (PRIAPISM) which persisted for 1 to 2 days. All patients were treated with corporeal aspiration and corpus cavernosum-corpus spongiosum shunts with good results. The authors postulated the mechanism to be due to peripheral adrenergic

blockade (Dorman & Schmidt, 1976).
c) An 11-year-old boy receiving thioridazine for attention deficit disorder presented to the emergency room with PRIAPISM 30 hours in duration. A penile block with 1% lidocaine was performed. Using a 27 gauge needle inserted into 1 corporeal body, 0.2 to 0.4 milliliters of phenylephrine 1 milligram/milliliter was instilled every 15 minutes until detumescence occurred. No adverse effects were observed (Siegel & Reda, 1997).
See Drug Consult reference: DRUG-INDUCED SEXUAL DYSFUNCTION

3.3.15 Respiratory Effects

3.3.15.A Thioridazine Hydrochloride

3.3.15.A.1 Pulmonary embolism
a) The use of psychotropic medications has been linked to an increased risk of fatal pulmonary embolism. In a case-control study including 62 cases of fatal pulmonary embolism and 243 matched controls, researchers found that compared to non-use, the current use of conventional antipsychotic medications (ie, thioridazine and haloperidol) was associated with an increased risk of fatal pulmonary embolism (adjusted odds ratio, 13.3; 95% confidence interval (CI), 2.3 to 76.3). In addition, low potency antipsychotics, such as thioridazine, were associated with the highest risk, with an odds ratio of 20.8 (95% CI, 1.7 to 259). The current use of antidepressants was also associated with an increased risk of fatal pulmonary embolism (adjusted odds ratio, 4.9; 95% CI, 1.1 to 22.5); however, current or past use of other psychotropic drugs was not associated with an increased risk (adjusted odds ratio, 1.4; 95% CI, 0.3 to 5.8). (Parkin et al, 2003).

3.3.16 Other

3.3.16.A Thioridazine Hydrochloride

Dead - sudden death

Death

Extrapyramidal disease

Withdrawal sign or symptom

3.3.16.A.1 Dead - sudden death
a) Sudden death has been associated with phenothiazines such as thioridazine (Shader & Greenblatt, 1998). Deaths are most likely of cardiac origin and may be attributable to phenothiazine-induced ventricular tachyarrhythmias.
b) A 68-year-old man being treated with thioridazine 25 milligrams 3 times daily for behavioral problems was found dead on the fifth day of treatment (Thomas & Cooper, 1998). His post-mortem examination revealed no coronary thrombosis, myocardial infarction, or other significant pathology except for ischemic heart disease. The certificate of death noted the cause of death as cardiac arrhythmia due to ischemic heart disease.
c) Thioridazine was associated with sudden death syndrome in a 20-year-old female hospitalized for bizarre behavior of 1 week duration and treated initially with chlorpromazine but with subsequent development of a skin rash (Goodson & Litkenhous, 1976). Therapy was changed to thioridazine 500 mg/day, and the patient remained hospitalized for 1 month, then was discharged. Approximately 7 months later, the patient was again admitted for bizarre behavior and received four 100-mg doses of chlorpromazine within 2 days before it was discovered that the patient was allergic to the drug. Treatment was immediately changed to thioridazine in a dose of 200 mg 4 times a day and following 4 days of treatment with thioridazine, the patient was found dead in bed. Autopsy revealed no cause of death.

3.3.16.A.2 Death
a) 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).

b) 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).

c) 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 9142 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 1.9). 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.A.3 Extrapyramidal disease

See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

3.3.16.A.4 Withdrawal sign or symptom

a) Labile hypertension occurred in a 62-year-old patient who was treated with thioridazine 200 mg per day (Thaker et al, 1985). Within 3 weeks after stopping the thioridazine episodes of hypertension (systolic pressure 150 to 180 mmHg, diastolic pressure 100 to 120 mmHg) lasting 4 to 8 hours were noted. After reinstituting thioridazine dosage at 300 mg per day, blood pressure was lowered to normal with no further hypertensive episodes.

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) Australian Drug Evaluation Committee's (ADEC) Category: C (Batagol, 1996)

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

2) Crosses Placenta: Yes

3) Clinical Management

a) In general, schizophrenia in pregnant patients represents a difficult clinical problem, for which few optimal

treatment options are available. If the benefits of treatment outweigh possible teratogenic risks (ie, if reality testing demonstrates a risk to life and limb, if the mother demonstrates gross inability to care for herself, and/or if supportive intervention including hospitalization is inadequate), antipsychotics should be used at the lowest effective dose to achieve adequate improvement in symptoms (Cohen et al, 1989; Spielvogel & Wile, 1986). Cautious use of high potency antipsychotics may yield the best therapeutic benefit with the least anticholinergic and sedative effects, however, clinical evaluations of comparative efficacy and safety are unavailable in this setting.

4) Literature Reports

a) In pooled data of 2,948 women exposed to phenothiazines during pregnancy, no increased risk for fetal malformations was demonstrated (relative risk: 1.03; 95% confidence interval: 0.88-1.22). One study did show a relationship between phenothiazine use and teratogenicity, but the study had many confounders (Magee et al, 2002).

b) Although phenothiazines have been implicated in several cases of congenital malformations (Freeman, 1972; Rafla, 1987), establishing a definite cause-effect relationship is extremely difficult; the incidence of malformations does not appear to be greater than that seen in the general population. Most studies have found phenothiazines to be safe for both mother and fetus if used in low doses during pregnancy (Ayd, 1976; Kris, 1965; Miklovich & van den Berg, 1976).

c) Extrapyramidal symptoms, including hypertonia, tremor, and abnormal hand posturing, which resolved between 10 and 22 months of age, were reported in an infant maternally exposed to thioridazine, trifluoperazine, and chlorpromazine (Hill et al, 1966).

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 when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

2) Clinical Management

a) No reports describing the use of thioridazine during human lactation are available and the effects on the nursing infant from exposure to the drug in milk are unknown. It is not known if thioridazine affects the quantity and composition of breastmilk. Until more data is available, use caution when considering the use of thioridazine in lactating women.

3) Literature Reports

a) No reports describing the use of thioridazine during human lactation or measuring the amount, if any, of the drug excreted into milk have been located.

4) Drug Levels in Breastmilk

a) Thioridazine Hydrochloride

1) Active Metabolites

a) mesoridazine (Cohen et al, 1979a)

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Food Combinations

Drug-Lab Modifications

3.5.1 Drug-Drug Combinations

Acecainide

Acetylcholine

Ajmaline

Amantadine

Amiodarone

Amisulpride

Amitriptyline

Amoxapine

Aprindine

Arsenic Trioxide

Astemizole

Azimilide

Belladonna

Belladonna Alkaloids

Benztropine

Bepridil

Betel Nut

Bretylium

Bromocriptine

Bupropion

Cabergoline

Chloral Hydrate

Chloroquine

Chlorpromazine

Cinacalcet

Cisapride

Clarithromycin

Clozapine

Darifenacin

Darunavir

Dehydroepiandrosterone

Desipramine

Dibenzepin

Diethylpropion

Disopyramide

Dofetilide

Dolasetron

Doxepin

Droperidol

Duloxetine

Encainide

Enflurane

Erythromycin

Evening Primrose

Fentanyl

Flecainide

Fluconazole

Fluoxetine

Fluvoxamine

Foscarnet

Fosphenytoin

Gatifloxacin

Gemifloxacin

Grepafloxacin

Halofantrine

Haloperidol

Halothane

Hydroquinidine

Ibutilide

Iloperidone

Imipramine

Iopamidol

Isoflurane

Isradipine

Kava

Ketanserin

Lapatinib

Levodopa

Levofloxacin

Levomethadyl

Levorphanol

Lidoflazine

Lithium

Lithospermum

Lorcainide

Lubeluzole

Lumefantrine

Mefloquine

Meperidine

Methadone

Methadone

Metoprolol

Metrizamide

Morphine

Morphine Sulfate Liposome

Moxifloxacin

Nortriptyline

Octreotide

Ondansetron

Orphenadrine

Oxycodone

Paliperidone

Paroxetine

Pentamidine

Phenobarbital

Phenylalanine

Phenytoin

Pimozide

Pindolol

Pirmenol

Porfimer

Prajmaline

Probucol

Procainamide

Procarbazine

Procaterol

Prochlorperazine

Procyclidine

Propafenone

Propranolol

Protirelin

Protriptyline

Quetiapine

Quinidine

Ranolazine

Rilonacept

Risperidone

Ritonavir

Roxithromycin

Sematilide

Sertindole

Sotalol

Sparfloxacin

Spiramycin

Sulfamethoxazole

Sultopride

Sunitinib

Tapentadol

Tedisamil

Telithromycin

Terfenadine

Tetrabenazine

Tramadol

Trazodone

Trifluoperazine

Trihexyphenidyl

Trimethoprim

Trimipramine

Vasopressin

Vitex

Ziprasidone

Zolmitriptan

Zotepine

Zotepine

3.5.1.A Acecainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Although no drug interaction studies have been performed, the manufacturer of thioridazine states that the concurrent use of thioridazine with other drugs known to prolong the QTc interval is contraindicated (Prod Info Thioridazine tablets, 2002). Class III antiarrhythmic agents may prolong the QT

interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes (Yamreudeewong et al, 2003; Prod Info Betapace(R), 2001; Prod Info Corvert(R), 2000; Corey et al, 1999; Karam et al, 1998).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval such as Class III antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.B Acetylcholine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, thioridazine should not be coadministered with other drugs which are also known to prolong the QTc interval, including acetylcholine (Prod Info Mellaril(R), 2000f).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.C Ajmaline
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class Ia antiarrhythmics have been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of thioridazine with other drugs known to prolong the QTc interval, including Class Ia antiarrhythmic agents, is not recommended (Prod Info Mellaril(R), 2002a; Prod Info Procanbid(R), 2000; Prod Info Quinaglute(R), 1999; Desai et al, 1981).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and thioridazine is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.D Amantadine
1) Interaction Effect: worsening tremor
2) Summary: Worsening of tremor has occurred in elderly patients with Parkinson's disease when amantadine was co-administered with thioridazine (Prod Info Symmetrel(R), 2002).
3) Severity: minor
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: If amantadine and thioridazine are co-administered, monitor the patient for signs of tremor emergence or recurrence.
7) Probable Mechanism: unknown

3.5.1.E Amiodarone
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although no drug interaction studies have been performed, the manufacturer of thioridazine states that the concurrent use of thioridazine with other drugs known to prolong the QTc interval is contraindicated (Prod Info Thioridazine tablets, 2002). Class III antiarrhythmic agents may prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes (Yamreudeewong et al, 2003; Prod Info Betapace(R), 2001; Prod Info Corvert(R), 2000; Corey et al, 1999; Karam et al, 1998).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval such as Class III antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.F Amisulpride
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001b). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), pimozide (Prod Info Orap(R), 2000), quetiapine (Owens, 2001c), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antipsychotics, and thioridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.G Amitriptyline
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Marshall & Forker, 1982).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of a tricyclic antidepressant and thioridazine is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.H Amoxapine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Marshall & Forker, 1982).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of a tricyclic antidepressant and thioridazine is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.I Aprindine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class I antiarrhythmic agents may prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Although pharmacokinetic studies between thioridazine and other drugs which prolong the QT interval have not been performed, an additive effect cannot be excluded. Therefore, the concurrent administration of thioridazine with a Class I antiarrhythmic agent is contraindicated (Prod Info Rythmol(R), 2002; Prod Info Mellaril(R), 2002; Prod Info Tambocor(R), 1998).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval, such as Class I antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.J Arsenic Trioxide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, neither thioridazine nor arsenic trioxide should be coadministered with other drugs which are also known to prolong the QTc interval (Prod Info Mellaril(R), 2000l; Prod Info Trisenox(R), 2001a).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval, such as arsenic trioxide, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) QT/QTc prolongation should be expected during treatment with arsenic trioxide and torsade de pointes as well as complete heart block has been reported. Over 460 ECG tracings from 40 patients with refractory or relapsed APL treated with arsenic trioxide were evaluated for QTc prolongation. Sixteen of 40 patients (40%) had at least one ECG tracing with a QTc interval greater than 500 msec. Prolongation of the QTc was observed between 1 and 5 weeks after arsenic trioxide infusion, and then returned towards baseline by the end of 8 weeks after arsenic trioxide infusion. In these ECG evaluations, women did not experience more pronounced QT prolongation than men, and there was no correlation with age (Prod Info Trisenox(R), 2001).

3.5.1.K Astemizole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, thioridazine should not be coadministered with other drugs which are also known to prolong the QTc interval, including astemizole (Prod Info Mellaril(R), 2002; Prod Info Hismanal(R), 1998).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval, such as astemizole, is contraindicated.

7) Probable Mechanism: additive cardiac effects

3.5.1.L Azimilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Although no drug interaction studies have been performed, the manufacturer of thioridazine states that the concurrent use of thioridazine with other drugs known to prolong the QTc interval is contraindicated (Prod Info Thioridazine tablets, 2002). Class III antiarrhythmic agents may prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes (Yamreudeewong et al, 2003; Prod Info Betapace(R), 2001; Prod Info Corvert(R), 2000; Corey et al, 1999; Karam et al, 1998).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval such as Class III antiarrhythmic agents is contraindicated.

7) Probable Mechanism: additive effect on QT interval

3.5.1.M Belladonna

1) Interaction Effect: increased manic, agitated reactions, or enhanced anticholinergic effects resulting in cardiorespiratory failure, especially in cases of belladonna overdose

2) Summary: 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). The anticholinergic activity of the active alkaloids present in belladonna may predispose the patient to excessive anticholinergic activity if taken with a phenothiazine (Shader & Greenblatt, 1971; Taylor et al, 1970a; Louria, 1969a). Because belladonna is typically available as a homeopathic preparation, the clinical severity of the interaction with phenothiazines is unknown. Belladonna alkaloids have been used as "spiking" agents in illicit drugs. In the amount of belladonna used for this purpose, the interaction is well known and severe (Taylor et al, 1970a). Phenothiazines should not be used to sedate patients with belladonna toxicity; alternatives include short-acting barbiturates, benzodiazepines, or chloral hydrate (Shader & Greenblatt, 1971; Louria, 1969a).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

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. Benzodiazepines, short-acting barbiturates, or chloral hydrate may be used to sedate patients with anticholinergic toxicity (Shader & Greenblatt, 1971).

7) Probable Mechanism: additive anticholinergic effect

8) Literature Reports

a) Central nervous system depression occurred in patients taking an anticholinergic agent with a phenothiazine. Belladonna alkaloids have been used for "spiking" of illicit drugs. Treatment of toxicity from such use with a phenothiazine enhances the anticholinergic effects and may lead to coma and cardiorespiratory failure (Taylor et al, 1970).

b) Use of chlorpromazine to treat drug overdose with the illicit anticholinergic drug 2,5-dimethoxy-4-

methyl amphetamine (STP) enhances mania and agitation, and may result in respiratory failure of cardiovascular collapse. Diazepam, chlordiazepoxide, or short-acting barbiturates may be treatment of choice for anticholinergic toxicity (Louria, 1969).

3.5.1.N Belladonna Alkaloids

1) Interaction Effect: increased manic, agitated reactions, or enhanced anticholinergic effects resulting in cardiorespiratory failure, especially in cases of belladonna overdose

2) Summary: 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). The anticholinergic activity of the active alkaloids present in belladonna may predispose the patient to excessive anticholinergic activity if taken with a phenothiazine (Shader & Greenblatt, 1971; Taylor et al, 1970a; Louria, 1969a). Because belladonna is typically available as a homeopathic preparation, the clinical severity of the interaction with phenothiazines is unknown. Belladonna alkaloids have been used as "spiking" agents in illicit drugs. In the amount of belladonna used for this purpose, the interaction is well known and severe (Taylor et al, 1970a). Phenothiazines should not be used to sedate patients with belladonna toxicity; alternatives include short-acting barbiturates, benzodiazepines, or chloral hydrate (Shader & Greenblatt, 1971; Louria, 1969a).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

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. Benzodiazepines, short-acting barbiturates, or chloral hydrate may be used to sedate patients with anticholinergic toxicity (Shader & Greenblatt, 1971).

7) Probable Mechanism: additive anticholinergic effect

8) Literature Reports

a) Central nervous system depression occurred in patients taking an anticholinergic agent with a phenothiazine. Belladonna alkaloids have been used for "spiking" of illicit drugs. Treatment of toxicity from such use with a phenothiazine enhances the anticholinergic effects and may lead to coma and cardiorespiratory failure (Taylor et al, 1970).

b) Use of chlorpromazine to treat drug overdose with the illicit anticholinergic drug 2,5-dimethoxy-4-methyl amphetamine (STP) enhances mania and agitation, and may result in respiratory failure of cardiovascular collapse. Diazepam, chlordiazepoxide, or short-acting barbiturates may be treatment of choice for anticholinergic toxicity (Louria, 1969).

3.5.1.O Benztropine

1) Interaction Effect: decreased phenothiazine serum concentrations, decreased phenothiazine effectiveness, enhanced anticholinergic effects (ileus, hyperpyrexia, sedation, dry mouth)

2) Summary: The concurrent use of anticholinergic agents (benztropine, orphenadrine, procyclidine, trihexyphenidyl) to control extrapyramidal side effects may reduce oral absorption of phenothiazines, antagonize the behavioral and antipsychotic effects of the phenothiazine, and enhance anticholinergic side effects (Rivera-Calimlim et al, 1976e; Mann & Boger, 1978g; Singh & Kay, 1979c; Gershon et al, 1965g; Buckle & Guillebaud, 1967c).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Anticholinergics (benztropine, orphenadrine, procyclidine, trihexyphenidyl) should not be used routinely with phenothiazine derivatives as prophylaxis against possible extrapyramidal symptoms; use should be reserved for situations where EPS occur and lowering of the antipsychotic dosage is not possible. Anticholinergic use should be reevaluated at least every three months.

7) Probable Mechanism: delayed gastric emptying, increased gut wall metabolism of phenothiazine, decreased absorption

8) Literature Reports

a) The concomitant administration of trihexyphenidyl and chlorpromazine has been shown to result in a decrease in chlorpromazine plasma levels (Rivera-Calimlim et al, 1973c; Gershon et al, 1965f). A crossover controlled study of the chlorpromazine-trihexyphenidyl interaction in psychiatric patients showed conclusively that trihexyphenidyl lowers plasma levels of chlorpromazine from 13% to 100% (Rivera-Calimlim et al, 1973c). The mechanism by which trihexyphenidyl lowers plasma levels of chlorpromazine was shown in rats to be an inhibition of gastric emptying by trihexyphenidyl, probably as a result of its anticholinergic activity (Rivera-Calimlim, 1976c). Slow gastric emptying will delay the transport of chlorpromazine to intestinal absorption sites and favor enhanced gastrointestinal metabolism.

b) Trihexyphenidyl may also directly reverse some of the therapeutic effects of chlorpromazine. A toxic psychosis has been commonly reported following usual therapeutic doses of anticholinergic drugs, particularly when these agents are used in conjunction with other drugs with anticholinergic properties. Symptoms may include visual hallucinations, confusion, disorientation, speech difficulty, emotional

lability and psychotic thinking (Perry et al, 1985c).
c) The chlorpromazine-trihexyphenidyl interaction may also include additive anticholinergic effects including constipation or paralytic ileus, dry mouth, blurred vision, increased intraocular pressure and urinary retention (Perry et al, 1985c). Hyperpyrexia has been reported, presumably due to blocking of exocrine sweat glands in combination with the hypothalamic dysregulation produced by antipsychotics (Mann & Boger, 1978f).
d) A significant reduction in fluphenazine serum levels occurred following addition of procyclidine in patients who were previously well stabilized. Following discontinuation of procyclidine, fluphenazine serum levels returned to baseline (Bamrah et al, 1986c). However, the addition of orphenadrine to perphenazine therapy resulted in no clinically relevant pharmacokinetic changes in the absorption, distribution, or elimination of perphenazine (Bolvig Hansen et al, 1979c).

3.5.1.P Bepridil
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, bepridil should not be coadministered with other drugs which are also known to prolong the QTc interval, including phenothiazines (Prod Info Compazine(R), 2002; Prod Info Mellaril(R), 2002d; Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002; Prod Info Serentil(R), 2001; Prod Info Vascor(R), 2000).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of bepridil and agents that prolong the QT interval, such as phenothiazines, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.Q Betel Nut
1) Interaction Effect: increased extrapyramidal side effects of phenothiazines
2) Summary: Case reports have described increased extrapyramidal side effects when betel nut was chewed by patients taking fluphenazine and fluphenthixol for schizophrenia (Deahl, 1989a). The extrapyramidal effects were not improved with anticholinergic therapy with procyclidine, and resolved with betel nut discontinuation (Deahl, 1989a). A similar effect may occur if betel nut is chewed with other phenothiazine therapy. The cholinergic activity of betel nut has been attributed to the arecoline content. When given with peripheral anticholinergics, arecoline increased the heart rate due to central muscarinic agonist activity (Nutt et al, 1978a). Case reports suggest the onset of betel nut activity to be within 3 weeks with resolution within 4 to 7 days after discontinuation (Deahl, 1989a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: It is unclear to what extent the cholinergic effect of betel nut may increase the incidence of extrapyramidal side effects of phenothiazines, especially if patients are treated with anticholinergic agents to control these side effects. Deterioration in symptoms of patients with Parkinson's disease or other extrapyramidal movement disorders may be expected. Persons who have been chewing betel nut have a characteristic red stain on the teeth which may help the clinician discover betel nut use.
7) Probable Mechanism: cholinergic effect of betel nut
8) Literature Reports
a) Within 3 weeks of initiating betel nut chewing, a 51-year-old Indian man experienced marked rigidity, bradykinesia, and jaw tremor. This patient had been stabilized on fluphenazine decanoate depot 50 milligrams (mg) every 3 weeks for schizophrenia and procyclidine 5 mg twice daily for a mild Parkinsonian tremor for the previous 2 years. Within one week of discontinuation of betel nut chewing, the patient's condition returned to baseline. This report appears to demonstrate decreased anticholinergic effects of procyclidine when coadministered with betel nut (Deahl, 1989).
b) A 45-year-old Indian man developed akathisia, tremor and stiffness following betel nut ingestion which was not affected by dosage escalations of up to 20 mg daily of procyclidine. This patient had been previously stabilized on fluphenthixol 60 mg depot every two weeks for the previous year for schizoaffective disorder without extrapyramidal side effects. His symptoms resolved over 4 days after discontinuing betel nut. It appears that the anticholinergic effects of procyclidine were diminished when betel nut was chewed concomitantly (Deahl, 1989).
c) High doses (5 mg, 10 mg, and 20 mg) of subcutaneous (SC) arecoline given one hour after SC administration of 0.5 mg of the peripheral anticholinergic agent methscopolamine increased the heart rate and blood pressure of six Huntington disease patients. Significant increases in blood pressure occurred at doses of 5 mg, 10 mg (p less than 0.01) and 20 mg (p less than 0.05). Heart rate increased at doses of 5 mg and 20 mg (p less than 0.01), and 10 mg (p less than 0.05). Subjective effects in some patients included tremor, flushing or pallor at the time of peak drug effect and nausea, weakness, and mental changes at the higher doses. No peripheral cholinergic effects were noted. The results indicated a central muscarinic effect for arecoline (Nutt et al, 1978).
d) A low dose (0.5 mg) of arecoline given intravenously 3 minutes after the peripheral anticholinergic agent glycopyrrolate 0.15 mg to 8 patients with major depressive disorder increased their heart rates.

The peak heart rate increase in a non-REM portion of the sleep cycle during the 10 minute post-infusion period was 6.75 +/- 12.9 beats per minute for placebo and 25 +/- 10.3 beats per minute for arecoline. The peak heart rates all began 1 to 8 minutes after the arecoline infusion, and the mean heart rate was significantly elevated over placebo from 2 to 10 minutes after arecoline infusion (p less than 0.05) (Abramson et al, 1985).
e) Though chewing betel nut alone does not significantly increase catecholamine levels, a popular betel nut preparation does. Six to eight minutes after chewing betel nut, 4 subjects had only a moderate increase in plasma noradrenaline from 266.2 +/- 105.7 picograms/milliliter (pg/mL) to 313.7 +/- 92.9 pg/mL (p equal to 0.0607). Combining betel nut with lime, catechu and Piper betel flower as is commonly done caused significant elevation of norepinephrine in nine subjects from 292.2 +/- 59.5 pg/mL to 375.1 +/- 130.0 pg/mL (p equal to 0.0244) and epinephrine from 62.5 +/- 23.9 pg/mL to 102.2 +/- 45.0 pg/mL (p equal to 0.0226). In this group dopamine was also elevated in 8 of 9 subjects, but the mean was not significant (Chu, 1995).

3.5.1.R Bretylium

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although no drug interaction studies have been performed, the manufacturer of thioridazine states that the concurrent use of thioridazine with other drugs known to prolong the QTc interval is contraindicated (Prod Info Thioridazine tablets, 2002). Class III antiarrhythmic agents may prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes (Yamreudeewong et al, 2003; Prod Info Betapace(R), 2001; Prod Info Corvert(R), 2000; Corey et al, 1999; Karam et al, 1998).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval such as Class III antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.S Bromocriptine

1) Interaction Effect: decreased bromocriptine effectiveness
2) Summary: Concomitant therapy with thioridazine and bromocriptine was reported to result in interference of the prolactin lowering effects of bromocriptine. In addition, a deterioration in visual fields was observed after 3 months of concurrent use, which resolved within 5 days of discontinuing thioridazine (Robbins et al, 1984).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Because bromocriptine and thioridazine have opposite effects on dopamine receptors, the concurrent use of these two drugs is illogical. Alternative therapy to either drug should be considered.
7) Probable Mechanism: antagonism at dopamine receptors

3.5.1.T Bupropion

1) Interaction Effect: increased plasma levels of thioridazine
2) Summary: It is recommended that thioridazine, an antipsychotic metabolized by the cytochrome P450 2D6 isoenzyme, be initiated at the lower end of the dose range when administered concomitantly with bupropion (Prod Info Wellbutrin XL(TM), 2003; Prod Info Zyban(R), 2000).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of bupropion and thioridazine should be approached with caution and should be initiated at the lower end of the dose range of thioridazine. If bupropion is added to the treatment regimen of a patient already receiving thioridazine, consider decreasing the dose of thioridazine.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated thioridazine metabolism

3.5.1.U Cabergoline

1) Interaction Effect: the decreased therapeutic effect of both drugs
2) Summary: Cabergoline is a long-acting dopamine receptor agonist with a high affinity for dopamine-2 receptors. It should not be administered concomitantly with dopamine-2 antagonists, such as phenothiazines, butyrophenones, thioxanthines, and metoclopramide (Prod Info Dostinex(R), 1996).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Cabergoline, a dopamine-2 receptor agonist, should not be used concurrently with a dopamine-2 antagonist, such as thioridazine.
7) Probable Mechanism: antagonistic pharmacologic effects

3.5.1.V Chloral Hydrate

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, thioridazine should not be coadministered with other drugs which are also known to prolong the QTc interval, including chloral hydrate (Prod Info Mellaril(R), 2000s; Young et al, 1986).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of chloral hydrate and thioridazine is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.W Chloroquine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, thioridazine should not be coadministered with other drugs which are also known to prolong the QTc interval, including chloroquine (Prod Info Mellaril(R), 2000ad; Prod Info Aralen(R), 1999).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of chloroquine and agents that prolong the QT interval, such as thioridazine, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.X Chlorpromazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT interval prolongation, torsades de pointes, cardiac arrest)
2) Summary: Because thioridazine may prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of thioridazine and other phenothiazines is contraindicated (Prod Info Mellaril(R), 2000l). Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002a; Prod Info Stelazine(R), 2002a; Prod Info Thorazine(R), 2002a). Other phenothiazines may have similar effects, though no reports are available.
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as thioridazine and other phenothiazines, is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.Y Cinacalcet

1) Interaction Effect: increased thioridazine plasma concentrations
2) Summary: Cinacalcet is partially metabolized by and is a strong inhibitor of the CYP2D6 isozyme. Cinacalcet may increase blood concentrations of drugs that are predominantly metabolized by CYP2D6 and have a narrow therapeutic index, such as thioridazine. Therefore, if cinacalcet and thioridazine are coadministered, dose adjustments of thioridazine may be required (Prod Info SENSIPAR(TM) oral tablets, 2007).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: If cinacalcet, a strong CYP2D6 inhibitor, is coadministered with a drug that is primarily metabolized by CYP2D6 and has a narrow therapeutic index, such as thioridazine, dose adjustments of the CYP2D6-metabolized drug may be necessary (Prod Info SENSIPAR(TM) oral tablets, 2007).
7) Probable Mechanism: inhibition of CYP2D6-mediated thioridazine metabolism

3.5.1.Z Cisapride

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cisapride therapy has resulted in serious cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, torsades de pointes, and QT prolongation. Because phenothiazines also may prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of cisapride with a drug from this class is contraindicated (Prod Info Propulsid(R), 2000).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The concurrent use of cisapride and phenothiazines is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AA Clarithromycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Clarithromycin can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes (Prod Info Biaxin(R), 2000). Because thioridazine may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of clarithromycin and thioridazine is contraindicated (Prod Info Mellaril(R), 2000ac).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as clarithromycin and thioridazine, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AB Clozapine

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), 2002).
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.AC Darifenacin

1) Interaction Effect: increased thioridazine exposure with an increased risk of QT prolongation and other side effects
2) Summary: Coadministered darifenacin may increase thioridazine exposure, causing a potential risk of QT prolongation or other serious adverse effects. Thioridazine, like imipramine, is metabolized primarily by the CYP2D6 isoenzyme and it has a narrow therapeutic window. The mean maximum concentration (Cmax) and area under the concentration-time curve (AUC) of imipramine increased 57% and 70%, respectively, when used together with darifenacin 30 mg once daily at steady-state. Note: The recommended dose of darifenacin is 7.5 or 15 mg once daily. The AUC of desipramine, the active metabolite of imipramine, increased 3.6-fold. Caution should be used with the coadministration of darifenacin and CYP2D6 substrates with a narrow therapeutic window, such as thioridazine (Prod Info Enablex, 2004).
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Use caution with the coadministration of darifenacin and other CYP2D6 substrates with a narrow therapeutic window, such as thioridazine. Monitor for thioridazine toxicity including QT prolongation.
7) Probable Mechanism: competitive inhibition of CYP2D6-mediated thioridazine metabolism

3.5.1.AD Darunavir

1) Interaction Effect: increased thioridazine plasma concentrations
2) Summary: Coadministration of ritonavir-boosted darunavir, a CYP2D6 inhibitor, and thioridazine, a CYP2D6 substrate, may result in increased plasma concentrations of thioridazine, possibly due to inhibition of CYP2D6-mediated thioridazine metabolism by darunavir/ritonavir. As this may result in thioridazine adverse effects, a lower dose of thioridazine should be considered with concomitant use is necessary (Prod Info PREZISTA(R) film coated oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of ritonavir-boosted darunavir and thioridazine may increase thioridazine plasma concentrations. Consider using a lower thioridazine dose when these agents are coadministered (Prod Info PREZISTA(R) film coated oral tablets, 2008).
7) Probable Mechanism: inhibition of CYP2D6-mediated thioridazine metabolism by darunavir/ritonavir

3.5.1.AE Dehydroepiandrosterone

1) Interaction Effect: reduced effectiveness of phenothiazines
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 phenothiazines for psychosis should avoid DHEA supplementation.

3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and phenothiazines. 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 phenothiazines
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 Cushinoid 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.AF Desipramine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Marshall & Forker, 1982).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of a tricyclic antidepressant and thioridazine is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.AG Dibenzepin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Marshall & Forker, 1982).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of a tricyclic antidepressant and thioridazine is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.AH Diethylpropion
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, thioridazine should not be coadministered with other drugs which are also known to prolong the QTc interval, including diethylpropion (Prod Info Mellaril(R), 2000z).
3) Severity: contraindicated

4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.AI Disopyramide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class Ia antiarrhythmics have been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of thioridazine with other drugs known to prolong the QTc interval, including Class Ia antiarrhythmic agents, is not recommended (Prod Info Mellaril(R), 2002a; Prod Info Procanbid(R), 2000; Prod Info Quinaglute(R), 1999; Desai et al, 1981).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and thioridazine is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.AJ Dofetilide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although no drug interaction studies have been performed, the manufacturer of thioridazine states that the concurrent use of thioridazine with other drugs known to prolong the QTc interval is contraindicated (Prod Info Thioridazine tablets, 2002). Class III antiarrhythmic agents may prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes (Yamreudeewong et al, 2003; Prod Info Betapace(R), 2001; Prod Info Corvert(R), 2000; Corey et al, 1999; Karam et al, 1998).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval such as Class III antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.AK Dolasetron
1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Dolasetron can cause QTc interval prolongation. These changes are related in magnitude and frequency to the blood levels of the active metabolite, hydrodolasetron. Although the changes in QTc interval are self-limiting with declining blood levels of hydrodolasetron, some patients may experience prolonged QTc intervals for 24 hours or longer. Because of dolasetron's ability to cause QTc prolongation, its use with thioridazine is contraindicated (Prod Info Anzemet(R), 1997; Prod Info Mellaril(R), 2002g).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of dolasetron and thioridazine is contraindicated, since each of these agents can cause prolongation of the QTc interval.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AL Doxepin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Marshall & Forker, 1982).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of a tricyclic antidepressant and thioridazine is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.AM Droperidol
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturers of some phenothiazines state that concomitant use

with other drugs which prolong the QT interval is contraindicated (Prod Info Thioridazine tablets, 2002). QT prolongation has been observed in patients treated with droperidol (Prod Info Inapsine(R), 2001). Other phenothiazines may have similar effects, though no reports are available.
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of droperidol and thioridazine is contraindicated as it may precipitate QT prolongation.
7) Probable Mechanism: additive cardiac effects

3.5.1.AN Duloxetine
1) Interaction Effect: increased thioridazine serum concentrations and risk of cardiac arrhythmia
2) Summary: Given thioridazine's tendency to prolong the QTc-interval in a dose-dependent manner, the attendant risk for developing serious or fatal ventricular arrhythmias precludes the safe concomitant use of duloxetine and thioridazine. Duloxetine is a moderately potent inhibitor of CYP2D6 (for which thioridazine is a substrate) and therefore, the coadministration of duloxetine with thioridazine is likely to produce elevated thioridazine plasma concentrations with attendant cardiotoxicity (Prod Info Mellaril(R), 2000c; Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of duloxetine and thioridazine is contraindicated (Prod Info Mellaril(R), 2000c).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated thioridazine metabolism

3.5.1.AO Encainide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class I antiarrhythmic agents may prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Although pharmacokinetic studies between thioridazine and other drugs which prolong the QT interval have not been performed, an additive effect cannot be excluded. Therefore, the concurrent administration of thioridazine with a Class I antiarrhythmic agent is contraindicated (Prod Info Rythmol(R), 2002; Prod Info Mellaril(R), 2002; Prod Info Tambocor(R), 1998).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval, such as Class I antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.AP Enflurane
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, thioridazine should not be coadministered with other drugs which may also prolong the QTc interval, including enflurane (Owens, 2001; Prod Info Mellaril(R), 2002b).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that may prolong the QT interval, such as enflurane, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AQ Erythromycin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Erythromycin significantly increased the mean QTc interval versus baseline in a retrospective study of 49 patients (Oberg & Bauman, 1995). Erythromycin has demonstrated QTc prolongation in combination with other drugs that prolong the QT interval (Prod Info PCE(R), 1997). Thioridazine has been shown to prolong the QT interval; the manufacturer states that the concurrent administration of thioridazine with other drugs known to prolong the QTc interval is contraindicated (Prod Info Mellaril(R), 2002e).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine with other agents that can prolong the QT interval, such as erythromycin, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AR Evening Primrose

1) Interaction Effect: increased risk of seizures
2) Summary: Evening primrose oil may reduce the seizure threshold when taken with phenothiazines. Seizures have been reported when evening primrose oil was added to phenothiazine therapy in schizophrenic patients (Holman & Bell, 1983a; Vaddadi, 1981a). Avoid concomitant use of evening primrose oil with anticonvulsants.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Avoid concomitant use of evening primrose oil with phenothiazines.
7) Probable Mechanism: evening primrose oil may reduce the seizure threshold
8) Literature Reports
a) A 43-year-old male on fluphenazine decanoate 50 mg every two weeks experienced a grand mal seizure after 12 weeks of using EPO 4 grams daily. After withdrawing EPO, no further seizure episodes occurred in the next 7 months (Holman & Bell, 1983).
b) Three schizophrenic patients unresponsive to phenothiazines were given evening primrose oil (EPO), which exacerbated symptoms and led to seizures. EPO was discontinued and carbamazepine initiated when electroencephalogram (EEG) showed temporal lobe epileptic disorders. Phenothiazine therapy was discontinued or reduced in all patients (Vaddadi, 1981).

3.5.1.AS Fentanyl

1) Interaction Effect: an increase in central nervous system and respiratory depression
2) Summary: The concomitant use of fentanyl and other central nervous system depressants including phenothiazines (e.g. chlorpromazine, promethazine, thioridazine) may result in additive CNS and respiratory depressant effects, including hypotension, profound sedation and/or coma . When administering fentanyl and a phenothiazine together, one or both agents dosage should be significantly reduced (Prod Info Duragesic(R), 2005). Monitor patient carefully for signs of respiratory depression, CNS depression, and hypotension.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Monitor patients for signs of respiratory depression, CNS depression, and hypotension. A dosage reduction of one or both drugs should be made.
7) Probable Mechanism: additive effects

3.5.1.AT Flecainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class I antiarrhythmic agents may prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Although pharmacokinetic studies between thioridazine and other drugs which prolong the QT interval have not been performed, an additive effect cannot be excluded. Therefore, the concurrent administration of thioridazine with a Class I antiarrhythmic agent is contraindicated (Prod Info Rythmol(R), 2002; Prod Info Mellaril(R), 2002; Prod Info Tambocor(R), 1998).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval, such as Class I antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.AU Fluconazole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2000i). Other phenothiazines may have similar effects, though no reports are available. Case reports have described QT prolongation and torsades de pointes associated with fluconazole (Khazan & Mathis, 2002; Wassmann et al, 1999).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the possibility of additive effects on the QT interval, the concomitant administration of fluconazole and thioridazine is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AV Fluoxetine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Fluoxetine inhibits the metabolism of thioridazine through inhibition of CYP2D6. The resulting elevated levels of thioridazine may enhance QT prolongation (Prod Info Mellaril(R), 2000w). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001). Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2000w).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and thioridazine is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated thioridazine metabolism; additive effects on QT prolongation

3.5.1.AW Fluvoxamine
1) Interaction Effect: an increased risk of thioridazine toxicity, cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Fluvoxamine inhibits the metabolism of thioridazine, possibly through the inhibition of cytochrome P450 2D6 (CYP2D6) resulting in toxicity. The resulting elevated levels of thioridazine would be expected to enhance the prolongation of the QT interval associated with thioridazine and may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as torsade de pointes-type arrhythmias (Prod Info Mellaril(R), 2000r).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Due to the potential for significant, possibly life-threatening, proarrhythmic effects, concurrent administration of thioridazine and fluvoxamine is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated thioridazine metabolism
8) Literature Reports
a) The serum concentrations of thioridazine and its two metabolites, mesoridazine and sulforidazine, were evaluated in ten male schizophrenic patients aged 36 to 78 years at three separate time points. All patients were receiving thioridazine monotherapy for the management of schizophrenia at a mean dose of 88 mg daily. Fluvoxamine 50 mg daily was coadministered for one week. Plasma levels of thioridazine and its metabolites were measured during monotherapy with thioridazine, after one week of concurrent therapy with thioridazine and fluvoxamine, and two weeks after fluvoxamine was discontinued. Following one week of combination therapy with fluvoxamine and thioridazine, thioridazine levels increased 225%, mesoridazine levels increased 219%, and sulforidazine concentrations rose 258%. Even two weeks after the discontinuation of fluvoxamine, three patients continued to show elevated thioridazine and metabolite levels. No clinical symptoms were attributed to the interaction between these two agents (Carrillo et al, 1999).
b) The metabolism of thioridazine is inhibited by drugs such as fluvoxamine due to reduced cytochrome P450 2D6 and 1A2 isozyme activity. The elevated levels of thioridazine would be expected to enhance the prolongation of the QT interval associated with thioridazine. This, in turn, may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as torsade de pointes-type arrhythmias (Prod Info Mellaril(R), 2000q).

3.5.1.AX Foscarnet
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Foscarnet can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes (Prod Info Foscavir(R), 1998). Because thioridazine may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of foscarnet and thioridazine is contraindicated (Prod Info Mellaril(R), 2000g).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of foscarnet and thioridazine is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.AY Fosphenytoin
1) Interaction Effect: increased or decreased phenytoin levels and possibly reduced phenothiazine levels
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). Concurrent phenothiazine and phenytoin therapy has been reported to increase, decrease, or cause no change in the serum levels of phenytoin (Sands et al, 1987; Vincent, 1980; Siris et al, 1974; Houghton & Richens, 1975). In one study, concomitant phenytoin reduced the serum levels of mesoridazine, but not thioridazine (Linnoila et al, 1980a).
3) Severity: minor
4) Onset: delayed

5) Substantiation: probable
6) Clinical Management: Consider monitoring phenytoin levels when a phenothiazine is added or discontinued from therapy; dosage adjustments may be needed in some cases. The patient should also be observed for any signs of phenytoin toxicity (ataxia, nystagmus, tremor, hyperreflexia), particularly in the case of adjustments to the phenothiazine dosage. Observe patients for phenothiazine efficacy.
7) Probable Mechanism: induction or inhibition of phenytoin metabolism; induction of phenothiazine metabolism
8) Literature Reports
a) Compelling data were reported suggesting that phenothiazines as a group decrease serum phenytoin concentrations, but the effect of individual phenothiazines was not evaluated. A total of 92 cases (institutionalized patients) who were receiving constant phenytoin doses and who were either initiating, discontinuing, increasing, or decreasing a phenothiazine were retrospectively reviewed. Approximately half of the patients received thioridazine, while the other half received either chlorpromazine or mesoridazine. Phenytoin concentrations decreased by 44% (p=0.001) when a phenothiazine was added; similarly, increases in phenothiazine dose caused a 33% decrease in phenytoin concentrations (p=0.001). In patients who discontinued a phenothiazine, phenytoin concentrations increased by 71% (p=0.001); similarly, decreases in phenothiazine dose caused a 55% increase in phenytoin concentrations (p=0.001). Although the combined results cannot be applied clinically to a particular phenothiazine, this study does suggest a remarkably strong trend among phenothiazines which is contrary to some individual case reports. Further study is needed (Haidukewych & Rodin, 1985).
b) The effects of concomitant treatment with phenytoin and/or phenobarbital on the steady-state serum concentrations of haloperidol, thioridazine, and mesoridazine were investigated in 2 groups of patients. The investigators found that concomitant anticonvulsant medication significantly reduced the plasma level of haloperidol and mesoridazine, but not thioridazine (Linnoila et al, 1980).

3.5.1.AZ Gatifloxacin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Gatifloxacin may prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes (Prod Info Tequin(TM), 1999). Although pharmacokinetic studies between gatifloxacin and other drugs which prolong the QT interval have not been performed, an additive effect cannot be excluded. According to the manufacturer, thioridazine should not be administered with other drugs which are also known to prolong the QTc interval (Prod Info Mellaril(R), 2000h).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of gatifloxacin and thioridazine is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BA Gemifloxacin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although pharmacokinetic studies between thioridazine and gemifloxacin, which may prolong the QT interval, have not been performed, gemifloxacin should not be used in patients receiving thioridazine (Prod Info Factive(R), 2003).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of thioridazine with other drugs that prolong the QT interval, such as gemifloxacin, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BB Grepafloxacin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Healthy volunteers who received grepafloxacin during a Phase I study experienced prolongation of the QTc interval. On an outpatient basis, grepafloxacin is contraindicated with other drugs that are known to also prolong the QTc interval or cause torsades de pointes, including phenothiazines. When appropriate cardiac monitoring can be assured, such as in the hospitalized patient, these two agents should be coadministered with caution (Prod Info Raxar(R), 1999).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The concurrent use of grepafloxacin and phenothiazines is contraindicated unless appropriate cardiac monitoring can be assured, such as in the hospitalized patient.
7) Probable Mechanism: additive cardiac effects

3.5.1.BC Halofantrine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Halofantrine can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes (Prod Info Halfan(R), 1998). Because thioridazine may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of halofantrine with thioridazine is contraindicated (Prod Info Thioridazine tablets, 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administration of halofantrine and thioridazine is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.BD Haloperidol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001b). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), pimozide (Prod Info Orap(R), 2000), quetiapine (Owens, 2001c), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antipsychotics, and thioridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.BE Halothane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, thioridazine should not be coadministered with other drugs which may also prolong the QTc interval, including halothane (Owens, 2001b; Prod Info Mellaril(R), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that may prolong the QT interval, such as halothane, is contraindicated.
7) Probable Mechanism: additive effects on the QT interval

3.5.1.BF Hydroquinidine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class Ia antiarrhythmics have been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of thioridazine with other drugs known to prolong the QTc interval, including Class Ia antiarrhythmic agents, is not recommended (Prod Info Mellaril(R), 2002a; Prod Info Procanbid(R), 2000; Prod Info Quinaglute(R), 1999; Desai et al, 1981).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and thioridazine is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.BG Ibutilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although no drug interaction studies have been performed, the manufacturer of thioridazine states that the concurrent use of thioridazine with other drugs known to prolong the QTc interval is contraindicated (Prod Info Thioridazine tablets, 2002). Class III antiarrhythmic agents may prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes (Yamreudeewong et al, 2003; Prod Info Betapace(R), 2001; Prod Info Corvert(R), 2000; Corey et al,

1999; Karam et al, 1998).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval such as Class III antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.BH Iloperidone
1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Due to the potential for additive effects on the QT interval and increased risk of torsade de pointes, caution should be used when iloperidone and drugs that prolong the QT interval are given concomitantly. Consideration should be given to monitoring cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) levels. Discontinue iloperidone in patients with persistent QTc measurements greater than 500 msec (Prod Info FANAPT(TM) oral tablets, 2009).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of iloperidone and drugs that prolong the QT interval may result in additive effects on the QT interval and an increased risk of torsade de pointes. Iloperidone should be avoided in patients with significant cardiovascular illness, eg, cardiac arrhythmia, QT prolongation, recent acute myocardial infarction, and uncompensated heart failure. If concomitant use is necessary, consider monitoring cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) levels. Discontinue iloperidone in patients with persistent QTc measurements greater than 500 msec(Prod Info FANAPT(TM) oral tablets, 2009).
7) Probable Mechanism: additive effects on the QT interval
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).

3.5.1.BI Imipramine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Marshall & Forker, 1982).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of a tricyclic antidepressant and thioridazine is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.BJ Iopamidol
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, thioridazine should not be coadministered with other drugs which are also known to prolong the QTc interval, including iopamidol (Prod Info Mellaril(R), 2000d).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.BK Isoflurane
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, thioridazine should not be coadministered with other drugs which may also prolong the QTc interval, including isoflurane (Owens, 2001a; Prod Info Mellaril(R), 2002c).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that may prolong the QT interval, such as isoflurane, is contraindicated.

7) Probable Mechanism: additive effects on the QT interval

3.5.1.BL Isradipine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Isradipine can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes (Prod Info DynaCirc(R), 2000). Because thioridazine may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of isradipine with thioridazine is contraindicated (Prod Info Mellaril(R), 2000v).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of isradipine and thioridazine is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.BM Kava

1) Interaction Effect: additive dopamine antagonist side effects
2) Summary: Theoretically, kava may add to the dopamine antagonism of phenothiazines, increasing the risk for adverse effects. Case reports describe what appears to be dopamine-blocking activity of kava manifested in patients as dystonia, dyskinesias, and Parkinsonism (Spillane et al, 1997a; Schelosky et al, 1995a). Kava extracts antagonized apomorphine-induced hyperreactivity to external stimuli in mice, suggesting dopamine blockade activity (Jamieson et al, 1989a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of kava with phenothiazines. The desired effect and/or adverse effects of phenothiazines may be increased or may be variable depending on the time of administration of kava and the quality of the kava product (i.e., whether it consistently contains a standardized amount of kava).
7) Probable Mechanism: additive dopamine antagonism
8) Literature Reports
a) A 27-year-old Aboriginal Australian male presented three times following heavy kava use with symptoms of severe choreoathetosis of the limbs, trunk, neck, and facial musculature, and athetosis of the tongue. Level of consciousness was not impaired. Symptoms resolved within 12 hours of intravenous diazepam on each occasion. Acute rheumatic fever was excluded, cerebrospinal fluid and computed tomography of the brain was normal, and urinary drug screen was negative. The only abnormalities found in hematological and biochemical tests were a serum alkaline phosphatase of 162 international units/liter (IU/L) (normal: 35-135 IU/L) and serum gamma-glutamyltransferase of 426 IU/L (normal less than 60 IU/L). These were attributed to kava use. The patient did not drink alcohol (Spillane et al, 1997).
b) A 76-year-old female with idiopathic Parkinson's disease of 17 years' duration treated for 8 years with levodopa 500 milligrams (mg) and benserazide 125 mg was prescribed kava extract (Kavasporal Forte(R)) 150 mg twice daily for complaints of inner tension. Within 10 days, she noted a pronounced increase in her daily "off" periods both in terms of duration and number. Within 2 days of discontinuing the kava product, symptoms had returned to her normal baseline (Schelosky et al, 1995).
c) A 63-year-old female experienced sudden and acute forceful involuntary oral and lingual dyskinesias on the fourth day of self-initiated therapy with kava extract (Kavasporal Forte(R)) 150 mg three times daily. She was treated successfully in the emergency room with biperiden 5 mg intravenously. She denied taking any other medications in the months preceding this event (Schelosky et al, 1995).
d) A 22-year-old female took kava extract (Laitan(R)) 100 mg once for anxiety and nervousness. Within four hours she experienced oral and lingual dyskinesias, tonic rotation of the head, and painful twisting trunk movements. She was treated successfully with biperiden 2.5 mg intravenously. She denied taking any other medications in the months preceding this event (Schelosky et al, 1995).
e) A 28-year-old male experienced acute involuntary neck extension with forceful upward deviation of the eyes within 90 minutes of taking kava extract (Laitan(R)) 100 mg. Symptoms resolved spontaneously within 40 minutes. This man had a history of acute dystonic reactions following exposure to promethacin (50 mg) and fluspirilene (1.5 mg), which had responded biperiden 5 mg intravenously 9 and 12 years previously (Schelosky et al, 1995).
f) In mice, kava extracts antagonized apomorphine-induced hyperreactivity to external stimuli. The number of hyperreactive mice after apomorphine 20 milligrams/kilogram (mg/kg) intraperitoneal administration was 6/6 in the saline treated group versus 0/6 in the group treated with kava resin (120 mg/kg) (p less than 0.005) or aqueous kava extract (p less than 0.001) (Jamieson et al, 1989).

3.5.1.BN Ketanserin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, thioridazine should not be coadministered with other drugs which are also known to prolong the QTc interval, including ketanserin

(Prod Info Mellaril(R), 2000a).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.BO Lapatinib
1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Due to the potential for additive effects on the QT interval and increased risk of torsade de pointes, caution should be used when lapatinib and drugs that prolong the QT interval are given concomitantly. Consideration should be given to monitoring cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) levels (Prod Info TYKERB oral tablets, 2008). Thirteen patients had either QTcF (corrected QT by the Friedericia method) greater than 480 msec or an increase in QTcF of greater than 60 msec in an uncontrolled, open-label, dose escalation study in advanced cancer patients (n=81) who received lapatinib doses ranging from 175 mg/day to 1800 mg/day, with serial ECGs collected on days 1 and 14 (Prod Info TYKERB oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of lapatinib and drugs that prolong the QT interval may result in additive effects on the QT interval and an increased risk of torsade de pointes. Therefore, caution should be used when these agents are given concomitantly. Consider monitoring cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) levels (Prod Info TYKERB oral tablets, 2008).
7) Probable Mechanism: additive effects on the QT interval

3.5.1.BP Levodopa
1) Interaction Effect: loss of levodopa efficacy
2) Summary: Because thioridazine is a dopamine antagonist, it is expected to antagonize the pharmacologic effects of levodopa (Prod Info Stalevo(TM), 2003; Prod Info Sinemet(R), 1998). In general, concomitant use should be avoided (Yahr & Duvoisin, 1972).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of thioridazine and levodopa should be avoided. If concomitant use is necessary, monitor the patient for loss of levodopa therapeutic efficacy.
7) Probable Mechanism: pharmacologic antagonism

3.5.1.BQ Levofloxacin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of levofloxacin and thioridazine may produce additive prolongation of the QTc interval and, thus, such use is contraindicated (Prod Info Mellaril(R), 2002; Prod Info Levaquin(R), 2000).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval, such as levofloxacin, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BR Levomethadyl
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, thioridazine should not be coadministered with other drugs which are also known to prolong the QTc interval, including levomethadyl (Prod Info Mellaril(R), 2002; Prod Info Orlaam(R), 2001).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Levomethadyl is contraindicated in patients being treated with thioridazine as it may precipitate QT prolongation.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BS Levorphanol
1) Interaction Effect: an increase in central nervous system and respiratory depression

2) Summary: The concomitant use of levorphanol and other central nervous system depressants including phenothiazines (e.g. chlorpromazine, promethazine, thioridazine) may result in additive CNS and respiratory depressant effects, including hypotension, profound sedation and/or coma . When administering levorphanol and a phenothiazine together, one or both agents dosage should be significantly reduced (Prod Info LEVO-DROMORAN(TM) injection, oral tablets, 2004). Monitor patient carefully for signs of respiratory depression, CNS depression, and hypotension.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Monitor patients for signs of respiratory depression, CNS depression, and hypotension. A dosage reduction of one or both drugs should be made.
7) Probable Mechanism: additive effects

3.5.1.BT Lidoflazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, thioridazine should not be coadministered with other drugs which are also known to prolong the QTc interval, including lidoflazine (Prod Info Mellaril(R), 2000b; Hanley & Hampton, 1983).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of lidoflazine and thioridazine is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BU 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.BV Lithospermum

1) Interaction Effect: increased dopaminergic side effects

2) Summary: Theoretically, the dopamine agonist activity of lithospermum may add to that of other dopamine agonists, increasing the risk of dopaminergic adverse effects. Lithospermum likely decreases prolactin secretion via dopamine stimulation (Sourgens et al, 1982a). Animal data suggest that the effect occurs rapidly within 3 hours after injection, subsiding within 6 to 9 hours (Sourgens et al, 1980a). The magnitude and clinical significance of this phenomenon has yet to be determined in humans. Furthermore, it is not known if the ability to stimulate dopamine receptors is limited to the hypothalamic region or if such an effect will be noted elsewhere (i.e., if patients with psychosis will experience worsening of their condition due to dopamine stimulation secondary to lithospermum). Caution is recommended until the effects on humans and possible implications of a drug-herb interaction with dopamine agonists can be fully determined.

3) Severity: minor

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use of lithospermum with phenothiazines. If the patient chooses to take lithospermum, monitor closely for symptoms of additive dopamine agonism such as nausea, headache, dizziness, fatigue, vomiting, and postural hypotension.

7) Probable Mechanism: additive dopaminergic effect

8) Literature Reports

a) Administration of freeze dried extracts (FDE) of Lithospermum officinale (Boraginaceae) by intravenous injection to rats resulted in reduced prolactin serum levels and hypophyseal stores. When administered diluent, prolactin levels decreased from 36 +/- 8 nanograms/milliliter (ng/mL) serum to 10 +/- 4 ng/mL serum (p less than 0.005) when administered Lithospermum officinale FDE (40 milligrams (mg)/100 grams body weight) within 3 hours post intravenous administration. The authors concluded that Lithospermum officinale possibly impacted prolactin secretion at the hypothalamic site via dopamine stimulation (Sourgens et al, 1982).

b) Prolactin levels decreased rapidly below basal values in rats within the first 3 hours following a single intravenous injection of Lithospermum officinale. Prolactin levels returned to control levels within 6 to 9 hours after the injection (Sourgens et al, 1980).

3.5.1.BW Lorcainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Class I antiarrhythmic agents may prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Although pharmacokinetic studies

between thioridazine and other drugs which prolong the QT interval have not been performed, an additive effect cannot be excluded. Therefore, the concurrent administration of thioridazine with a Class I antiarrhythmic agent is contraindicated (Prod Info Rythmol(R), 2002; Prod Info Mellaril(R), 2002; Prod Info Tambocor(R), 1998).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval, such as Class I antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.BX Lubeluzole
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, thioridazine should not be coadministered with other drugs which are also known to prolong the QTc interval, including lubeluzole (Prod Info Mellaril(R), 2000t).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.BY Lumefantrine
1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Due to the potential for additive effects on QT interval prolongation, concomitant use of artemether/lumefantrine with drugs that prolong the QT interval should be avoided (Prod Info COARTEM(R) oral tablets, 2009).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of artemether/lumefantrine with drugs that prolong the QT interval should be avoided due to the potential for additive effects on QT interval prolongation (Prod Info COARTEM(R) oral tablets, 2009).
7) Probable Mechanism: additive effects on QT interval prolongation
8) Literature Reports
a) Concurrent administration of a single dose of IV quinine 10 mg/kg with the final dose of a 6-dose regimen of artemether/lumfantrine did not alter the systemic exposure to quinine, lumefantrine, or dihydroartemisinin (active metabolite of artemether). Although artemether exposure was decreased, it was not believed to be clinically significant. The effects on QT prolongation were not reported in this study (Prod Info COARTEM(R) oral tablets, 2009).

3.5.1.BZ Mefloquine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2000u). Mefloquine was associated with significant QT prolongation in a study of 46 healthy subjects (Davis et al, 1996).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and any other drug which prolongs the QT interval, such as mefloquine, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CA Meperidine
1) Interaction Effect: an increase in central nervous system and respiratory depression
2) Summary: Phenothiazines may potentiate the analgesic effects of meperidine, resulting in CNS depression, hypotension, and respiratory depression. Several studies report the potentiation of analgesia by the addition of promethazine, chlorpromazine, and propiomazine to narcotic analgesics (Fromhagen & Carswell, 1961a; Winne, 1961a; Glessner & Allis, 1964a; Jackson & Smith, 1956; Eisenstein, 1964). Other studies and reviews however, do not confirm these findings (Dundee, 1963a; Siker et al, 1966; Keats, 1961; McGee & Alexander, 1979). When administered concomitantly with phenothiazines, the dose of meperidine may need to be reduced by 25% to 50% (Prod Info Demerol(R), 1997).
3) Severity: moderate
4) Onset: rapid

5) Substantiation: probable
6) Clinical Management: Monitor patients for signs of respiratory depression, CNS depression, and hypotension. A dosage reduction or discontinuation of one or both drugs may be necessary.
7) Probable Mechanism: additive effects
8) Literature Reports
a) Promethazine and meperidine combinations have been the most widely studied. It has been concluded from a controlled study in 296 patients during labor that meperidine 50 mg and promethazine 25 mg produced significantly greater analgesia than 50 mg of meperidine alone (Fromhagen & Carswell, 1961).
b) No difference in analgesic efficacy was found when promethazine 25 mg and meperidine 50 mg was alternated with meperidine 100 mg in 26 post-surgical patients (Glessner & Allis, 1964).
c) A controlled study in 51 post-operative hemorrhoidectomy patients concluded that injections of 50 mg of meperidine combined with 50 mg of promethazine gave the same amount of pain relief as a 100 mg injection of meperidine (Winne, 1961). Even though these studies were controlled, response to pain was still subjective in nature and only post-operative pain was being measured. Pain of this type varies considerably from patient to patient and no definite conclusions can be drawn from these studies.
d) In opposition to these studies is the detailed investigation by other researchers (Dundee, 1963). By applying various amounts of pressure to the anterior surface of the tibia, they measured the analgesic effects of 13 phenothiazines given by deep intramuscular injection. Using this technique, promethazine alone was shown to have an antianalgesic effect (increased the patients' sensitivity to somatic pain). It was shown that injections of meperidine 100 mg combined with promethazine 50 mg has less analgesic effect than 100 mg of meperidine alone. Promazine was the only phenothiazine that showed an additive analgesic effect with meperidine.
e) Arterial blood gases were measured to determine the effect of methotrimeprazine in 31 healthy volunteers (Zsigmond & Flynn, 1988). Methotrimeprazine, administered alone, caused no significant respiratory depression but was found to potentiate the respiratory depression caused by meperidine. When methotrimeprazine (0.15 mg per kg intravenously) was given alone, PaO2, PaCO2, pH, and base excess remained unchanged. When methotrimeprazine and meperidine were combined, significant increases in PaCO2 and pH reductions were observed, which confirms the potentiation of meperidine-induced respiratory depression by methotrimeprazine.
f) The pharmacokinetics of meperidine were not significantly altered when chlorpromazine was administered concomitantly in a two-way crossover study of 10 healthy patients. Subjects were given meperidine (26 mg per meter squared) with either chlorpromazine (30 mg per meter squared) or placebo. The effect of chlorpromazine on the serum concentration-time curve and metabolism of meperidine was investigated in order to determine if concomitant administration of a phenothiazine and meperidine alters the metabolism of meperidine, resulting in additive CNS and respiratory depression. When the two drugs were combined, N-demethylation activity was increased as evidenced by elevated urinary excretion of normeperidine (a toxic metabolite) and normeperidinic acid. Excretion of normeperidine is slower than that of meperidine, thus repeated dosing of the combination (chlorpromazine and meperidine) could lead to increased cardiac and central nervous system toxicity (Stambaugh & Wainer, 1981).

3.5.1.CB Methadone
1) Interaction Effect: an increase in central nervous system and respiratory depression
2) Summary: The concomitant use of methadone and other central nervous system depressants including phenothiazines (e.g. chlorpromazine, promethazine, thioridazine) may result in additive CNS and respiratory depressant effects, including hypotension, profound sedation and/or coma (Prod Info METHADOSE(R) oral concentrate, sugar-free oral concentrate, 2005). Monitor patient carefully for signs of respiratory depression, CNS depression, and hypotension.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Monitor patients for signs of respiratory depression, CNS depression, and hypotension.
7) Probable Mechanism: additive effects

3.5.1.CC Methadone
1) Interaction Effect: an increased risk of QTc interval prolongation
2) Summary: Cases of QT interval prolongation and serious arrhythmias, including torsade de pointes, have been reported with methadone use (Prod Info DOLOPHINE(R) HYDROCHLORIDE oral tablets, 2006). Treatment with thioridazine has also been associated with QTc prolongation and sudden death due to torsade de pointes-type arrhythmias. Concurrent administration of methadone and thioridazine is contraindicated due to the potential for additive effects on QTc interval prolongation (Prod Info Mellaril(R), 2000n).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of methadone and thioridazine is contraindicated due to the

potential for additive effects on QT interval prolongation (Prod Info Mellaril(R), 2000n).
7) Probable Mechanism: additive effects on QTc interval prolongation

3.5.1.CD Metoprolol
1) Interaction Effect: increased plasma levels of metoprolol
2) Summary: Concurrent use of metoprolol, a CYP2D6 enzyme substrate, and thioridazine, a potent CYP2D6 enzyme inhibitor, may increase metoprolol exposure. Use caution when metoprolol is administered concomitantly with thioridazine, and monitor closely for metoprolol adverse effects (such as bradycardia) (Prod Info LOPRESSOR(R) oral tablets, IV injection, 2006).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of metoprolol with thioridazine, a potent CYP2D6-inhibitor, should be approached with caution. Monitor adverse reactions related to metoprolol toxicity, such as bradycardia (Prod Info LOPRESSOR(R) oral tablets, IV injection, 2006).
7) Probable Mechanism: inhibition of CYP2D6-mediated metoprolol metabolism

3.5.1.CE Metrizamide
1) Interaction Effect: an increased seizure risk
2) Summary: Concomitant administration of metrizamide and phenothiazines has predisposed patients to metrizamide-induced seizure activity (Hindmarsh & Brucher, 1975a). However, most available data supporting this interaction is anecdotal in nature, and specific documentation of the interaction is lacking. Animal studies demonstrate that concurrent administration of phenothiazines and metrizamide results in a significantly higher frequency of seizures compared to when these drugs are administered alone (Gonsette & Brucher, 1977a).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Chlorpromazine (and possibly other phenothiazines) should be discontinued at least five days prior to using metrizamide. Halothane, isoflurane, or narcotic/relaxant techniques are appropriate if general anesthesia is necessary in patients receiving metrizamide.
7) Probable Mechanism: decreased seizure threshold
8) Literature Reports
a) A patient who had a seizure after being injected with metrizamide was the only patient in well over 1,000 patients in this series having major complications (Hindmarsh & Brucher, 1975). The patient had been on chlorpromazine for 4 months due to a psychiatric disorder. Medication was reduced to 50 mg from his normal 75 mg the day before the metrizamide injection and reduced again to 25 mg the day of the procedure. This patient had no prior history of epileptic seizures. Three and a half hours after the administration of metrizamide the patient sustained a grand mal seizure that lasted 1 minute and stopped without treatment. Five hours after the first attack the patient exhibited a second attack which was brought under control by 10 mg of diazepam. This was a single case that suggested the possibility of a correlation between subarachnoid use of metrizamide and phenothiazines.
b) Over 500,000 applications of metrizamide were reviewed (Ahlgren, 1980). There were 42 reported convulsions after treatment. A causal relationship between phenothiazine pretreatment and development of seizures could not be established. The author further stated that the addition of levomepromazine 40 mg may actually decrease the number of side effects such as headaches and nausea. One study examined 77 patients, 26 receiving pretreatment with levomepromazine and 51 without the medication (Standness, 1982). EEGs were taken before, during and after treatment. There were no differences between the groups.
c) In a study of rabbits, pericerebral injection of metrizamide and intravenous injection of chlorpromazine administered separately produced no clinical seizure activity, but the combination produced clinical seizures in 66% of the animals (Gonsette & Brucher, 1977). Upon histologic examination, inflammatory reactions were found in 66% of the animals receiving the combination, compared to 5% seen with chlorpromazine alone and 0% seen with metrizamide alone. Animals pretreated with phenobarbital were protected from the enhanced seizure activity of the combination while animals pretreated with diazepam were not.

3.5.1.CF Morphine
1) Interaction Effect: an increase in central nervous system and respiratory depression
2) Summary: The concomitant use of morphine and other central nervous system depressants including phenothiazines (e.g. chlorpromazine, promethazine, thioridazine) may result in additive CNS and respiratory depressant effects, including hypotension, profound sedation and/or coma . When administering morphine and a phenothiazine together, one or both agents dosage should be significantly reduced (Prod Info MS CONTIN(R) controlled-release oral tablets, 2005). Monitor patient carefully for signs of respiratory depression, CNS depression, and hypotension.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical

6) Clinical Management: Monitor patients for signs of respiratory depression, CNS depression, and hypotension. A dosage reduction of one or both drugs should be made.
7) Probable Mechanism: additive effects

3.5.1.CG Morphine Sulfate Liposome
1) Interaction Effect: an increase in central nervous system and respiratory depression
2) Summary: The concomitant use of morphine sulfate liposome and other central nervous system depressants including phenothiazines (e.g. chlorpromazine, promethazine, thioridazine) may result in additive CNS and respiratory depressant effects, including hypotension, profound sedation and/or coma (Prod Info DEPODUR(TM) extended release liposome injection, 2005). Monitor patient carefully for signs of respiratory depression, CNS depression, and hypotension.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Monitor patients for signs of respiratory depression, CNS depression, and hypotension.
7) Probable Mechanism: additive effects

3.5.1.CH Moxifloxacin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, thioridazine should not be coadministered with other drugs which are also known to prolong the QTc interval, including moxifloxacin (Prod Info Mellaril(R), 2002; Prod Info Avelox(TM), 2000).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval, such as moxifloxacin, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CI Nortriptyline
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Marshall & Forker, 1982).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of a tricyclic antidepressant and thioridazine is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.CJ Octreotide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturers of some phenothiazines state that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Thioridazine tablets, 2002). QT prolongation has been observed in patients treated with octreotide (Prod Info Sandostatin(R), 1999). Other phenothiazines may have similar effects, though no reports are available.
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of octreotide and thioridazine is contraindicated as it may precipitate QT prolongation.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CK Ondansetron
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Rarely, and predominantly with the intravenous formulation, transient ECG changes including QT interval prolongation have occurred with ondansetron (Prod Info ZOFRAN(R) oral tablets, oral solution, ZOFRAN ODT(R) orally disintegrating tablets, 2006). Thioridazine has been shown to prolong the QTc interval in a dose related manner, and should be avoided in combination with other drugs that are known to prolong the QTc interval, including ondansetron (Prod Info Mellaril(R), 2000k).
3) Severity: contraindicated
4) Onset: unspecified

5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ondansetron and agents that may prolong the QT interval, such as thioridazine, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CL Orphenadrine
1) Interaction Effect: decreased phenothiazine serum concentrations, decreased phenothiazine effectiveness, enhanced anticholinergic effects (ileus, hyperpyrexia, sedation, dry mouth)
2) Summary: The concurrent use of anticholinergic agents (benztropine, orphenadrine, procyclidine, trihexyphenidyl) to control extrapyramidal side effects may reduce oral absorption of phenothiazines, antagonize the behavioral and antipsychotic effects of the phenothiazine, and enhance anticholinergic side effects (Rivera-Calimlim et al, 1976a; Mann & Boger, 1978a; Singh & Kay, 1979; Gershon et al, 1965a; Buckle & Guillebaud, 1967).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Anticholinergics (benztropine, orphenadrine, procyclidine, trihexyphenidyl) should not be used routinely with phenothiazine derivatives as prophylaxis against possible extrapyramidal symptoms; use should be reserved for situations where EPS occur and lowering of the antipsychotic dosage is not possible. Anticholinergic use should be reevaluated at least every three months.
7) Probable Mechanism: delayed gastric emptying, increased gut wall metabolism of phenothiazine, decreased absorption
8) Literature Reports
a) The concomitant administration of trihexyphenidyl and chlorpromazine has been shown to result in a decrease in chlorpromazine plasma levels (Rivera-Calimlim et al, 1973; Gershon et al, 1965). A crossover controlled study of the chlorpromazine-trihexyphenidyl interaction in psychiatric patients showed conclusively that trihexyphenidyl lowers plasma levels of chlorpromazine from 13% to 100% (Rivera-Calimlim et al, 1976). The mechanism by which trihexyphenidyl lowers plasma levels of chlorpromazine was shown in rats to be an inhibition of gastric emptying by trihexyphenidyl, probably as a result of its anticholinergic activity (Rivera-Calimlim, 1976). Slow gastric emptying will delay the transport of chlorpromazine to intestinal absorption sites and favor enhanced gastrointestinal metabolism.
b) Trihexyphenidyl may also directly reverse some of the therapeutic effects of chlorpromazine. A toxic psychosis has been commonly reported following usual therapeutic doses of anticholinergic drugs, particularly when these agents are used in conjunction with other drugs with anticholinergic properties. Symptoms may include visual hallucinations, confusion, disorientation, speech difficulty, emotional lability and psychotic thinking (Perry et al, 1985).
c) The chlorpromazine-trihexyphenidyl interaction may also include additive anticholinergic effects including constipation or paralytic ileus, dry mouth, blurred vision, increased intraocular pressure and urinary retention (Perry et al, 1985). Hyperpyrexia has been reported, presumably due to blocking of exocrine sweat glands in combination with the hypothalamic dysregulation produced by antipsychotics (Mann & Boger, 1978).
d) A significant reduction in fluphenazine serum levels occurred following addition of procyclidine in patients who were previously well stabilized. Following discontinuation of procyclidine, fluphenazine serum levels returned to baseline (Bamrah et al, 1986). However, the addition of orphenadrine to perphenazine therapy resulted in no clinically relevant pharmacokinetic changes in the absorption, distribution, or elimination of perphenazine (Bolvig Hansen et al, 1979).

3.5.1.CM Oxycodone
1) Interaction Effect: an increase in central nervous system and respiratory depression
2) Summary: The concomitant use of oxycodone and other central nervous system depressants including phenothiazines (e.g. chlorpromazine, promethazine, thioridazine) may result in additive CNS and respiratory depressant effects, including hypotension, profound sedation and/or coma . When administering oxycodone and a phenothiazine together, the oxycodone dose should be reduced by 1/3 to 1/2 (Prod Info OXYCONTIN (R) controlled release tablets, 2005). Monitor patient carefully for signs of respiratory depression, CNS depression, and hypotension.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Monitor patients for signs of respiratory depression, CNS depression, and hypotension. A dosage reduction of 1/3 to 1/2 of oxycodone should be made.
7) Probable Mechanism: additive effects

3.5.1.CN Paliperidone
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001b). Several

antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), pimozide (Prod Info Orap(R), 2000), quetiapine (Owens, 2001c), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antipsychotics, and thioridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.CO Paroxetine
1) Interaction Effect: an increased risk of thioridazine toxicity, cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Paroxetine inhibits the metabolism of thioridazine, possibly through the inhibition of cytochrome P450 2D6 (CYP2D6) resulting in toxicity. The resulting elevated levels of thioridazine would be expected to enhance the prolongation of the QT interval and may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as torsade de pointes-type arrhythmias (Prod Info Paxil(R), 2003; Prod Info Mellaril(R), 2000p).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Due to the potential for significant, possibly life-threatening, proarrhythmic effects, concurrent administration of thioridazine and paroxetine is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated thioridazine metabolism
8) Literature Reports
a) The metabolism of thioridazine is inhibited by drugs such as paroxetine due to reduced cytochrome P450 2D6 isozyme activity. The elevated levels of thioridazine would be expected to enhance the prolongation of the QTc interval associated with thioridazine. This, in turn, may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as torsade de pointes-type arrhythmias (Prod Info Mellaril(R), 2000o).

3.5.1.CP Pentamidine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturers of some phenothiazines state that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Thioridazine tablets, 2002). Torsades de pointes has been associated with pentamidine (Lindsay et al, 1990).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Pentamidine is contraindicated in patients being treated with thioridazine as it may precipitate QT prolongation.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CQ Phenobarbital
1) Interaction Effect: decreased phenobarbital or thioridazine effectiveness
2) Summary: Phenobarbital may decrease thioridazine concentrations due to its ability to induce hepatic microsomal enzymes (Ellenor et al, 1978a). Phenobarbital and thioridazine have also been reported to produce lower serum levels of both drugs when given concomitantly (Gay & Madsen, 1983a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: If concurrent therapy is required, a dosage adjustment for thioridazine or phenobarbital may be required in order to maintain or achieve a therapeutic effect.
7) Probable Mechanism: induction of hepatic microsomal enzymes
8) Literature Reports
a) Seven retarded patients on concurrent phenobarbital and thioridazine therapy experienced an increase in their thioridazine and metabolite levels when phenobarbital was withdrawn. The most likely explanation is that withdrawal of phenobarbital resulted in a reversal of the phenobarbital-induced increase in hepatic drug metabolizing enzyme activity (Ellenor et al, 1978).
b) Retarded adults on phenobarbital and thioridazine 100 mg to 200 mg per day were matched to retarded adults on antiepileptic therapy alone. When given concomitantly, phenobarbital and thioridazine produced lower serum levels of both drugs than when either drug was given alone. The presumed mechanism was induction of microsomal enzymes (Gay & Madsen, 1983).

3.5.1.CR 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. It was hypothesized that some patients with depression may have deficient phenylalanine hydroxylase (as in phenylketonuria (PKU)), or deficient dihydropteridine reductase (as in atypical PKU) (Gardos et al, 1992a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Caution is advised if phenylalanine is administered with a neuroleptic agent. Monitor the patient closely for signs of tardive dyskinesia.
7) Probable Mechanism: reduced brain availability of other large neutral amino acids and interference with catecholamine synthesis
8) Literature Reports
a) Phenylalanine tended to increase the incidence of tardive dyskinesia in patients taking neuroleptics in an open study. Three groups of patients were studied: (1) patients with unipolar depression with tardive dyskinesia (n=11), (2) patients with no tardive dyskinesia with current or past exposure to greater than or equal to 100 milligrams (mg) of a chlorpromazine equivalent for at least 3 months (n=10), and (3) patients with no tardive dyskinesia not previously exposed to a neuroleptic drug (n=10). Neuroleptic agents were taken during the study by 6 patients in group 1, and 5 patients in group 2. Patients received powdered phenylalanine 100 mg/kilogram dissolved in orange juice after an overnight fast. Blood samples were obtained just prior to phenylalanine administration and 2 hours after administration. Three patients in group 1 (with tardive dyskinesia) had the highest postloading phenylalanine plasma levels; this group as a whole had higher (though nonsignificant) mean phenylalanine levels than the other groups. Tardive dyskinesia score (measured using the Abnormal Involuntary Movements Scale (AIMS)) nonsignificantly increased in group 1. Postloading phenylalanine level and postloading AIMS scores were significantly positively correlated in group 1 (rs=0.347, p less than 0.05; Spearman correlation coefficient 0.543, p less than 0.05). Postloading phenylalanine level and baseline AIMS scores demonstrated a trend toward correlation (rs=0.246, p=0.092; Spearman correlation coefficient 0.679, p less than 0.05). In all patients, phenylalanine loading increased plasma phenylalanine levels approximately eight-fold, and plasma tyrosine increased 2.5 times as a result of conversion of phenylalanine to tyrosine. Plasma levels of competing large neutral amino acids such as tryptophan decreased slightly (Gardos et al, 1992).

3.5.1.CS Phenytoin

1) Interaction Effect: increased or decreased phenytoin levels and possibly reduced phenothiazine levels
2) Summary: Concurrent phenothiazine and phenytoin therapy has been reported to increase, decrease, or cause no change in the serum levels of phenytoin (Sands et al, 1987a; Vincent, 1980a; Siris et al, 1974a; Houghton & Richens, 1975a). In one study, concomitant phenytoin reduced the serum levels of mesoridazine, but not thioridazine (Linnoila et al, 1980c).
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Consider monitoring phenytoin levels when a phenothiazine is added or discontinued from therapy; dosage adjustments may be needed in some cases. The patient should also be observed for any signs of phenytoin toxicity (ataxia, nystagmus, tremor, hyperreflexia), particularly in the case of adjustments to the phenothiazine dosage. Observe patients for phenothiazine efficacy.
7) Probable Mechanism: induction or inhibition of phenytoin metabolism; induction of phenothiazine metabolism
8) Literature Reports
a) Compelling data was reported suggesting that phenothiazines as a group decrease serum phenytoin concentrations, but the effect of individual phenothiazines was not evaluated. A total of 92 cases (institutionalized patients) who were receiving constant phenytoin doses and who were either initiating, discontinuing, increasing, or decreasing a phenothiazine were retrospectively reviewed. Approximately half of the patients received thioridazine, while the other half were about evenly split between chlorpromazine and mesoridazine. Phenytoin concentrations decreased by 44% (p=0.001) when a phenothiazine was added; similarly, increases in phenothiazine dose caused a 33% decrease in phenytoin concentrations (p=0.001). In patients who discontinued a phenothiazine, phenytoin concentrations increased by 71% (p=0.001); similarly, decreases in phenothiazine dose caused a 55% increase in phenytoin concentrations (p=0.001). Although the combined results cannot be applied clinically to a particular phenothiazine, this study does suggest a remarkably strong trend among phenothiazines which is contrary to some individual case reports. Further study is needed (Haidukewych & Rodin, 1985a).
b) The effects of concomitant treatment with phenytoin and/or phenobarbital on the steady-state serum concentrations of haloperidol, thioridazine, and mesoridazine were investigated in two groups of patients. The investigators found that concomitant anticonvulsant medication significantly reduced the plasma level of haloperidol and mesoridazine, but not thioridazine (Linnoila et al, 1980b).

3.5.1.CT Pimozide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001b). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), pimozide (Prod Info Orap(R), 2000), quetiapine (Owens, 2001c), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2004).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antipsychotics, and thioridazine, is contraindicated.

7) Probable Mechanism: additive QT prolongation

3.5.1.CU Pindolol

1) Interaction Effect: an increased risk of thioridazine toxicity, cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Pindolol has been beneficial in the treatment of patients with behavior and management problems secondary to organic brain disease (Greendyke & Gulya, 1988a). Fluoxetine inhibits the metabolism of thioridazine, possibly through the inhibition of cytochrome P450 2D6 (CYP2D6) resulting in toxicity. The resulting elevated levels of thioridazine would be expected to enhance the prolongation of the QT interval and may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as torsade de pointes-type arrhythmias (Prod Info Mellaril(R), 2000ab).

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Due to the potential for significant, possibly life-threatening, proarrhythmic effects, concurrent administration of thioridazine and pindolol is contraindicated.

7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated thioridazine metabolism

8) Literature Reports

a) Twenty-six male patients with intermittent explosive disorder secondary to organic brain disease were studied to determine the effect of pindolol and thioridazine coadministration. All patients were already receiving treatment with thioridazine, haloperidol, phenytoin, or phenobarbital. Pindolol therapy was started at 5 mg twice daily with total daily increments of 10 mg every three days for a total dose of 40 mg. It was then reduced by 10 mg increments to zero with a reversal of the schedule. Results showed moderate, dose-related increases in serum levels of thioridazine and two of its metabolites when coadministered with pindolol. Serum pindolol levels were also higher than expected in patients receiving thioridazine. No serum level increases were found for phenytoin, phenobarbital, or haloperidol. This fact led the authors to believe that the elevation in thioridazine and pindolol levels was due to mutually competitive interference with their hepatic metabolism (Greendyke & Gulya, 1988).

b) The metabolism of thioridazine is inhibited by drugs such as pindolol due to reduced cytochrome P450 2D6 isozyme activity. The elevated levels of thioridazine would be expected to enhance the prolongation of the QTc interval associated with thioridazine. This, in turn, may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as torsade de pointes-type arrhythmias (Prod Info Mellaril(R), 2000h).

3.5.1.CV Pirmenol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Class Ia antiarrhythmics have been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of thioridazine with other drugs known to prolong the QTc interval, including Class Ia antiarrhythmic agents, is not recommended (Prod Info Mellaril(R), 2002a; Prod Info Procanbid(R), 2000; Prod Info Quinaglute(R), 1999; Desai et al, 1981).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and thioridazine is contraindicated.

7) Probable Mechanism: additive cardiac effects

3.5.1.CW Porfimer

1) Interaction Effect: excessive intracellular damage in photosensitized tissues

2) Summary: Coadministration of porfimer with other photosensitizing agents, including phenothiazines,

may increase the severity of photosensitivity reactions and lead to excessive tissue damage (Prod Info Photofrin(R), 1995). Caution should be used if thioridazine is to be given to patients receiving porfimer for photodynamic therapy.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Patients who are receiving phenothiazine therapy along with photodynamic therapy should be counseled to avoid exposure of skin and eyes to direct sunlight or bright indoor light for 30 days after administration of porfimer. Application of sunscreens does not protect against photosensitivity reactions.
7) Probable Mechanism: additive photosensitizing effects

3.5.1.CX Prajmaline
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class Ia antiarrhythmics have been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of thioridazine with other drugs known to prolong the QTc interval, including Class Ia antiarrhythmic agents, is not recommended (Prod Info Mellaril(R), 2002a; Prod Info Procanbid(R), 2000; Prod Info Quinaglute(R), 1999; Desai et al, 1981).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and thioridazine is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.CY Probucol
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, thioridazine should not be coadministered with other drugs which are also known to prolong the QTc interval (Prod Info Mellaril(R), 2000j). Probucol has been shown to prolong the QTc interval (Gohn & Simmons, 1992; Prod Info Lorelco(R), 1991).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval, such as probucol, is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.CZ Procainamide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class Ia antiarrhythmics have been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of thioridazine with other drugs known to prolong the QTc interval, including Class Ia antiarrhythmic agents, is not recommended (Prod Info Mellaril(R), 2002a; Prod Info Procanbid(R), 2000; Prod Info Quinaglute(R), 1999; Desai et al, 1981).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and thioridazine is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.DA Procarbazine
1) Interaction Effect: CNS depression
2) Summary: The combined use of phenothiazines and monoamine oxidase inhibitors (MAOI) has resulted in prolonged phenothiazine effects (Sjoqvist, 1965). To minimize CNS depression and possible potentiation, coadministration of procarbazine and phenothiazines should be approached with caution (Prod Info Matulane(R), 2002).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The coadministration of procarbazine and phenothiazines should be approached with caution.
7) Probable Mechanism: unknown

3.5.1.DB Procaterol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, thioridazine should not be coadministered with other drugs which are also known to prolong the QTc interval, including procaterol (Prod Info Mellaril(R), 2000x).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.DC Prochlorperazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT interval prolongation, torsades de pointes, cardiac arrest)
2) Summary: Because thioridazine may prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of thioridazine and other phenothiazines is contraindicated (Prod Info Mellaril(R), 2000l). Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002a; Prod Info Stelazine(R), 2002a; Prod Info Thorazine(R), 2002a). Other phenothiazines may have similar effects, though no reports are available.
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as thioridazine and other phenothiazines, is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.DD Procyclidine

1) Interaction Effect: decreased phenothiazine serum concentrations, decreased phenothiazine effectiveness, enhanced anticholinergic effects (ileus, hyperpyrexia, sedation, dry mouth)
2) Summary: The concurrent use of anticholinergic agents (benztropine, orphenadrine, procyclidine, trihexyphenidyl) to control extrapyramidal side effects may reduce oral absorption of phenothiazines, antagonize the behavioral and antipsychotic effects of the phenothiazine, and enhance anticholinergic side effects (Rivera-Calimlim et al, 1976d; Mann & Boger, 1978e; Singh & Kay, 1979b; Gershon et al, 1965e; Buckle & Guillebaud, 1967b).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Anticholinergics (benztropine, orphenadrine, procyclidine, trihexyphenidyl) should not be used routinely with phenothiazine derivatives as prophylaxis against possible extrapyramidal symptoms; use should be reserved for situations where EPS occur and lowering of the antipsychotic dosage is not possible. Anticholinergic use should be reevaluated at least every three months.
7) Probable Mechanism: delayed gastric emptying, increased gut wall metabolism of phenothiazine, decreased absorption
8) Literature Reports

a) The concomitant administration of trihexyphenidyl and chlorpromazine has been shown to result in a decrease in chlorpromazine plasma levels (Rivera-Calimlim et al, 1973b; Gershon et al, 1965d). A crossover controlled study of the chlorpromazine-trihexyphenidyl interaction in psychiatric patients showed conclusively that trihexyphenidyl lowers plasma levels of chlorpromazine from 13% to 100% (Rivera-Calimlim et al, 1973b). The mechanism by which trihexyphenidyl lowers plasma levels of chlorpromazine was shown in rats to be an inhibition of gastric emptying by trihexyphenidyl, probably as a result of its anticholinergic activity (Rivera-Calimlim, 1976b). Slow gastric emptying will delay the transport of chlorpromazine to intestinal absorption sites and favor enhanced gastrointestinal metabolism.

b) Trihexyphenidyl may also directly reverse some of the therapeutic effects of chlorpromazine. A toxic psychosis has been commonly reported following usual therapeutic doses of anticholinergic drugs, particularly when these agents are used in conjunction with other drugs with anticholinergic properties. Symptoms may include visual hallucinations, confusion, disorientation, speech difficulty, emotional lability and psychotic thinking (Perry et al, 1985b).

c) The chlorpromazine-trihexyphenidyl interaction may also include additive anticholinergic effects including constipation or paralytic ileus, dry mouth, blurred vision, increased intraocular pressure and urinary retention (Perry et al, 1985b). Hyperpyrexia has been reported, presumably due to blocking of exocrine sweat glands in combination with the hypothalamic dysregulation produced by antipsychotics (Mann & Boger, 1978d).

d) A significant reduction in fluphenazine serum levels occurred following addition of procyclidine in patients who were previously well stabilized. Following discontinuation of procyclidine, fluphenazine

serum levels returned to baseline (Bamrah et al, 1986b). However, the addition of orphenadrine to perphenazine therapy resulted in no clinically relevant pharmacokinetic changes in the absorption, distribution, or elimination of perphenazine (Bolvig Hansen et al, 1979b).

3.5.1.DE Propafenone

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class I antiarrhythmic agents may prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Although pharmacokinetic studies between thioridazine and other drugs which prolong the QT interval have not been performed, an additive effect cannot be excluded. Therefore, the concurrent administration of thioridazine with a Class I antiarrhythmic agent is contraindicated (Prod Info Rythmol(R), 2002; Prod Info Mellaril(R), 2002; Prod Info Tambocor(R), 1998).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval, such as Class I antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.DF Propranolol

1) Interaction Effect: an increased risk of thioridazine toxicity, cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: In two case reports, large doses of propranolol (more than 400 mg daily) resulted in a 3-fold to 5-fold increase of thioridazine concentration in patients on large doses of thioridazine (more than 500 mg daily) (Silver et al, 1986). Long-acting propranolol resulted in significant dose-related increases in thioridazine plasma levels in five patients (Greendyke & Kanter, 1987). Fluoxetine inhibits the metabolism of thioridazine, possibly through the inhibition of cytochrome P450 2D6 (CYP2D6) resulting in toxicity. The resulting elevated levels of thioridazine would be expected to enhance the prolongation of the QT interval and may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as torsade de pointes-type arrhythmias (Prod Info Mellaril(R), 2000y).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Due to the potential for significant, possibly life-threatening, proarrhythmic effects, concurrent administration of thioridazine and propranolol is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated thioridazine metabolism
8) Literature Reports
a) The metabolism of thioridazine is inhibited by drugs such as propranolol due to reduced cytochrome P450 2D6 isozyme activity. The elevated levels of thioridazine would be expected to enhance the prolongation of the QT interval associated with thioridazine. This, in turn, may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as torsade de pointes-type arrhythmias (Prod Info Mellaril(R), 2000c).

3.5.1.DG Protirelin

1) Interaction Effect: decreased TSH response
2) Summary: Chronic thioridazine therapy in psychiatric patients may significantly decrease the thyroid-stimulating hormone (TSH) response to protirelin (Lamberg et al, 1977). Protirelin 200 mcg was administered intravenously to 10 patients receiving thioridazine 100 mg to 700 mg daily for over one year. The mean change in serum TSH levels from baseline was 5.8 microunits/mL in patients on thioridazine, which was significantly less than those seen in healthy controls (12.5 micrograms/mL).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients for a decreased response to thyroid-stimulating hormone (TSH).
7) Probable Mechanism: unknown

3.5.1.DH Protriptyline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Marshall & Forker, 1982).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of a tricyclic antidepressant and thioridazine is contraindicated.

7) Probable Mechanism: additive effect on QT interval

3.5.1.DI Quetiapine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001b). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), pimozide (Prod Info Orap(R), 2000), quetiapine (Owens, 2001c), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antipsychotics, and thioridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.DJ Quinidine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class Ia antiarrhythmics have been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of thioridazine with other drugs known to prolong the QTc interval, including Class Ia antiarrhythmic agents, is not recommended (Prod Info Mellaril(R), 2002a; Prod Info Procanbid(R), 2000; Prod Info Quinaglute(R), 1999; Desai et al, 1981).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and thioridazine is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.DK Ranolazine

1) Interaction Effect: an increase in thioridazine serum concentration and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Ranolazine, and/or its metabolites, partially inhibit cytochrome P450-2D6-mediated thioridazine metabolism resulting in increased thioridazine exposure. Ranolazine and thioridazine have been shown to increase QTc interval in a dose-dependent manner. Concurrent administration of ranolazine and thioridazine is contraindicated (Prod Info thioridazine hcl oral tablets, 2003).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Using ranolazine and thioridazine together is contraindicated due to the additive effects on QTc prolongation.(Prod Info thioridazine hcl oral tablets, 2003).
7) Probable Mechanism: ranolazine inhibition of cytochrome P450-2D6-mediated metabolism of thioridazine and additive effects on QTc prolongation

3.5.1.DL Rilonacept

1) Interaction Effect: altered thioridazine plasma concentrations
2) Summary: In states of chronic inflammation, the formation of CYP450 enzymes is suppressed by increased levels of cytokines such as interleukin-1 (IL-1). Upon administration of an IL-1 blocker, such as rilonacept, the formation of CYP450 enzymes could be normalized. In patients receiving CYP450 substrates with a narrow therapeutic index concomitantly, such normalization may have a clinically relevant effect on the CYP450 substrate levels. If rilonacept therapy is initiated in a patient being treated with a CYP450 substrate that has a narrow therapeutic index, such as thioridazine, the therapeutic effect of thioridazine should be monitored and thioridazine dose should be adjusted if necessary (Prod Info ARCALYST(TM) subcutaneous injection, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: If rilonacept therapy is initiated in a patient being treated with a CYP450 substrate with a narrow therapeutic index, such as thioridazine, monitor for therapeutic effect of thioridazine and adjust thioridazine dose as needed (Prod Info ARCALYST(TM) subcutaneous injection, 2008).
7) Probable Mechanism: interference with CYP450-mediated thioridazine metabolism

3.5.1.DM Risperidone

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001b). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), pimozide (Prod Info Orap(R), 2000), quetiapine (Owens, 2001c), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antipsychotics, and thioridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.DN Ritonavir
1) Interaction Effect: increased thioridazine serum concentrations and potential toxicity (hypotension, sedation, extrapyramidal effects, arrhythmias)
2) Summary: Coadministered ritonavir may increase serum concentrations of thioridazine, resulting in thioridazine toxicity (Prod Info NORVIR(R), 2005).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Use caution and monitor patients for signs and symptoms of neuroleptic toxicity (hypotension, sedation, extrapyramidal effects, arrhythmias). Reduce doses of thioridazine as required.
7) Probable Mechanism: decreased thioridazine metabolism

3.5.1.DO Roxithromycin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, thioridazine should not be coadministered with other drugs which are also known to prolong the QTc interval, including roxithromycin (Prod Info Mellaril(R), 2000e).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.DP Sematilide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although no drug interaction studies have been performed, the manufacturer of thioridazine states that the concurrent use of thioridazine with other drugs known to prolong the QTc interval is contraindicated (Prod Info Thioridazine tablets, 2002). Class III antiarrhythmic agents may prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes (Yamreudeewong et al, 2003; Prod Info Betapace(R), 2001; Prod Info Corvert(R), 2000; Corey et al, 1999; Karam et al, 1998).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval such as Class III antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.DQ Sertindole
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001b). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), pimozide (Prod Info Orap(R), 2000), quetiapine (Owens, 2001c), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2004).
3) Severity: contraindicated

4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antipsychotics, and thioridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.DR Sotalol
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although no drug interaction studies have been performed, the manufacturer of thioridazine states that the concurrent use of thioridazine with other drugs known to prolong the QTc interval is contraindicated (Prod Info Thioridazine tablets, 2002). Class III antiarrhythmic agents may prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes (Yamreudeewong et al, 2003; Prod Info Betapace(R), 2001; Prod Info Corvert(R), 2000; Corey et al, 1999; Karam et al, 1998).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval such as Class III antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.DS Sparfloxacin
1) Interaction Effect: prolongation of the QTc interval and/or torsades de pointes
2) Summary: Torsades de pointes has been reported in patients receiving sparfloxacin concomitantly with disopyramide and amiodarone. The use of sparfloxacin is contraindicated with drugs which produce an increase in the QTc interval and/or torsades de pointes, including phenothiazines. Sparfloxacin is also contraindicated in persons with known QTc prolongation (Prod Info Zagam(R), 1998).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Sparfloxacin is contraindicated in individuals with known QTc prolongation or in patients being treated concurrently with drugs that are known to increase the QTc interval and/or cause torsades de pointes.
7) Probable Mechanism: additive effects on QTc prolongation
8) Literature Reports
a) In clinical trials involving 1489 patients with a baseline QTc measurement, the mean prolongation of the QTc interval at sparfloxacin steady-state was 10 msec (2.5%). Of these subjects, 0.7% had a QTc interval greater than 500 msec at steady-state. However, no arrhythmic effects were seen in any of the patients. The magnitude of the QTc effect does not increase with repeated administration of sparfloxacin, and the QTc interval returns to baseline within 48 hours after discontinuation of sparfloxacin (Prod Info Zagam(R), 1996).
b) A case of sparfloxacin-induced torsades de pointes is described (Dupont et al, 1996). A 47-year old woman hospitalized for suppurative otitis media and mastoiditis was treated with sparfloxacin due to an allergy to betalactam antibiotics. On day six of treatment she felt dizzy and lost consciousness. This was attributed to torsades de pointes on the cardioscope and was followed by cardiac arrest which required cardiopulmonary resuscitation. Her pre-treatment electrocardiogram showed QT and QTc intervals of 0.34 and 0.46 seconds, respectively. An electrocardiogram post-arrest revealed QT and QTc intervals of 0.35 and 0.60 seconds, respectively. A 24-hour continuous electrocardiography confirmed numerous episodes of torsades de pointes occurring after episodes of sino-auricular block. Sparfloxacin was discontinued and the QTc returned to baseline within a week. Upon further testing, it was determined that the patient suffered from a mild idiopathic long QT syndrome. Due to the onset of symptoms with administration of sparfloxacin and the relief of symptoms following discontinuation of the drug, it is highly probable that sparfloxacin contributed to the torsades de pointes.

3.5.1.DT Spiramycin
1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2000aa). QT prolongation has been reported with spiramycin (Stramba-Badiale et al, 1997).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of spiramycin and thioridazine is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.DU Sulfamethoxazole
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac

arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2000m). Q and T wave distortions have been observed in patients taking cotrimoxazole (Lopez et al, 1987). Other phenothiazines may have similar effects, though no reports are available.
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administration of cotrimoxazole and thioridazine is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.DV Sultopride
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001b). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), pimozide (Prod Info Orap(R), 2000), quetiapine (Owens, 2001c), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antipsychotics, and thioridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.DW Sunitinib
1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Sunitinib has been associated with prolongation of the QT interval in a dose dependent manner, with torsade de pointes occurring in less than 0.1% patients exposed to sunitinib (Prod Info SUTENT(R) oral capsules, 2008). Thioridazine has also been shown to prolong the QT interval in a dose dependent manner. Due to the potential for additive effects on the QT interval and increased risk for torsade de pointes, the concomitant use of thioridazine and other drugs that prolong the QT interval is contraindicated (Prod Info MELLARIL(R) oral tablet, solution, USP, MELLARIL-S(R) oral suspension, USP, 2000).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of thioridazine and drugs that prolong the QT interval, such as sunitinib, is contraindicated due to the potential for additive effects on the QT interval and an increased risk of torsade de pointes (Prod Info MELLARIL(R) oral tablet, solution, USP, MELLARIL-S(R) oral suspension, USP, 2000).
7) Probable Mechanism: additive effects on the QT interval

3.5.1.DX Tapentadol
1) Interaction Effect: an increase in central nervous system and respiratory depression
2) Summary: The concomitant use of tapentadol with central nervous system depressants including phenothiazines (e.g. chlorpromazine, promethazine, thioridazine) may result in additive CNS and respiratory depressant effects, including hypotension, profound sedation and/or coma. When administering tapentadol and a phenothiazine together, dosage of one or both agents may be reduced (Prod Info tapentadol immediate release oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Consider monitoring the patient for cardiorespiratory depression when tapentadol and phenothiazines are used in combination. A reduction in dose of one or both drugs may be necessary (Prod Info tapentadol immediate release oral tablets, 2008).
7) Probable Mechanism: additive effects

3.5.1.DY Tedisamil
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although no drug interaction studies have been performed, the manufacturer of thioridazine states that the concurrent use of thioridazine with other drugs known to prolong the QTc interval is contraindicated (Prod Info Thioridazine tablets, 2002). Class III antiarrhythmic agents may prolong the QT

interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes (Yamreudeewong et al, 2003; Prod Info Betapace(R), 2001; Prod Info Corvert(R), 2000; Corey et al, 1999; Karam et al, 1998).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval such as Class III antiarrhythmic agents is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.DZ Telithromycin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, thioridazine should not be coadministered with other drugs which are also known to prolong the QTc interval, including telithromycin (Owens, 2001d; Prod Info Mellaril(R), 2002h).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine and agents that may prolong the QT interval, such as telithromycin, is contraindicated.
7) Probable Mechanism: additive effects on the QT interval

3.5.1.EA Terfenadine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturers of some phenothiazines state that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2002f; Prod Info Serentil(R), 2000). Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002b; Prod Info Stelazine(R), 2002b; Prod Info Thorazine(R), 2002b). Other phenothiazines may have similar effects, though no reports are available. Even though no formal drug interaction studies have been done, the coadministration of terfenadine and other drugs known to prolong the QTc interval, including phenothiazines, is contraindicated (Anon, 1997).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of terfenadine and a phenothiazine is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.EB Tetrabenazine
1) Interaction Effect: increased risk of QT interval prolongation
2) Summary: Tetrabenazine causes a small increase in the corrected QT interval. As the degree of prolongation increases, QT prolongation can develop into torsade de pointes-type VT. The concomitant use of tetrabenazine with other drugs known for QT prolongation (eg, thioridazine) should be avoided (Prod Info XENAZINE(R) oral tablets, 2008). In a randomized, double-blind, placebo controlled crossover study of healthy subjects, the effect of a single 25 mg or 50 mg dose of tetrabenazine on the QT interval was studied with moxifloxacin as a positive control. The 50 mg dose of tetrabenazine caused an approximate 8 millisecond mean increase in QT (Prod Info XENAZINE(R) oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of tetrabenazine with thioridazine or other drugs that prolong the QT interval should be avoided due to the potential for additive effects on the QT interval and increased risk of torsade de pointes (Prod Info XENAZINE(R) oral tablets, 2008). However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval.
7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.EC 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 phenothiazine medications with tramadol may enhance the risk of seizures and CNS and respiratory depression (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 phenothiazine therapy. If possible, avoid this combination, especially in patients with underlying conditions

that might predispose to seizures.
7) Probable Mechanism: unknown

3.5.1.ED Trazodone
1) Interaction Effect: hypotension
2) Summary: Concomitant administration of trazodone with chlorpromazine or trifluoperazine resulted in additive hypotensive effects in two case reports. Withdrawal of trazodone resulted in resolution of the hypotension (Asayesh, 1986).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor blood pressure, particularly in patients who might be sensitive to this effect. Advise patient to rise slowly from laying or sitting position.
7) Probable Mechanism: additive hypotensive effects
8) Literature Reports
a) In one study, 11 depressed patients received trazodone 150 mg or 300 mg at bedtime for one to 18 weeks. In addition, thioridazine 40 mg daily was given for one week, and blood samplings were obtained prior to and after the coadministration. Thioridazine significantly increased plasma concentrations of both trazodone and m-chlorophenylpiperazine, the active metabolite of trazodone. These results suggest the involvement of cytochrome P4502D6 (CYP2D6) in the metabolism of trazodone, since thioridazine is a known inhibitor of this isozyme (Yasui et al, 1995).

3.5.1.EE Trifluoperazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT interval prolongation, torsades de pointes, cardiac arrest)
2) Summary: Because thioridazine may prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of thioridazine and other phenothiazines is contraindicated (Prod Info Mellaril(R), 2000l). Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002a; Prod Info Stelazine(R), 2002a; Prod Info Thorazine(R), 2002a). Other phenothiazines may have similar effects, though no reports are available.
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as thioridazine and other phenothiazines, is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.EF Trihexyphenidyl
1) Interaction Effect: decreased phenothiazine serum concentrations, decreased phenothiazine effectiveness, enhanced anticholinergic effects (ileus, hyperpyrexia, sedation, dry mouth)
2) Summary: The concurrent use of anticholinergic agents (benztropine, orphenadrine, procyclidine, trihexyphenidyl) to control extrapyramidal side effects may reduce oral absorption of phenothiazines, antagonize the behavioral and antipsychotic effects of the phenothiazine, and enhance anticholinergic side effects (Rivera-Calimlim et al, 1976c; Mann & Boger, 1978c; Singh & Kay, 1979a; Gershon et al, 1965c; Buckle & Guillebaud, 1967a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Anticholinergics (benztropine, orphenadrine, procyclidine, trihexyphenidyl) should not be used routinely with phenothiazine derivatives as prophylaxis against possible extrapyramidal symptoms; use should be reserved for situations where EPS occur and lowering of the antipsychotic dosage is not possible. Anticholinergic use should be reevaluated at least every three months.
7) Probable Mechanism: delayed gastric emptying, increased gut wall metabolism of phenothiazine, decreased absorption
8) Literature Reports
a) The concomitant administration of trihexyphenidyl and chlorpromazine has been shown to result in a decrease in chlorpromazine plasma levels (Rivera-Calimlim et al, 1973a; Gershon et al, 1965b). A crossover controlled study of the chlorpromazine-trihexyphenidyl interaction in psychiatric patients showed conclusively that trihexyphenidyl lowers plasma levels of chlorpromazine from 13% to 100% (Rivera-Calimlim et al, 1976b). The mechanism by which trihexyphenidyl lowers plasma levels of chlorpromazine was shown in rats to be an inhibition of gastric emptying by trihexyphenidyl, probably as a result of its anticholinergic activity (Rivera-Calimlim, 1976a). Slow gastric emptying will delay the transport of chlorpromazine to intestinal absorption sites and favor enhanced gastrointestinal metabolism.
b) Trihexyphenidyl may also directly reverse some of the therapeutic effects of chlorpromazine. A toxic psychosis has been commonly reported following usual therapeutic doses of anticholinergic drugs, particularly when these agents are used in conjunction with other drugs with anticholinergic properties. Symptoms may include visual hallucinations, confusion, disorientation, speech difficulty, emotional

lability and psychotic thinking (Perry et al, 1985a).
c) The chlorpromazine-trihexyphenidyl interaction may also include additive anticholinergic effects including constipation or paralytic ileus, dry mouth, blurred vision, increased intraocular pressure and urinary retention (Perry et al, 1985a). Hyperpyrexia has been reported, presumably due to blocking of exocrine sweat glands in combination with the hypothalamic dysregulation produced by antipsychotics (Mann & Boger, 1978b).
d) A significant reduction in fluphenazine serum levels occurred following addition of procyclidine in patients who were previously well stabilized. Following discontinuation of procyclidine, fluphenazine serum levels returned to baseline (Bamrah et al, 1986a). However, the addition of orphenadrine to perphenazine therapy resulted in no clinically relevant pharmacokinetic changes in the absorption, distribution, or elimination of perphenazine (Bolvig Hansen et al, 1979a).

3.5.1.EG Trimethoprim
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2000m). Q and T wave distortions have been observed in patients taking cotrimoxazole (Lopez et al, 1987). Other phenothiazines may have similar effects, though no reports are available.
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administration of cotrimoxazole and thioridazine is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.EH Trimipramine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Marshall & Forker, 1982).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of a tricyclic antidepressant and thioridazine is contraindicated.
7) Probable Mechanism: additive effect on QT interval

3.5.1.EI Vasopressin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Thioridazine and vasopressin have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Mellaril(R), 2000n; Mauro et al, 1988). Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of drugs that prolong the QT interval, such as thioridazine and vasopressin, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.EJ Vitex
1) Interaction Effect: increased dopaminergic side effects
2) Summary: Theoretically, the dopamine agonist activity of Vitex may add to that of other dopamine agonists, increasing the risk of dopaminergic adverse effects. Vitex has been effective in alleviating luteal phase defects due to hyperprolactinemia and in relieving symptoms related to premenstrual tension syndrome (Milewicz et al, 1993a; Lauritzen et al, 1997a). Vitex reduced prolactin secretion in humans (Milewicz et al, 1993a). In vitro, Vitex inhibited prolactin release by binding to the D2 receptor (Jarry et al, 1994a).
3) Severity: minor
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Avoid concomitant use of Vitex with phenothiazines. If the patient chooses to take Vitex, monitor closely for symptoms of additive dopamine agonism such as nausea, headache, dizziness, fatigue, vomiting, and postural hypotension.
7) Probable Mechanism: additive dopaminergic effect

8) Literature Reports

a) Vitex agnus castus effectively normalized prolactin release in a randomized double-blind, placebo-controlled trial of 52 women with luteal phase defects due to latent hyperprolactinemia. Administration of Vitex agnus castus 20 mg daily for three months reduced prolactin release (from 23.7 to 22.5 nanogram (ng)/mL; p equal to 0.23), normalized shortened luteal phases (from 5.5 days to 10.5 days; p less than 0.005), and eliminated deficits in luteal progesterone synthesis (from 2.46 ng/mL to 9.69 ng/mL; p less than 0.001). No side effects were noted (Milewicz et al, 1993).

b) Vitex agnus castus and pyridoxine caused a similar reduction on the premenstrual tension scale (PMTS) in a randomized, controlled trial of 127 women with PMTS. Patients taking Vitex agnus castus (Agnolyt(R)) experienced more relief from breast tenderness, inner tension, headache, edema, constipation, and depression than those taking pyridoxine. Patients in the Vitex agnus castus group receive one capsule of Agnolyt(R) and one placebo capsule daily for 3 menstrual cycles. Patients in the pyridoxine group received one placebo capsule twice daily on days 1-15 of the menstrual cycle and pyridoxine 100 mg twice daily on days 16 to 35 of the menstrual cycle for 3 menstrual cycles. Unspecified gastrointestinal disturbances occurred in the treatment group along with two cases of skin reaction and one transient headache (Lauritzen et al, 1997).

c) In vitro, Vitex (Agnus castus) was found to bind to the D2 receptor in rat pituitary cell cultures. Basal prolactin release was significantly inhibited by 0.5 milligram (mg) and 1 mg of Vitex extract/mL culture medium (p less than 0.05). Agnus castus extract doses from 0.125 mg/mL to 1 mg/mL significantly suppressed prolactin release in cells stimulated by thyrothropin releasing hormone (TRH) (p less than 0.05). Dopaminergic action was demonstrated in the rat corpus striatum membrane dopamine receptor assay. Agnus castus extract did not affect basal luteinizing hormone (LH) or follicle-stimulating hormone (FSH), indicating selectivity for prolactin secretion, and not generalized inhibition of pituitary hormone secretion. The effect was not due to a cytotoxic effect as demonstrated by the lack of effect on the MTT-conversion test. The authors concluded that Agnus castus exerted its prolactin inhibiting effect via stimulation of D2 receptors in the pituitary (Jarry et al, 1994).

3.5.1.EK Ziprasidone

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001b). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), pimozide (Prod Info Orap(R), 2000), quetiapine (Owens, 2001c), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2004).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antipsychotics, and thioridazine, is contraindicated.

7) Probable Mechanism: additive QT prolongation

3.5.1.EL Zolmitriptan

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of thioridazine states that thioridazine should not be coadministered with other drugs which are also known to prolong the QTc interval (Prod Info Thioridazine tablets, 2002). Zolmitriptan has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Zomig(R), 2001).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of thioridazine and agents that prolong the QT interval, such as zolmitriptan, is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.EM Zotepine

1) Interaction Effect: increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Although no drug interaction studies have been performed, the manufacturer of thioridazine states that coadministration of thioridazine with drugs known to prolong the QTc interval is contraindicated (Prod Info Mellaril(R), 2001a). Zotepine can prolong the QTc interval (Sweetman, 2004).

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Concurrent administration of agents that prolong the QT interval, such as zotepine and thioridazine, is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Since zotepine can prolong the QT interval it is recommended that an ECG is performed before starting treatment. Patients with pre-existing prolongation of the QT interval should not be given zotepine (Sweetman, 2004).

3.5.1.EN Zotepine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001b). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), pimozide (Prod Info Orap(R), 2000), quetiapine (Owens, 2001c), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antipsychotics, and thioridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.2 Drug-Food Combinations

3.5.2.A Ethanol
1) Interaction Effect: increased central nervous system depression and an increased risk of extrapyramidal reactions
2) Summary: Concomitant administration of ethanol and phenothiazines has been reported to result in additive central nervous system depression (Zirkle et al, 1959; Milner & Landauer, 1971; Fazekas et al, 1955; Sutherland et al, 1960). Neuroleptic-induced extrapyramidal side effects triggered by alcohol have also been reported (Lutz, 1976; Freed, 1981).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Counsel patients on potential for increased risk of central nervous system depression and extrapyramidal side effects, including akathisia and dystonia, when alcohol is ingested with phenothiazines. Patients should be instructed to avoid alcohol consumption while taking phenothiazines.
7) Probable Mechanism: unknown; probable additive CNS depression

3.5.3 Drug-Lab Modifications

Salicylate measurement

Urine chorionic gonadotrophin measurement

3.5.3.A Salicylate measurement
1) Interaction Effect: false positives on salicylate assay in urine
2) Summary: Thioridazine at a concentration of greater than or equal to 2 mg/dl in urine has been demonstrated to result in interference with spectrophotometric screening tests based upon the method of Trinder (Frings, 1973). Thioridazine causes a green color change under these conditions, whereas the screening test is based upon a purple color change caused by salicylates.
3) Severity: minor
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Salicylate spectrophotometric screening tests based upon the method of Trinder should be avoided in patients receiving thioridazine.
7) Probable Mechanism: salicylate assay interference

3.5.3.B Urine chorionic gonadotrophin measurement
1) Interaction Effect: falsely positive or negative pregnancy test results
2) Summary: Interpret pregnancy test results with caution in patients receiving phenothiazines due to the possibility of false-negative or false-positive results for tests based on immunological reactions between human chorionic gonadotropin (HCG) and anti-HCG (Prod Info promethazine hcl oral tablets, 2005). Promethazine administration produced false-positive pregnancy results with the Gravindex(R) method and

false-negative results with the Prepuerin(R) and DAP-test(R) methods when administered to patients or added to urine specimens or serum in vitro (Tait, 1971). In one study, where 3 major phenothiazine groups (dimethylamines (chlorpromazine), piperazines (perphenazine, carphenazine, trifluoperazine, fluphenazine), and piperidines (thioridazine)), were given to both male and female subjects as monotherapy for at least one week, HCG(R) tests consistently gave false positive results for all 3 categories of phenothiazines in both males and females (Ravel et al, 1969).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Phenothiazines may cause false-negative or false-positive results for pregnancy tests based on immunological reactions between human chorionic gonadotropin (HCG) and anti-HCG (Prod Info promethazine hcl oral tablets, 2005; Tait, 1971). Drug therapy should be evaluated when interpreting pregnancy test results.

7) Probable Mechanism: interference based on immunological reactions between human chorionic gonadotropin (HCG) and anti-HCG

8) Literature Reports

a) Promethazine administration produced false-positive results with the Gravindex(R) method and false-negative results with the Prepuerin(R) and DAP-test(R) methods when administered to patients or added to urine specimens or serum in vitro (Tait, 1971). Results indicate promethazine may interfere with latex agglutination with the Gravindex(R) and DAP-tests(R), leading to false-positive and false-negative results, respectively. With the Prepuerin(R) method, promethazine inhibited disagglutination of red cells, causing false-negative results. Of the three tests, the DAP-test(R) was most affected by promethazine, giving false results 50% of the time. In the DAP-test(R), agglutination is reduced by promethazine as it reacts with HCG, thereby not permitting it to bind the anti-HCG on the latex particles, leading to false-negative results.

b) Urine pregnancy tests were evaluated on both men and nonpregnant women who were receiving a phenothiazine as monotherapy for at least one week. All three major phenothiazine groups were represented in this study: dimethylamines (chlorpromazine), piperazines (perphenazine, carphenazine, trifluoperazine, fluphenazine), and piperidines (thioridazine). Commercially available urine pregnancy tests which were used included Gravindex(R), HCG(R) test, Natatel(R), UCG(R), Pregslide(R), and DAP(R). Results showed that the HCG(R) test consistently gave false positive results in all three categories of phenothiazines, both in male and female subjects. In some of the false-positive HCG(R) cases, retesting the same urine specimen produced negative findings, while others confirmed the initial false-positive result. The authors concluded that drug effects should be thoroughly evaluated on any pregnancy test (Ravel et al, 1969).

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) Thioridazine Hydrochloride

1) Therapeutic

a) Physical Findings

1) Decrease in severity or elimination of target psychotic symptoms:

a) Positive psychotic symptoms (delusions, auditory hallucinations, racing thoughts)

b) Negative psychotic symptoms (anhedonia, apathy, lack of motivation, ambivalence).

2) Improvement in socialization, grooming, and attention to activities of daily living.

2) Toxic

a) Laboratory Parameters

1) Complete blood counts (every 6 months)

2) Hepatic function tests (every 6 months)

3) Baseline serum potassium levels with periodic evaluations during therapy, especially when making dose adjustments

b) Physical Findings
1) Abnormal involuntary movement scale (AIMS) examination or similar test for tardive dyskinesia every 6 months.
2) Assessment for extrapyramidal symptoms (EPS) during dose adjustment and every 3 months.
3) Periodic eye examination for ocular changes (retinopathy)
4) Baseline EKG evaluation for QTc-interval prolongation with periodic evaluations during therapy, especially when making dose adjustments

4.2 Patient Instructions

A) Thioridazine (By mouth)

Thioridazine

Treats the symptoms of schizophrenia.

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to thioridazine, if you have a history of heart rhythm problems or extreme high or low blood pressure, or if you have a genetic defect involving an enzyme called cytochrome P450. You should not take thioridazine if you are also taking medicines for depression (such as amitriptyline, Paxil®, Prozac®, Zoloft®), blood pressure medicine (such as atenolol, metoprolol, propranolol), medicines for heart rhythm problems, or other antipsychotic medicines (Haldol®, Risperdal®). There are many other medicines, including over-the-counter medicines, that you should not use while you are taking thioridazine. Make sure your doctor knows about all other medicines you are using.

How to Use This Medicine:
Tablet, Liquid
Your doctor will tell you how much of this medicine to take and how often. Your dose may need to be changed several times in order to find out the what works best for you. Do not take more medicine or take it more often than your doctor tells you to.
Measure the oral liquid medicine with a marked measuring spoon or medicine cup, or use the dropper that came with the medicine.
You may mix the oral liquid concentrate with a half glass of distilled water or orange juice. Mix only enough medicine for one dose and drink all the liquid right away.

If a Dose is Missed:
If you miss a dose or forget to take your medicine, take it as soon as you can. If it is almost time for your next dose, wait until then to take the medicine and 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 at room temperature in a closed container, away from heat, moisture, and direct light. Do not freeze.
Keep all medicine out of the reach of 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.
Certain drugs should not be used while using thioridazine. Using these drugs can cause very serious medical problems, heart problems, or even death.
Avoid drinking alcohol.
Make sure your doctor knows if you are using any medicines that make you sleepy (such as sleeping pills, cold and allergy medicine, narcotic pain killers, or sedatives).

Warnings While Using This Medicine:
If you are pregnant or breast feeding, talk to your doctor before taking this medicine. False positive (incorrect) pregnancy tests have been reported in patients taking this medicine.
Check with your doctor before taking thioridazine if you have an unusually slow heartbeat, low levels of potassium in your blood, seizures, or heart disease, or if you have ever had breast cancer. Also, tell your doctor if you have ever had a reaction to similar medicines, such as Thorazine® or Trilafon®.
Thioridazine can make some people feel dizzy or drowsy. Be careful if driving a car or operating machinery.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Dizziness, fainting
Fever, severe muscle stiffness, excessive sweating
Irregular or fast heartbeat
Muscle spasms of the neck, face, or tongue, or other body movements you cannot control
Severe chest pain
Trouble breathing

Unusual bleeding or bruising, seizures (convulsions)

If you notice these less serious side effects, talk with your doctor:
Changes in menstrual cycle
Changes in vision, such as trouble focusing, changes in how you see colors, or trouble seeing at night
Dry mouth
Lightheadedness, especially when standing up
Nausea, vomiting, diarrhea, or constipation
Sleepiness
Tremors or shaking

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

4.3 Place In Therapy

A) Thioridazine

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

B) Thioridazine Hydrochloride

1) Current users of atypical antipsychotic drugs and typical antipsychotic drugs (including thioridazine) 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 thioridazine users in 15,715 person-years was 3.19 (95% CI, 2.41 to 4.21, 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 typical antipsychotic use, the incidence rate ratio increased from 1.31 (95% CI, 0.97 to 1.77) in low-dose use to 2.42 (95% CI, 1.91 to 3.06) 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).

2) Thioridazine (Mellaril(R)) is FDA labeled for use ONLY in schizophrenic patients who fail to respond adequately to treatment with other antipsychotic drugs. These restrictions are due to the increased risk of significant, potentially life-threatening, proarrhythmic effects associated with thioridazine therapy. The manufacturer recommends at least 2 drug trials, each with a different antipsychotic, be conducted prior to the initiation of treatment with thioridazine (Prod Info Mellaril(R), 2000).

3) Thioridazine is a phenothiazine with weak potency as an antipsychotic agent. It also has a low incidence of extrapyramidal symptoms, but has a high incidence of sedation, anticholinergic effects, and cardiovascular effects.

4) Clinical evidence demonstrates that all of the commonly marketed neuroleptic agents have therapeutic equivalence when adequate doses are utilized (Baldessarini, 1985). When a flexible dosage regimen is used to titrate the chosen agent to maximum effect, all neuroleptics will demonstrate statistical equivalence in a study population. However, one agent may be effective while another will not. Pharmacokinetic and pharmacodynamic differences as well as possible multiple etiologies of the patient's schizophrenia may be reasons for the individual variance (Young & Koda-Kimble, 1988). The patient's past medication history of neuroleptic agents should play an important role in drug selection. The patient's subjective response to neuroleptics should also be used in deciding on a specific agent. Lastly, adverse effects may determine drug selection. Side effects vary in incidence and severity among antipsychotic agents and avoidance of specific effects may determine drug selection.

4.4 Mechanism of Action / Pharmacology

A) Thioridazine Hydrochloride

1) MECHANISM OF ACTION

a) Thioridazine is a piperidine phenothiazine, which is effective in controlling psychotic symptoms of schizophrenia. It is believed to work by blocking post synaptic dopamine (D2) receptors in the brain, especially in the mesolimbic and mesocortical tracts. Thioridazine possesses calcium antagonist activity which may relate to its cardiac and sexual side effects (Gould et al, 1984).

4.5 Therapeutic Uses

4.5.A Thioridazine Hydrochloride

Behavioral syndrome

Borderline personality disorder

Dementia

Depression

Female infertility

Schizophrenia, Refractory

4.5.A.1 Behavioral syndrome

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 A; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Thioridazine (Mellaril(R)) is no longer approved by the FDA for the treatment of behavioral problems due to its potential for significant proarrhythmic effects
Has been used for the treatment of multiple symptoms such as agitation, anxiety, depressed mood, tension, sleep disturbances, and fears in geriatric patients
Use with caution in the treatment of agitation or behavior problems in cognitively impaired patients
Overall efficacy has been modest and use exposes patients to major risks (Eimer, 1992)

c) Adult:

1) A meta-analysis of 7 double-blind studies showed that thioridazine is not more effective than placebo or other neuroleptic drugs for improving behavioral-, global clinical-, or cognitive-states of elderly patients with dementia (Kirchner et al, 1999). Anxiety scores were improved in more patients receiving thioridazine than placebo (p less than 0.0001) or diazepam (p=0.03). However, no comparisons were reported regarding adverse effects of thioridazine versus diazepam.

2) Two agitated patients with ALZHEIMER'S DISEASE failed to respond or worsened with conventional, low-dose neuroleptic treatment (thioridazine 25 milligrams as needed). Both patients showed sustained improvement with very low-dose neuroleptics (haloperidol 0.125 milligram, thioridazine 5 milligrams). Clinical, pharmacokinetic and pharmacodynamic factors may have been responsible for this positive response (Risse et al, 1987).

3) Chlormethiazole and thioridazine were found to be equally effective in the management of the agitation component of agitated confusional states in the elderly. Confusion and nocturnal awakening were controlled more effectively with chlormethiazole than with thioridazine. Chlormethiazole also caused less physical disability than thioridazine (Ather et al, 1986a).

4) Thioridazine and loxapine were only modestly effective in controlling anxiety, excitement, emotional lability, and uncooperativeness in nursing home patients with dementia. Patients with the most severe symptoms responded the best. Sedation, EPS, and hypotension were commonly occurring side effects (Barnes et al, 1982).

d) Pediatric:

1) Thioridazine has been used to control SELF-ABUSIVE BEHAVIOR in mentally retarded patients in daily doses up to 400 milligrams (Heistad et al, 1982). Thioridazine tablets were shown to be equally effective to thioridazine suspension in the treatment of emotionally-disturbed/retarded children (Jakab, 1984).

2) In a double-blind study of 30 children with subaverage IQs and psychiatric diagnoses of attention deficit disorder (ADD) and/or conduct disorder (CD), clinical response to METHYLPHENIDATE (MP) was greater than the response to THIORIDAZINE (TDZ). Each treatment was given for 3 weeks. The dosage of MP was 0.4 mg/kg/day and that for TDZ was 1.75 milligrams/kilogram/day. Significant improvements were confined to conduct and hyperactivity problems according to teacher ratings (Aman et al, 1991).

4.5.A.2 Borderline personality disorder

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:
Patients with borderline personality disorder were less symptomatic while on thioridazine

c) Adult:
1) Thioridazine (TDZ) exerted prominent effects on 11 outpatients (8 female, 3 male) with Borderline Personality Disorder (BPD) in a 12-week open study. Mean TDZ dose was 92 milligrams/day for the duration of the study. At endpoint, there was a significant reduction in BPRS scores and patients appeared to be less symptomatic on the impulse action patterns, affects, and psychosis subscales of the Diagnostic Interview for Borderline Patients (DIB). Subjects completing the entire study (N=6) also showed improvement in interpersonal relations. Weight gain was not a significant problem, but sedation and erectile dysfunction were problematic (Teicher et al, 1989).

4.5.A.3 Dementia
See Drug Consult reference: BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

4.5.A.4 Depression
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:
Thioridazine (Mellaril(R)) is no longer approved by the FDA for the treatment of depression due to its potential for significant proarrhythmic effects
Has been used for the short-term treatment of moderate to marked depression with variable degrees of anxiety
First and second generation antidepressants are preferred

c) Adult:
1) Combination therapy with thioridazine and desipramine was reported to produce greater improvement in depressive symptoms than desipramine alone (Bennett et al, 1984a). Fourteen patients received a constant dose of DESIPRAMINE (200 milligrams daily) for 21 days, while 7 patients received additional thioridazine (100 milligrams daily) for the first 7 days of treatment. Greater improvement over baseline on the Hamilton Depression Scale was observed during the first 7 days with concomitant therapy.

4.5.A.5 Female infertility
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:
Improve infertility in one study
Effect may be explained by anxiolytic properties at low dosage

c) Adult:
1) Thioridazine was used to treat unexplained infertility (Sharma & Sharma, 1992). From a total of 452 women with unexplained infertility, 310 were given one 5-milligram thioridazine tablet one hour after dinner from the eighth to the 18th day of the menstrual cycle. Coitus was advised 1 to 2 hours after ingestion of the tablet. One hundred forty-two patients were given placebo along with the same instructions. At one-year follow-up, 30% of the study group conceived compared with 15% of the control group. Incidence of abortions, congenital malformations, and mode of delivery were not significantly different in the two groups.

4.5.A.6 Schizophrenia, Refractory
FDA Labeled Indication

a) Overview
FDA Approval: Adult, yes; Pediatric, yes
Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Indicated for the management of schizophrenia in patients who have failed to respond to other

antipsychotic agents
The association between thioridazine and QT interval prolongation resulted in the designation of the drug for use following failure of treatment with other antipsychotic agents
The efficacy of thioridazine in refractory schizophrenia is not known

c) Adult:

1) Thioridazine therapy for new-onset psychosis in five HIV-positive men produced modest, but significant reduction in overall level of psychosis and in positive symptoms, but not in negative symptoms (Sewell et al, 1994a). The mean daily dose of thioridazine was 145 milligrams. Three of the five patients developed noticeable side effects.

2) Seven patients with refractory schizophrenia who failed to respond to chlorpromazine 1800 milligrams/day responded to mesoridazine 400 milligrams/day (3 patients) and thioridazine 800 milligrams/day (4 patients) as assessed by the Brief Psychiatric Rating Scale. A higher neuroleptic blood level was achieved with mesoridazine or thioridazine at less than half the reference chlorpromazine dosage. Correlations between neuroleptic blood level and clinical response were positive for mesoridazine, negative for chlorpromazine, and non-significant for thioridazine. Drug-resistant schizophrenic patients seem to improve with mesoridazine or thioridazine. This difference may be a function of the selective dopamine receptor blockade by mesoridazine (Vital-Herne et al, 1986).

d) Pediatric:

1) Of 21 schizophrenic adolescents given thiothixene or thioridazine, many responded poorly or experienced sedation. Because sedation necessitates dose reductions which limit therapeutic response, high potency neuroleptics may be preferable to the more sedating, low potency drugs for schizophrenic adolescents (Realmuto et al, 1984a).

4.6 Comparative Efficacy / Evaluation With Other Therapies

Bromazepam

Chlormethiazole

Chlorprothixene

Desipramine

Diazepam

Haloperidol

Mesoridazine

Methylphenidate

Molindone

Periciazine

Remoxipride

Thiothixene

4.6.A Bromazepam

4.6.A.1 Anxiety

a) Thioridazine was inferior to bromazepam in a study of 80 outpatients with various anxiety, phobic, and obsessive-compulsive disorders. Bromazepam was more effective in controlling anxiety symptoms and was more "activating" than thioridazine. Symptoms of hostility responded better to thioridazine (Dencker & Fasth, 1986).

4.6.B Chlormethiazole

4.6.B.1 Delirium

a) Chlormethiazole and thioridazine were found to be equally effective in the management of the agitational

component of agitated confusional states in the elderly. Confusion and nocturnal awakening were controlled more effectively with chlormethiazole than with thioridazine. Chlormethiazole also caused less physical disability than thioridazine (Ather et al, 1986).

4.6.C Chlorprothixene

4.6.C.1 Behavioral syndrome

a) Chlorprothixene was more effective than thioridazine in controlling behavioral symptoms such as aggressiveness, hostility, and hyperactivity. Chlorprothixene (up to 375 milligrams/day) was compared with thioridazine (up to 375 milligrams/day) in a 12-week, double-blind, crossover study involving 59 patients with mental retardation (LeVann, 1970).

4.6.D Desipramine

4.6.D.1 Depression

a) Combination therapy with thioridazine and desipramine was reported to produce greater improvement in depressive symptoms than desipramine alone (Bennett et al, 1984). Fourteen patients received a constant dose of desipramine (200 milligrams daily) for 21 days, while 7 patients received additional thioridazine (100 milligrams daily) for the first 7 days of treatment. Greater improvement over baseline on the Hamilton Depression Scale was observed during the first 7 days with concomitant therapy.

4.6.E Diazepam

Anxiety

Behavioral syndrome

4.6.E.1 Anxiety

a) Diazepam was more effective for anxiety symptoms in 47 patients who were treated with diazepam 4 to 40 milligrams every day and thioridazine 20 to 200 milligrams every day to relieve mixed anxiety depressive symptoms (Rosenthal & Bowden, 1973).

b) In 36 patients with anxiety or depression, no difference was found between diazepam 5 to 10 milligrams 3 to 4 times daily and thioridazine 25 to 50 milligrams 3 to 4 times daily in the relief of symptoms (Schuster et al, 1972).

4.6.E.2 Behavioral syndrome

a) One study reported the superiority of oral thioridazine (10 to 200 milligrams daily) over oral diazepam (2 to 40 milligrams daily), and placebo, in the treatment of emotional and behavioral disorders in elderly, non-psychotic patients in geriatric wards, state hospitals, or nursing homes (Stotsky, 1984). Greater improvement in the majority of symptoms assessed by the Hamilton Anxiety Scale and NOSIE were observed in patients receiving thioridazine.

4.6.F Haloperidol

4.6.F.1 Psychotic disorder

a) In a single-blind, randomized parallel study lasting six weeks, haloperidol (mean dose of 2.9 milligrams/day) was compared with thioridazine (mean dose of 145 milligrams/day) in 13 patients with psychosis associated with HIV infection. Based on several scales for assessing psychoses, the two drugs produced modest improvement, but were not statistically different in the outcomes produced. All haloperidol-treated patients developed extrapyramidal side effects, while 60% of those taking thioridazine developed them (Sewell et al, 1994).

4.6.G Mesoridazine

4.6.G.1 Schizophrenia

a) Mesoridazine has been compared with its parent compound, thioridazine, and has been found to be similar in therapeutic effect and toxicity in the treatment of chronic schizophrenia. Available data indicate that, although the drug appears to be 2 to 3 times more potent on a milligram basis, there appears to be no significant or marked clinical differences or advantages with either of the 2 drugs (Prusmack, 1966; Mena et al, 1966).

b) Mesoridazine 50 to 400 milligrams daily provided a significantly greater improvement in somatic concern, hostility, suspiciousness, and retardation factor in chronic schizophrenic patients compared with thioridazine 100 to 800 milligrams daily (Gardos et al, 1978).

c) Mesoridazine may be effective in schizophrenic patients refractory to treatment with thioridazine. This may be related to its slow rate of inactivation and to the relatively large proportion of free mesoridazine that

is available for penetration to the target sites in the brain (Gershon, 1981).

4.6.H Methylphenidate

1) Adverse Effects

a) One group of investigators reported a controlled study of methylphenidate and thioridazine in improving cognitive and motor performance in intellectually subaverage children. Twenty-seven children with subaverage IQs participated in a double-blind, placebo-controlled, cross-over study comparing methylphenidate (0.4 milligrams/kilogram/day and thioridazine (1.75 milligrams/kilogram/day. The children were tested for IQ performance, breadth of attention, and performance on a series of electronically-controlled cognitive-motor tests. Methylphenidate improved accuracy on a memory task, reduced omission errors on an attentional task, and reduced seat movements on two tasks. Thioridazine had no significant effects in improving cognitive-motor performance. It did not produce deleterious effects on IQ performance when subjects received reinforcers for correct answers. Thioridazine at the given dose did not adversely effect performance on any of the cognitive-motor performance tests (Aman et al, 1991).

4.6.I Molindone

4.6.I.1 Disruptive behavior disorder

a) Molindone and thioridazine were equally efficacious in an 8-week, double-blind, placebo-controlled, parallel design study that compared molindone (n=15) with thioridazine (n=16) in 31 aggressive male children with conduct disorder (Greenhill et al, 1985). Both drugs resulted in significant improvement in Aggression Scale score and CPRS evaluation of hostility and antisocial and violent behavior when compared to the placebo periods before and after the 4-week treatment cycle. The overall mean molindone dose was 1.3 milligrams/kilogram/day and the thioridazine mean dose was 4.64 milligrams/kilogram/day.

4.6.J Periciazine

Psychotic disorder, chronic

Schizophrenia

4.6.J.1 Psychotic disorder, chronic

a) Neither periciazine (40 to 60 mg daily) nor thioridazine (200 to 300 mg daily) produced significant improvement (BPRS scales) in the symptomatology of chronic psychosis patients in one study (Deutsch et al, 1971). Failure was ascribed to subtherapeutic doses of each agent.

4.6.J.2 Schizophrenia

a) Available comparisons do not suggest any advantage of oral periciazine daily over oral thioridazine in the management of chronic schizophrenic patients (Anon, 1967; Barker & Miller, 1969; Deutsch et al, 1971). Periciazine has tended to be superior for paranoid delusions, although the significance of this is doubtful.

4.6.K Remoxipride

4.6.K.1 Schizophrenia

a) SUMMARY: One controlled study has reported the overall similar efficacy of remoxipride and thioridazine in schizophrenia; however, definite trends toward the superiority of thioridazine were observed.

b) The efficacy of remoxipride and thioridazine were compared in the treatment of acute schizophrenia in a double-blind study involving 61 patients (McCreadil et al, 1988). Following discontinuance of previous medication and a 7-day placebo period, patients were randomized to receive either remoxipride 25 to 125 mg three times daily or thioridazine 50 to 250 mg three times daily for a 6-week period. All patients were inpatients for the first 4 weeks of therapy. No statistically significant difference was seen between the 2 agents on the Brief Psychiatric Rating Scale (BPRS), although there was a definite trend in favor of thioridazine over remoxipride. Both drugs produced similar reductions in positive symptoms, including hallucinations and unusual thought content. Mean maintenance doses during the study were 238 mg daily for remoxipride and 440 mg daily for thioridazine. General adverse effects were observed more frequently in thioridazine patients, including sedation, anticholinergic effects, autonomic dysfunction, and weight gain. Akathisia appeared more severe in remoxipride treated patients. Sleep disorder was more frequent in the remoxipride group, and breast swelling and galactorrhea were observed with remoxipride but not with thioridazine. Orthostatic hypotension (n=1) and ECG changes (n=2) were reported in remoxipride-treated patients. ECG abnormalities were seen in 2 thioridazine-treated patients. This study suggests that in the doses employed remoxipride is, at best, as effective as thioridazine. Definite trends toward the superiority of thioridazine were observed. Adverse effects in general were less with remoxipride; extrapyramidal effects appeared similar with each drug.

c) The efficacy and safety of remoxipride (RMX) were compared with that of thioridazine (TDZ) in 18 hospitalized elderly psychotic patients. Patients ranged in age from 66 to 90 years (median=78). Over the 6-

week study period, 9 patients each received either RMX or TDZ in a dosage range of 50 to 200 milligrams/day. Responses using the BPRS and CGI indicated that both treatments were effective in reducing psychotic symptoms over the 6-week study. Adverse effects were "low" in both groups with the exception of severe drowsiness in 3 TDZ patients. It was concluded that remoxipride was well-tolerated in the elderly and its efficacy in the dosage used was promising (Phanjoo & Link, 1990).

4.6.L Thiothixene

4.6.L.1 Schizophrenia

a) Thiothixene and thioridazine had comparable efficacy in a double-blind study in 21 adolescent schizophrenic patients. Many in both groups responded poorly. The patients in the thioridazine group experienced much more sedation which necessitated dosage reductions which could potentially limit therapeutic response. The results suggest that the two drugs were equally effective, but that high potency neuroleptics (such as thiothixene) may be preferred in adolescents because of less dose-limiting sedation as opposed to low potency drugs (such as thioridazine) (Realmuto et al, 1984).

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