DRUGDEX® Evaluations

DOXEPIN

0.0 Overview

1) Class

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

Antianxiety
Antidepressant
Antidepressant, Tricyclic
Antiulcer
Dermatological Agent

2) Dosing Information

a) Doxepin Hydrochloride

1) Adult

a) Alcoholism - Anxiety - Depression

1) very mild, 25 to 50 mg/day ORALLY initially, gradually increase as needed (max, 300 mg/day) (Prod Info SINEQUAN(R) capsule, oral concentrate, 2005)

2) mild to moderate, 75 mg ORALLY per day in single or divided doses, increase as needed; usual range is 75 to 150 mg/day (max, 300 mg/day) (Prod Info SINEQUAN(R) capsule, oral concentrate, 2005)

b) Anxiety - Depression

1) very mild, 25 to 50 mg/day ORALLY initially, gradually increase as needed (max, 300 mg/day) (Prod Info SINEQUAN(R) capsule, oral concentrate, 2005)

2) mild to moderate, 75 mg ORALLY per day in single or divided doses, increase as needed; usual range is 75 to 150 mg/day (max, 300 mg/day) (Prod Info SINEQUAN(R) capsule, oral concentrate, 2005)

c) Anxiety - Depression - Psychoneurotic personality disorder

1) outpatients: 75 mg/day ORALLY (divided into 1-3 doses); may increase up to a MAX of 150 mg/day

2) inpatients: 150 mg/day ORALLY (divided into 1-3 doses); may increase up to a MAX of 300 mg/day

d) Pruritus (Moderate), Due to atopic dermatitis or lichen simplex chronicus

1) 10 mg ORALLY at bedtime; may gradually increase to 25 mg ORALLY at bedtime

2) apply a thin film TOPICALLY to skin 4 times a day (3-4 hr between applications) for a MAX of 8 days

2) Pediatric

a) safety and effectiveness in children below the age of 12 years have not been established

1) Alcoholism - Anxiety - Depression

a) (12 years and older) very mild, 25 to 50 mg/day ORALLY initially, gradually increase as needed (max, 300 mg/day) (Prod Info SINEQUAN(R) capsule, oral concentrate, 2005)

b) (12 years and older) mild to moderate, 75 mg ORALLY per day in single or divided doses, increase as needed; usual range is 75 to 150 mg/day (max, 300 mg/day) (Prod Info SINEQUAN(R) capsule, oral concentrate, 2005)

2) Anxiety - Depression

a) (12 years and older) very mild, 25 to 50 mg/day ORALLY initially, gradually increase as needed (max, 300 mg/day) (Prod Info SINEQUAN(R) capsule, oral concentrate, 2005)

b) (12 years and older) mild to moderate, 75 mg ORALLY per day in single or divided doses, increase as needed; usual range is 75 to 150 mg/day (max, 300 mg/day) (Prod Info SINEQUAN(R) capsule, oral concentrate, 2005)

3) Contraindications

a) Doxepin Hydrochloride

1) glaucoma (Prod Info SINEQUAN(R) oral capsules, 2007)

2) hypersensitivity to doxepin, other dibenzoxepines, or any component of the product (Prod Info SINEQUAN(R) oral capsules, 2007)

3) urinary retention (Prod Info SINEQUAN(R) oral capsules, 2007)

4) Serious Adverse Effects

a) Doxepin Hydrochloride

1) Agranulocytosis
2) Depression, worsening
3) Hypertension
4) Hypotension
5) Leukopenia
6) Pancytopenia
7) Purpuric disorder
8) Suicidal thoughts
9) Suicide
10) Tachyarrhythmia

11) Thrombocytopenia

5) Clinical Applications
a) Doxepin Hydrochloride
1) FDA Approved Indications
a) Alcoholism - Anxiety - Depression
b) Anxiety - Depression
c) Anxiety - Depression - Psychoneurotic personality disorder
d) Pruritus (Moderate), Due to atopic dermatitis or lichen simplex chronicus

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
Doxepin
Doxepin HCl
Doxepin Hydrochloride
C) Physicochemical Properties
1) Molecular Weight
a) 316 (Prod Info Zonalon, 94)

1.2 Storage and Stability

A) Oral route
1) Preparation and storage of bulk dilutions of the concentrate is not recommended (Prod Info Sinequan(R), 2004).
2) Store capsules at a controlled room temperature of 15 to 30 degrees Celsius (59 to 86 degrees Fahrenheit). Dispense in a tight, light-resistant container with a child-resistant closure (Prod Info Adapin(R), 1995).
3) Store doxepin topical cream at or below 27 degrees C (80 degrees F) (Prod Info Zonalon(R), 2004).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Geriatric Patients

Dosage Adjustment During Dialysis

1.3.1 Normal Dosage

1.3.1.A Doxepin Hydrochloride

Oral route

Rectal route

Topical application route

1.3.1.A.1 Oral route

Anxiety - Depression

Urticaria

1.3.1.A.1.a Anxiety - Depression

1) Dosage ranges of 75 to 150 milligrams daily have been shown effective in anxiety associated with depression (Goldberg & Finnerty, 1972; Smith, 1971); (Goldstein, 1973)(Goldstein & Pinosky, 1969).

2) Doxepin in doses of 200 milligrams daily also have been shown effective and well tolerated in the elderly for anxiety-depression states (Bohlau et al, 1972).

3) Anxiety patients with psychotic symptoms may require higher doses than with neurotic illness (Pinder et al, 1977e).

4) DEPRESSION

a) Dosage must be individualized. Usual dosage range for outpatients is 75 to 150 milligrams daily and for hospitalized patients 150 to 300 milligrams daily (Grof et al, 1974; Bianchi et al, 1971a; Kiev, 1974; Gillmer, 1970). Additional therapeutic benefit is rarely obtained by using more than 300 milligrams/day (Prod Info Sinequan(R), 2004)(Prod Info Adapin(R), 1995a). However, initial and maintenance doses of 500 milligrams daily have been used (Krakowski, 1968).

b) Pulse dosing of doxepin (250 milligrams every 6 days) has not been found to be more effective than conventional dosing (Deuschle et al, 1997).

c) For patients on once-a-day dosing, the maximum recommended dose is 150 milligrams/day, usually given at bedtime (Prod Info Sinequan(R), 2004).

1.3.1.A.1.b Urticaria

1) Doxepin in doses of 10 to 30 milligrams orally daily has been effective in the treatment of IDIOPATHIC COLD URTICARIA (Neittaanmaki et al, 1984a).

2) Doxepin 5 milligrams orally twice daily was reported effective in the treatment of chronic idiopathic URTICARIA in a controlled study (Harto et al, 1985; Ledo et al, 1985).

3) Doxepin 25 milligrams orally three times daily was effective in the treatment of CHRONIC IDIOPATHIC URTICARIA in a placebo-controlled trial involving 16 adult patients (Goldsobel et al, 1986).

1.3.1.A.2 Rectal route

1.3.1.A.2.a Cancer pain; Adjunct

1) Doxepin capsules were administered rectally in four severely debilitated cancer patients with clinical neuropathic pain (Storey & Trumble, 1992). Commercially available capsules without modification were inserted rectally. Serum concentrations of N-desmethyldoxepin after two to five days of treatment with a constant dose of doxepin were 573 micrograms/milliliter and 403 micrograms/milliliter (with 50 milligrams three times daily), 204 micrograms/milliliter (with 50 milligrams twice daily) and less than 25 micrograms/milliliter (with 25 milligrams daily).

1.3.1.A.3 Topical application route

1.3.1.A.3.a Pruritus (Moderate), Due to atopic dermatitis or lichen simplex chronicus

1) Doxepin cream (5%), applied four times a day, with at least 3 to 4 hour intervals between applications, provides effective short-term (up to 8 days) management of moderate pruritus in adults with atopic dermatitis and lichen simplex chronicus (Prod Info Zonalon(R), 2004). Occlusive dressings should not be used with doxepin cream as it may increase dermal absorption.

1.3.1.A.4 MUCOSAL LOCAL

a) ORAL MUCOSAL PAIN

1) Five milliliters of a solution of doxepin 5 milligrams/milliliter, held in the mouth for 5 minutes and spat out, relieved mucosal pain in patients (n=41) with mucosal damage caused by cancer or cancer treatment. Relief lasted for more than 3 hours (Epstein et al, 2001).

1.3.1.A.5 LONG-TERM THERAPY

a) Long-term maintenance therapy with doxepin is safe and effective (Ayd, 1975a). Forty patients (31 to 73 years of age) were treated with doxepin 50 to 300 milligrams daily over a period of 57 to 93 months (total dose 194, 100 to 508, 500 milligrams) for recurrent depression. All patients experienced mood elevation, improved sleep and appetite, and increased energy and interest. Laboratory values revealed no serious toxicity and blood pressure was not significantly affected throughout therapy. Transient tachycardia with doses greater than 200 milligrams daily occurred in several patients and

weight gain in the first 6 months in a few other patients. Otherwise, adverse reactions were minimal.
b) Doxepin therapy has been used continuously for up to 15 years in the treatment of chronic depressive illness, with maintenance of efficacy and a low order of toxicity. Continuous therapy for 5 to 15 years in 52 patients did not reveal any changes in hematologic, renal or hepatic function tests, and the drug was well tolerated in patients with concomitant cardiovascular disorders (Ayd, 1984).

1.3.1.A.6 ONCE DAILY DOSING

a) The major portion or total daily dose of doxepin administered at bedtime is effective and may be of benefit in decreasing the incidence of daytime drowsiness. SINGLE BEDTIME DOSE is also of benefit in patients with mixed anxiety-depression with resultant sleep disturbances (Goldberg et al, 1974; Mendels & Schless, 1975). If the once-a-day schedule is used, the maximum daily dose is 150 milligrams/day (Prod Info Adapin(R), 1995a).

1.3.1.A.7 ORAL CONCENTRATE DILUTION

a) Doxepin oral concentrate should be diluted just prior to administration, with 120 milliliters water, skim milk, whole milk, orange juice, grapefruit juice, tomato juice, prune juice, or pineapple juice (Prod Info Sinequan(R), 2004).
b) Doxepin oral concentrate is not compatible in many carbonated beverages (Prod Info Sinequan(R), 2004).
c) Patients who are on methadone maintenance and require doxepin concentrate can mix the methadone and doxepin together and then dilute the mixture in Gatorade(R), lemonade, orange juice, sugar water, Tang(R), or water. Grape juice should not be used (Prod Info Sinequan(R), 2004).

1.3.1.A.8 WITHDRAWAL SCHEDULE

a) Delirium upon abrupt withdrawal of doxepin has been reported in a single case (Santos and McCurdy, 1980). After 2 weeks of therapy for depression, doxepin was abruptly discontinued because of lack of response and undue sedation. Two days later, the patient exhibited impaired attention, concentration, and short-term memory. He was agitated and moderately diaphoretic. Two days later, an abnormal EEG was recorded. Symptoms disappeared and the EEG returned to normal in 2 weeks. The patient had also been taking disulfiram, which could have contributed to the reaction.
b) Gradual reduction in dosage will prevent development of withdrawal symptoms (Prod Info Adapin (R), 1995a).

1.3.2 Dosage in Renal Failure

A) Doxepin Hydrochloride

1) Based upon the small amount of doxepin excreted unchanged in the urine, no dosage adjustment would appear to be necessary (Bennett et al, 1994a).

1.3.3 Dosage in Hepatic Insufficiency

A) Doxepin Hydrochloride

1) Data for other tricyclic antidepressants suggests the use of doxepin in patients with liver disease may result in increases in the incidence of adverse reactions. Dosage should be reduced and adjusted gradually.

1.3.4 Dosage in Geriatric Patients

A) Doxepin Hydrochloride

1) Caution should be taken when selecting a dosage schedule in an elderly patient. Therapy should be initiated on the low end of the dosing range to account for decreased hepatic, renal, or cardiac function or concomitant diseases/drug regimens that may be present in this patient population (Prod Info Sinequan(R), 2004)(FDA, 2000).
2) Dosage should be individualized with adjustments based upon patient response. Initial dosage should be 25 to 50 milligrams with adjustments made gradually (Pinder et al, 1977e).
3) Clinical guidelines for utilizing antidepressants in the treatment of depression in geriatric patients have been reviewed (Salzman, 1985).

1.3.5 Dosage Adjustment During Dialysis

A) Doxepin Hydrochloride

1) No dosage supplement is required in patients following hemodialysis or peritoneal dialysis (Bennett et al, 1994a).

1.4 Pediatric Dosage

1.4.1 Normal Dosage

1.4.1.A Doxepin Hydrochloride

1.4.1.A.1 Oral route

a) DOXEPIN is not recommended for use in children under 12 years of age (Prod Info Sinequan(R), 2004).

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset

1) Initial Response

a) Depression, oral: 2 to 3 weeks (Gilman et al, 1985b).

1) DOXEPIN may have an onset sooner than other tricyclic antidepressants (Barranco et al, 1979).

b) Anxiety, oral: 5 to 6 days (Pereira & Lipke, 1970)(DuBois, 1969).

2.2 Drug Concentration Levels

A) Therapeutic Drug Concentration

1) Depression, greater than 100 ng/mL (parent compound with active metabolite, desmethyldoxepin) (Amsterdam et al, 1980).

a) Other studies have found no correlation between serum concentration and therapeutic response (Ward et al, 1982; Brunswick et al, 1983; Norman et al, 1980).

b) Therapeutic response has been associated with 20 ng/mL or above of the active metabolite desmethyldoxepin (Pinder et al, 1977b).

B) Time to Peak Concentration

1) Oral: 30 minutes to 1 hour (Pinder et al, 1977b).

2) TOPICAL: 1.32 hours (Drake et al, 1999).

a) Time to peak concentration was 1.32 hours with a maximum concentration of 0.41 mcg/L in 12 subjects with pruritic atopic dermatitis who applied topical DOXEPIN 4 times daily every 4 hours for 7 days (Drake et al, 1999).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

Extracorporeal Elimination

2.3.1 Absorption

A) Bioavailability

1) Oral: well-absorbed (Pinder et al, 1977b).

2) Topical, percutaneous absorption may occur (Prod Info Zonalon(R), 1999).

a) Plasma DOXEPIN concentrations ranged from undetectable to 46 ng/mL in 19 eczema patients using topical doxepin (Prod Info Zonalon(R), 1999).

2.3.2 Distribution

A) Distribution Sites

1) Protein Binding

a) 79% to 84% (Virtanen et al, 1982)

2) OTHER DISTRIBUTION SITES

a) Tissues, initially high in the liver, kidney, spleen and lung. Large amounts of the active metabolite (desmethyldoxepin) also found in tissues (Hobbs, 1969).

B) Distribution Kinetics

1) Volume of Distribution

a) 9 to 33 L/kg (Bennett et al, 1994).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics
1) LIVER
a) DOXEPIN undergoes hepatic metabolism to the active metabolite desmethyldoxepin (Prod Info Zonalon(R), 1999).
B) Metabolites
1) Desmethyldoxepin, active (Pinder et al, 1977b).
2) Doxepin-N-oxide, hydroxydoxepin and hydroxydoxepin glucuronide (Hobbs, 1969).

2.3.4 Excretion
A) Kidney
1) Renal Excretion (%)
a) 0.5% (Kimura, 1972a).
B) Other
1) OTHER EXCRETION
a) Bile, small amounts (Kimura, 1972).

2.3.5 Elimination Half-life
A) Parent Compound
1) ELIMINATION HALF-LIFE
a) 16.8 hours (range: 8 to 25 hours) (Bennett et al, 1994; Faulkner et al, 1983; Amsterdam et al, 1980).
B) Metabolites
1) Desmethyldoxepin, 51.3 hours (range: 33.2 to 80.7 hours) (Amsterdam et al, 1980).
a) Desmethyldoxepin half-life ranges from 28 to 52 hours (Prod Info Zonalon(R), 1999).

2.3.6 Extracorporeal Elimination
A) Hemodialysis
1) Dialyzable: No (Anderson et al, 1976).
a) Only 7.6% of DOXEPIN and 13.9% of desmethyldoxepin is extracted by hemodialysis (Faulkner et al, 1984).
B) Peritoneal
1) Dialyzable: No (Anderson et al, 1976).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING
1) Doxepin Hydrochloride
a) Oral (Capsule; Solution)
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 doxepin hydrochloride 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. Doxepin hydrochloride is not approved for use in pediatric patients (Prod Info SINEQUAN(R) oral capsules, 2007).

3.1 Contraindications
A) Doxepin Hydrochloride
1) glaucoma (Prod Info SINEQUAN(R) oral capsules, 2007)
2) hypersensitivity to doxepin, other dibenzoxepines, or any component of the product (Prod Info SINEQUAN(R)

oral capsules, 2007)
3) urinary retention (Prod Info SINEQUAN(R) oral capsules, 2007)

3.2 Precautions

A) Doxepin Hydrochloride

1) suicidal ideation and behavior or worsening depression; increased risk, particularly in children, adolescents, and young adults during the first few months of therapy or following changes in dosage (Prod Info SINEQUAN(R) oral capsules, 2007)
2) alcohol, excessive use; increased danger of intentional or unintentional doxepin overdose (Prod Info SINEQUAN(R) oral capsules, 2007)
3) bipolar disorder; increased risk of precipitation of a mixed/manic episode(Prod Info SINEQUAN(R) oral capsules, 2007)
4) concomitant use of monoamine oxidase inhibitors (MAOIs) or use of doxepin within 14 days of MAOI discontinuation (Prod Info SINEQUAN(R) oral capsules, 2007)
5) elderly; increased risk of confusion and oversedation (Prod Info SINEQUAN(R) oral capsules, 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

Otic Effects

Psychiatric Effects

Renal Effects

Reproductive Effects

Other

3.3.1 Cardiovascular Effects

3.3.1.A Doxepin Hydrochloride

Abnormal ECG

Cardiovascular finding

Hypotension

3.3.1.A.1 Abnormal ECG

a) ELECTROCARDIOGRAPHIC CHANGES have been reported with doxepin and manifest as INCREASED PR INTERVAL and PROLONGATION OF QRS COMPLEX. Some studies suggest doxepin has a relatively lesser influence on intracardiac conduction than other tricyclic antidepressants (Pinder et al, 1977f).

b) Available evidence does not support the contention that DOXEPIN is the antidepressant of choice for the treatment of depression in cardiac patients or the elderly. The incidence of toxicity of the drug in therapeutic and toxic doses appears to be similar to that of other tricyclic antidepressants. In therapeutic doses, doxepin is capable of producing prolongations of the PR, QRS, and QTc intervals, ST-T changes, sinus tachycardia, bundle branch block, arrhythmias, orthostatic hypotension, and rarely congestive heart failure. Additionally, in higher doses (overdose), the drug is capable of producing second or third degree AV block, atrial or ventricular arrhythmias, supine hypotension, and decreases in myocardial contractility (Marshall & Forker, 1982ah). However, therapeutic doses of doxepin in healthy adult patients are generally free of clinically important adverse cardiovascular effects, except for orthostatic hypotension (Mahapatra et al, 1986; Cassem, 1982; Glassman, 1984; Glassman & Bigger, 1981). Patients at highest risk are those with preexisting bundle branch block; these patients are at greater risk of developing potentially serious conduction abnormalities during tricyclic antidepressant therapy as compared to patients with normal pretreatment EKG's (Roose et al, 1987; Glassman & Bigger, 1981).

c) Tricyclic antidepressants are thought to resemble quinidine with respect to certain effects on cardiac rhythm (Glassman, 1984; Glassman & Bigger, 1981). Doxepin may be associated with the improvement of ventricular arrhythmias when used in the treatment of depression in some patients. The efficacy of doxepin as an antiarrhythmic agent was studied in 10 cardiac patients with symptoms of frequent ventricular premature depolarizations in a dose-ranging study. Suppression of ventricular premature depolarizations (equal to or greater than 80%) was observed in 4 patients (40%) with doxepin administration; 4 of 8 patients with pairs arrhythmia and 4 of 6 with ventricular tachycardia had 90% or greater suppression. Mean maximal doxepin doses were 115 mg daily, with mean nadir total doxepin concentrations being 61 ng/mL (mean nadir total desmethyldoxepin concentrations, 51 ng/mL). Increases in heart rate and PR, QRS and QTc intervals were also observed. No significant change in resting mean left ventricular ejection fraction was observed with doxepin, even in patients with moderate to severely diminished left ventricular performance. However, sedation and other side effects (dry mouth, weight gain, light-headedness, constipation, hypotension) limited dose ranging in this study, precluding complete evaluation of the antiarrhythmic efficacy of doxepin (Giardina et al, 1987a). More studies are required in larger patient populations, possibly using lower doses, to more fully evaluate antiarrhythmic effects of doxepin.

3.3.1.A.2 Cardiovascular finding

a) According to one study, the use of higher-dose tricyclic antidepressants (TCAs) was associated with an increased risk of SUDDEN CARDIAC DEATH, while lower doses did not increase this risk. In a cohort study including 481,744 persons and 1487 cases of sudden cardiac death occurring in a community setting, researchers found that compared to non-use, the current use of TCAs was associated with a dose-related increase in the risk of sudden cardiac death. For doses lower than 100 milligrams (mg) (amitriptyline or its equivalent), the rate ratio was 0.97 (95% CI, 0.72 to 1.29), however this increased to 2.53 (95% CI, 1.04 to 6.12) for doses of 300 mg or more (p=0.03, test for dose-response). In the entire cohort, users of TCAs 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). However, TCAs taken in doses of less than 100 mg (amitriptyline or its equivalent) were not associated with an increased risk of sudden cardiac death in the entire cohort or in any subgroups, including persons with treated cardiovascular disease. Use of selective serotonin reuptake inhibitors was not associated with an increased risk of sudden cardiac death (rate ratio, 0.95; 95% CI, 0.42 to 2.15) (Ray et al, 2004).

b) A systematic study of the cardiovascular effects of doxepin was conducted in depressed patients with preexisting cardiovascular disease. Doxepin had little effect on heart rate and did not adversely affect left ventricular function, but did have a significant antiarrhythmic effect, slowed cardiac conduction, and caused a significant increase in orthostatic hypotension. Five (16%) of the 32 patients dropped out of the study due to cardiovascular effects. The authors concluded that doxepin provided no more cardiovascular safety than imipramine or nortriptyline (Roose et al, 1991).

c) In a comparison of the cardiovascular effects of maprotiline (75 to 225 mg/day) with doxepin (50 to 200 mg/day) in 49 elderly depressed patients, there were no significant differences in orthostatic hypotension. Maprotiline caused fewer premature ventricular contractions (PVCs) and a longer PRS interval. Both drugs had a small but significant effect on heart rate and PR interval (Ahles et al, 1984).

d) VENTRICULAR ARRHYTHMIAS associated with doxepin and amitriptyline occurred in a 57-year-old man with preexisting heart disease. The patient was treated with a total doxepin dose of 250 mg/day, and after discontinuation of the cardiac medications, he developed a quadrigeminy pattern of ventricular premature depolarizations (VPDs) without atrioventricular or intraventricular conduction defects. Upon discontinuation of doxepin, progressive decrease of the VPDs were seen. Subsequent challenge with amitriptyline again resulted in VPDs which also ceased upon discontinuation of the drug. For this

patient, doxepin had no advantage over amitriptyline in terms of relative cardiotoxicity. A significant correlation was found between the occurrence of premature ventricular depolarization and serum levels of both antidepressants (Todd & Faber, 1983).
e) Since an overdose of tricyclic antidepressants has been associated with cardiotoxicity, it has been assumed that tricyclic antidepressants should not be used in cardiac patients. This theory has been evaluated in a double-blind, randomized trial involving 24 depressed patients with heart disease treated with imipramine, doxepin, or placebo for 4 weeks (Veith et al, 1982). Many patients were also receiving cardiac medications throughout the trial period. Patients were administered imipramine or doxepin 50 milligrams (mg) at bedtime or placebo. Doses were gradually increased every 3 days until side effects or a dose of 150 mg given at bedtime was achieved. After examination revealed that there was no evidence of cardiovascular adverse effects in patients receiving tricyclic antidepressants, dosages were allowed to be increased over 150 mg. Two patients required doses less than 50 mg/day due to severe nausea, ataxia, and sedation. As measured by radionuclide ventriculograms, tricyclic antidepressants had no effect on left ventricular ejection fraction at rest or during maximal exercise. The incidence of premature ventricular contractions was reduced in patients treated with imipramine; however, no consistent change was observed in patients receiving doxepin or placebo. Imipramine- and doxepin-treated patients showed a significant improvement (p less than 0.001) in depression when compared with placebo-treated patients. This study would indicate that in the absence of severe impairment of myocardial performance, depressed patients with preexisting heart disease can be treated effectively with imipramine or doxepin without an adverse effect on ventricular rhythm or hemodynamic function. However, further evaluation of the tricyclics and their effect on cardiovascular function is required.
f) The literature was reviewed to ascertain the validity of suggestions that doxepin caused fewer cardiovascular effects than other antidepressants (Luchins, 1983). After reviewing the studies comparing antidepressant effects on cardiac conduction, cardiac rhythm, heart rate, blood pressure, and mechanical function of the heart, the author concluded that there is little evidence that doxepin has fewer cardiovascular effects than other antidepressants.

3.3.1.A.3 Hypotension

a) Incidence: rare
b) POSTURAL HYPOTENSION and TACHYCARDIA have been reported during doxepin therapy at an incidence of 3% to 4% (Pitts, 1969).

3.3.2 Dermatologic Effects

3.3.2.A Doxepin Hydrochloride

Contact dermatitis

Skin irritation

3.3.2.A.1 Contact dermatitis

a) Severe allergic contact dermatitis was reported in 6 patients after they used doxepin 5% cream for 2 weeks to 7 months (Shelley et al, 1996). Even though dosage recommendations limit its use to 8 days, many patients use it for a much longer period. Angioedema-like swelling, photodermatitis, and generalized weeping dermatitis were some of the reactions described. All patients were patch tested to rule out a reaction to the vehicle ingredients in the cream. The authors suggest that doxepin's histamine blocking activity may augment cell-mediated hypersensitivity.
b) A 40-year-old man developed vesicular eczema on his arms and legs within 2 weeks of initiation of DOXEPIN 5% cream for pruritic epidermolysis bullosa pruriginosa. The eczema cleared after withdrawal of doxepin. He had not previously used the oral form of this drug (Wakelin & Rycroft, 1999).

3.3.2.A.2 Skin irritation

a) The manufacturer reports that 23% of patients treated with doxepin 5% cream experienced stinging and/or burning at the site of application. Although mild in most instances, 25% of the patients who experienced this reaction categorized it as severe (Prod Info Zonalon(R), 2004).

3.3.3 Endocrine/Metabolic Effects

3.3.3.A Doxepin Hydrochloride

Body temperature above normal

Endocrine finding

Syndrome of inappropriate antidiuretic hormone secretion

Weight gain

3.3.3.A.1 Body temperature above normal

a) Drug fever associated with antidepressant use was reported in a 47-year-old woman with a history of major depression who was treated with a variety of antidepressants including doxepin, amitriptyline, trazodone, imipramine, maprotiline, and fluoxetine. Each time the remission of depression coincided with a low-grade fever, malaise, and sore throat. Upon discontinuation of the drug, the symptoms resolved and depression reappeared. The authors postulated this may be due to the action of serotonin on thermoregulation and this was a particularly sensitive individual to this mechanism (Zajecka et al, 1991).

b) A NEUROLEPTIC MALIGNANT SYNDROME (NMS)-like condition occurred with the use of lithium and doxepin in a 64-year-old male with a history of depression with psychotic features. Previously, he had been successfully treated with lithium and haloperidol or electroconvulsive therapy (ECT); he was then treated with lithium 300 mg twice a day and doxepin 100 mg at bedtime for recurrent depression. In two weeks, he began having periods of confusion and disorientation and in another two weeks was admitted for urinary retention. His symptoms worsened after discontinuing the lithium and doxepin with gradual improvement shown on days 5 to 8. He demonstrated classic NMS symptoms in the absence of neuroleptic exposure (fever, muscle rigidity, changes in levels of consciousness, autonomic dysfunction). He later showed improvement with ECT (Rosenberg & Pearlman, 1991).

3.3.3.A.2 Endocrine finding

a) Changes in libido, GYNECOMASTIA, GALACTORRHEA, changes in blood sugar levels, and weight gain have also been reported with doxepin (Prod Info Adapin(R), 1995).

3.3.3.A.3 Syndrome of inappropriate antidiuretic hormone secretion

a) SIADH-induced hyponatremia has been reported rarely with tricyclic antidepressant use.

3.3.3.A.4 Weight gain

a) Weight gain has occurred during doxepin therapy (Forsen, 1975).

3.3.4 Gastrointestinal Effects

3.3.4.A Doxepin Hydrochloride

Dental caries

Disorder of taste

Gastroesophageal reflux disease

Gastrointestinal tract finding

Increased appetite

Stomatitis

3.3.4.A.1 Dental caries

a) Doxepin has moderate anticholinergic properties which may lead to decreased salivation resulting in the development of dental caries (Kastrup, 1987; Winer & Bahn, 1967).

3.3.4.A.2 Disorder of taste

a) Decreased taste sensitivity has been reported with doxepin use.

3.3.4.A.3 Gastroesophageal reflux disease

a) Gastroesophageal reflux has been reported rarely with tricyclic antidepressant use.

3.3.4.A.4 Gastrointestinal tract finding

a) NAUSEA and sometimes VOMITING has been associated with doxepin (Sterlin, 1970)(Pinder et al, 1977f).

b) DRY MOUTH has been reported to occur in up to 15% of patients treated with doxepin (Pinder et al,

1977f).
c) CONSTIPATION has been reported to occur in approximately 4% of patients receiving therapeutic doses of doxepin (Pinder et al, 1977f).

3.3.4.A.5 Increased appetite
a) An increased appetite and craving for sweets was reported in geriatric outpatients receiving doxepin and other antidepressants for depressive disorders or other psychiatric illnesses. Of 93 patients, 34% were taking doxepin (average daily dose 119 mg) and this group showed the highest positive relationship to excessive appetite, craving for sweets, and weight gain (Stein et al, 1985).

3.3.4.A.6 Stomatitis
a) A 34-year-old depressed, asthmatic patient was placed on doxepin (50 mg at bedtime) and suffered severe anticholinergic effects manifested as dry mouth, blurred vision, and constipation. During the second week of therapy, the dose was increased to 100 mg at bedtime and 5 days later the patient developed stomatitis. The symptoms completely resolved 4 days after discontinuation of doxepin (Salem et al, 1981).
b) Approximately 7 days after beginning ampicillin and doxepin 25 mg three times/day plus 100 mg at bedtime, a 48-year-old female developed painful papular lesions on the dorsal surface of her tongue. The lesions resolved over a 3-week period following discontinuation of both medications. Because doxepin was relieving her depression, she began 25 mg three times/day and 50 mg at bedtime for a second time. Eight days later, generalized pain and erythema of the tongue developed and subsided over a 2-week period following doxepin discontinuation (Ives & Stewart, 1980).

3.3.5 Hematologic Effects

3.3.5.A Doxepin Hydrochloride

Hematology finding

Thrombocytopenia

3.3.5.A.1 Hematology finding
a) Isolated cases of ANEMIA, LEUKOPENIA, LYMPHOPENIA, AGRANULOCYTOSIS, and NEUTROPHILIA have occurred during doxepin therapy (Prod Info Adapin(R), 1995; Swanson & Cook, 1977).
b) Surveying the literature, the hematological effects of doxepin (Sinequan(R)) seem infrequent and limited to rare cases of transient neutrophilia (Voina et al, 1971)(Glick, 1973). Only one case of thrombocytopenia has been attributed to doxepin, within our knowledge (Nixon, 1972). A 73-year-old female was given 75 mg/day for depression, prior to admission into a hospital. Initiation of symptoms occurred 6 days afterwards with bone marrow aspirations revealing megakaryocytic hyperplasia. The author did not rule out other concurrent antidepressants administered, such as amitriptyline, not the rapid discontinuation of prednisone therapy for bleeding diathesis, as the possible cause. However, the time relationship between doxepin dosing and subsequent adverse effects and doxepin structural similarity to amitriptyline, which is known to cause blood dyscrasias, did not rule out its chance as the source.
c) Coombs-positive HEMOLYTIC ANEMIA and thrombocytopenia with acute renal failure occurred after a patient received doxepin for approximately 5 weeks (50 to 100 mg orally daily). The patient recovered following withdrawal of doxepin, exchange transfusion, and repeated hemodialysis. Doxepin was the only medication taken by the patient (Wolf et al, 1989).
d) Four patients who were receiving tricyclic antidepressants developed severe unexpected postsurgical bleeding and loss of local anesthetic effect after undergoing nasal surgery. The authors suggested that this resulted from vasodilation resulting from chronic tricyclic antidepressant administration leading to increased blood supply as well as enhanced removal of cocaine from its site of action (Schechter et al, 1982).

3.3.5.A.2 Thrombocytopenia
a) Incidence: rare
b) Thrombocytopenia has been reported secondary to doxepin (Nixon, 1972). A 73-year-old female received doxepin 75 mg daily over a period of 6 days for severe depressive reaction. On the sixth day of therapy, the patient developed SUBCONJUNCTIVAL HEMORRHAGES, generalized oozing from the mouth, and showers of PETECHIAE over the extremities and trunk. Lab data at this time revealed platelet count 1200/cubic mm, prothrombin time 15/13 seconds, and normal PTT and Lee white clotting time. Immunoelectrophoresis was normal. Bone marrow aspirations revealed MEGAKARYOCYTIC-HYPERPLASIA with many young megakaryocytes and decreased iron stores. Doxepin was discontinued and the patient was treated with prednisone 60 mg daily. The platelet count increased to

103,000/cubic mm within 3 days. Prednisone dose was tapered and the patient was started on imipramine. This had no effect on platelet count and was ineffective in the treatment of her depression. Amitriptyline was started resulting in the development of thrombocytopenia which was unresponsive to prednisone. Amitriptyline was discontinued and the platelet count returned to normal.

3.3.6 Hepatic Effects

3.3.6.A Doxepin Hydrochloride

3.3.6.A.1 Hepatotoxicity

a) A previously well, 50-year-old man, experienced 3 separate episodes of acute hepatitis one week after taking small doses of doxepin (25 to 50 mg). Due to the patient's complete recovery between doxepin doses, the absence of other possible causes for recurrent hepatitis, and the temporal relationship between doxepin dose and icteric symptoms, a causal relationship was assumed (Keegan, 1993).

b) Liver function tests have been reported as abnormal in several studies with doxepin (Pinder et al, 1977f).

3.3.7 Immunologic Effects

3.3.7.A Doxepin Hydrochloride

3.3.7.A.1 Cross sensitivity reaction

a) Two patients developed a skin rash during therapy with desipramine (Norpramin(R)) and amitriptyline (Elavil(R)). Discontinuation of these medications in each patient resulted in subsidence of the skin rash. Doxepin was substituted in the patient receiving desipramine and imipramine was substituted in the patient receiving amitriptyline. On both occasions, recurrence of the rash did not occur. These data would suggest that substitution of a structurally dissimilar antidepressant agent is a viable alternative in patients developing allergic skin reactions (Salem et al, 1982).

b) In a double-blind, single dose, noncrossover study, 33 healthy adult volunteers (32 males, 1 female) received a single 25-mg dose of oral desipramine or doxepin. The duration of H1-receptor blockade by these two tricyclic antidepressants, doxepin (the most potent antihistamine) and desipramine (the least potent) were compared. Results showed significant differences in the suppression of the weal-and-flare responses to histamine between the two drugs (Rao et al, 1988a). Desipramine suppressed the wheal for 2 days and flare for one day, whereas doxepin suppressed the wheal for 4 days and flare for 6 days. These results suggest that doxepin should be withheld for at least 7 days before allergy skin testing.

3.3.8 Musculoskeletal Effects

3.3.8.A Doxepin Hydrochloride

Fracture of bone, Nonvertebral

Hip fracture

3.3.8.A.1 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 tricyclic antidepressant (TCA), including amitriptyline, clomipramine, dosulepine, doxepine, imipramine, maprotiline, nortriptyline, and opipramol, compared to those who were not exposed to antidepressants. Current TCA use was associated with an increased risk of nonvertebral fracture (hazard ratio (HR), 1.6; 95% confidence interval (CI), 1.08 to 2.38) compared with no antidepressant use. Current TCA use was also associated with an increased risk of nonvertebral fracture (HR, 1.6; 95% CI, 1.02 to 2.5) compared with past antidepressant use (n=1217). Duration of TCA use of greater than 6 months was not associated with an increased risk of fractures when compared with no antidepressant use and with past antidepressant use. Fractures of the hip (most frequent), wrist, humerus, and pelvis were reported (Ziere et al, 2008).

3.3.8.A.2 Hip fracture

a) An increased incidence of hip fracture was reported in elderly patients receiving psychotropic agents. This study was a case-control evaluation of 1021 patients with hip fractures and 5606 controls. An increased risk of hip fracture was observed with the use of hypnotic/anxiolytic agents with a long elimination half-life (greater than 24 hours), tricyclic antidepressants, and antipsychotic agents. Current users were defined as subjects who had received a prescription in the 30-day period prior to the admission date for initial hospitalization. The long half-life hypnotic/anxiolytic agents studied were

lorazepam, diazepam, chlordiazepoxide, and barbiturates (excluding phenobarbital). The tricyclic antidepressants included amitriptyline, doxepin, and imipramine; antipsychotic agents evaluated were thioridazine, haloperidol, chlorpromazine, and perphenazine-amitriptyline. In contrast, shorter-acting hypnotic-anxiolytic agents (half-life of 24 hours or less) were not associated with an increased risk of hip fracture in these patients. The most frequently used agents in this category were diphenhydramine, hydroxyzine, and chloral hydrate. The increased risk of hip fracture observed in this study was directly related to the doses of the drugs. Analysis for confounding by dementia did not alter the results. Additional studies are needed to confirm these results in this and other populations and to evaluate the effects of other psychotropic drugs that have less pronounced sedative effects (Ray et al, 1987).

3.3.9 Neurologic Effects

Doxepin

Doxepin Hydrochloride

3.3.9.A Doxepin

3.3.9.A.1 Seizure

See Drug Consult reference: COMPARATIVE INCIDENCE OF SEIZURES FROM ANTIDEPRESSANTS

3.3.9.B Doxepin Hydrochloride

Central nervous system finding

Extrapyramidal sign

Myoclonus

Seizure

Tardive dyskinesia

3.3.9.B.1 Central nervous system finding

a) DROWSINESS is the most frequently reported side effect of doxepin and appears to be dose related (Sterlin et al, 1970; Toru et al, 1972a; Goldstein & Pinosky, 1969). Even topically applied doxepin cream (5%) has caused drowsiness in greater than 20% of patients who used it, particularly when applied to greater than 10% of total body surface area (Prod Info Zonalon(R), 2004).
b) Euphoria does not appear to occur with doxepin therapy and there are no cases of PHYSICAL DEPENDENCE associated with the drug (Pinder et al, 1977f).
c) In a case report, topical administration of doxepin 5% cream resulted in altered mental status in a 5-year-old female. Due to a generalized eczematous rash over approximately 50% of the body surface, the patient was prescribed doxepin 5% cream to alleviate itching. Over the course of 24 hours, 30 grams of cream was applied to the rash and the following day the patient was difficult to arouse and responded only to noxious stimuli. Physical examination revealed 3 millimeter bilaterally active pupils, a temperature of 37.2 degrees Celsius, blood pressure of 102/62, sinus tachycardia (heart rate = 120 beats per minute), and a respiratory rate of 24 breaths per minute. Serum concentrations of doxepin and desmethyldoxepin (major active metabolite) were 11.95 nanograms per milliliter (ng/mL) and 17.71 ng/mL, respectively. Eighteen hours following skin decontamination with soap and water, a full recovery was made and the patient was discharged (Zell-Kanter et al, 2000).
d) Confusion, dizziness disorientation, headache, fatigue, weakness, numbness, paresthesias, and ataxia have also been reported with doxepin (Prod Info Adapin(R), 1995).

3.3.9.B.2 Extrapyramidal sign

a) Extrapyramidal side effects including TREMOR, AKATHISIA and GAIT DISTURBANCES have been reported (Pinder et al, 1977f).
b) Extrapyramidal symptoms were seen in 109 of 1116 patients receiving doxepin less than 75 mg to greater than 300 mg daily for periods of 4 to 52 weeks (Pitts, 1969).
c) A dystonic reaction occurred in a 30-year-old female who had been on antidepressant (amitriptyline 100 mg at bedtime) therapy for 3 years before discontinuing for a pregnancy. After giving birth, she took a 75-mg dose for insomnia and immediately developed dystonic symptoms. Treatment with doxepin

was started and titrated up to 300 mg at bedtime. After the third 300-mg dose, she had another dystonic reaction. Later she took a single 150-mg dose for insomnia with another reaction. All symptoms resolved within 24 hours after discontinuing the medication (Lee, 1988).

3.3.9.B.3 Myoclonus

a) A high incidence of myoclonus during cyclic antidepressant therapy was reported with imipramine, desipramine, amitriptyline, doxepin, trazodone, nortriptyline, and maprotiline (Garvey & Tollefson, 1987). Ninety-eight patients with major depression (93) or panic disorder were treated with these agents in initial doses of 50 mg daily of imipramine or its equivalent increasing to a maximum of 300 mg daily after several weeks. Of these patients, 39 (40%) developed myoclonus that was clinically significant in 9 (9%) and resulted in withdrawal of the antidepressant or a medication change. Myoclonus occurred within 1 month of therapy in 81% of the 39 patients, with 46% of patients developing myoclonus within 2 weeks. The mean dose of antidepressant being administered at the time of myoclonus was 169 mg daily in imipramine equivalents, which was similar to the mean dose utilized by the patients not developing myoclonus (164 mg daily). Myoclonus was reversible upon withdrawal of the antidepressant but persisted if medication changes were not initiated; however, spontaneous remission of myoclonus was observed in 9 patients. No predictors for the development of myoclonus were observed.

3.3.9.B.4 Seizure

a) A retrospective review of 47 patients treated with doxepin for anxious or agitated depression revealed a seizure disorder in 19 patients. In these 19 patients, 15 exhibited improved seizure control during therapy with doxepin, while 2 exhibited no change and 2 exhibited decreased control. The authors concluded that doxepin reduced seizure frequency, and postulated 1 or a combination of 3 mechanisms: a direct antiepileptic effect; an indirect effect caused by improved affective state; or, a drug interaction with other anticonvulsants (Ojemann et al, 1983).

b) Seizures are a potential complication of doxepin overdosage, but the clinical data is quite limited with few case reports. In depressed patients, doxepin produces EEG changes that are similar to other tricyclic antidepressants (Pinder et al, 1977f).

3.3.9.B.5 Tardive dyskinesia

a) A prevalence study of tardive dyskinesia (TD) in the course of antidepressant therapy was conducted in 50 patients (Yassa et al, 1987). Of the 23 patients treated with doxepin, 2 men receiving doxepin 100 milligrams daily developed TD. The first was a 74-year-old man suffering from a major depressive disorder. He developed marked buccolingual chewing, lip smacking, and choreoathetoid movements of the body and extremities forty-five days after the start of antidepressant therapy. Seven months after the onset of TD the patient still had occasional lip smacking. The second man who developed TD was 64 years old. He had been started on doxepin 75 milligrams and increased to 100 milligrams daily after one month. Two days after the increase, chewing movements and lateral tongue movements of moderate intensity were noted without any signs of extrapyramidal symptoms. These movements persisted three months later despite a decrease in his dose to 50 milligrams daily.

3.3.10 Ophthalmic Effects

3.3.10.A Doxepin Hydrochloride

3.3.10.A.1 Eye / vision finding

a) BLURRED VISION is an autonomic (anticholinergic) side effect and has been reported to occur in approximately 3% of patients receiving therapeutic doses of doxepin (Pinder et al, 1977f).

b) OCULOGYRIC CRISIS has been reported following the use of doxepin 300 milligrams (Lee, 1988).

3.3.11 Otic Effects

3.3.11.A Doxepin Hydrochloride

3.3.11.A.1 Ototoxicity

a) Tinnitus has been reported during treatment of depression with doxepin in therapeutic doses in a 66-year-old female. The tinnitus recurred upon rechallenge (Golden et al, 1983).

3.3.12 Psychiatric Effects

3.3.12.A Doxepin Hydrochloride

Aggressive behavior

Suicidal thoughts

3.3.12.A.1 Aggressive behavior

a) Aggressiveness has been reported rarely with tricyclic antidepressant use.

3.3.12.A.2 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 treating patients with other psychiatric and nonpsychiatric disorders. If these symptoms are observed, therapy should be reevaluated 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. Patients and their caregivers should be provided with the Medication Guide that is available for this drug (Anon, 2004).

b) A causal role for antidepressants in inducing suicidality has been established in pediatric patients. Anyone considering the use of antidepressants in a child or adolescent must balance this risk with the clinical need. In pooled analyses of 24 short-term, placebo-controlled trials of nine antidepressants (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, bupropion, mirtazapine, nefazodone, and venlafaxine extended-release) including over 4400 pediatric patients with major depressive disorder, obsessive compulsive disorder, or other psychiatric disorders, a greater risk of suicidal behavior or ideation during the first few months of therapy was demonstrated in patients receiving antidepressants as compared with placebo (4% vs 2%, respectively). The risk of suicidality was most consistently observed in the trials that included patients with major depressive disorder, but there were signs of risk emerging from trials in other psychiatric indications, such as obsessive compulsive disorder and social anxiety disorder. No suicides occurred in these trials. The risk of suicidality during longer-term use (ie, beyond several months) in pediatric patients is not known. It is also unknown whether this risk extends to adult patients (Anon, 2004).

3.3.13 Renal Effects

3.3.13.A Doxepin Hydrochloride

Nephrotoxicity

Urinary incontinence

3.3.13.A.1 Nephrotoxicity

a) Coombs-positive hemolytic anemia and thrombocytopenia with acute renal failure occurred in a patient who received doxepin for approximately 5 weeks (50 to 100 mg orally daily). The patient recovered following withdrawal of doxepin, exchange transfusion, and repeated hemodialysis. Doxepin was the only medication taken by the patient (Wolf et al, 1989).

3.3.13.A.2 Urinary incontinence

a) Urinary incontinence was described as a side effect of doxepin. An elderly patient received 25 mg doxepin four times a day over a period of 1 year for depression. The patient began voiding every hour and continued to have frequent urinary tract infections. In addition, he commonly had an itching rash which appeared on the thighs and buttocks. The rash did not respond to soothing lotions and doxepin was discontinued resulting in continuation of rash and disappearance of incontinence (Kimbrough, 1972).

3.3.14 Reproductive Effects

3.3.14.A Doxepin Hydrochloride

Priapism

Sexual dysfunction

3.3.14.A.1 Priapism

a) One case of priapism is reported in a patient receiving doxepin 20 mg at bedtime. Symptoms of testicular swelling and tingling resolved upon discontinuation (Mitchell & Popkin, 1983).

3.3.14.A.2 Sexual dysfunction

a) EJACULATORY DYSFUNCTION has been reported in patients taking doxepin, which resolves on

discontinuation. Decreased libido has also been reported (Mitchell & Popkin, 1983).
b) Improved sexual functioning has been noted in depressed patients with sexual dysfunction after 4 weeks of doxepin therapy in a mean dose of 122.2 mg (Renshaw, 1975).

3.3.16 Other

3.3.16.A Doxepin Hydrochloride

Adverse reaction to drug, General

Drug tolerance - finding

3.3.16.A.1 Adverse reaction to drug, General

a) Doxepin therapy has been used continuously for up to 15 years in the treatment of chronic depressive illness, with maintenance of efficacy and a low order of toxicity. Continuous therapy for 5 to 15 years in 52 patients did not reveal any changes in hematologic, renal or hepatic function tests, and the drug was well tolerated in patients with concomitant cardiovascular disorders (Ayd, 1984).

3.3.16.A.2 Drug tolerance - finding

a) Oral doxepin has not been shown to produce physical tolerance or psychological dependence (Prod Info Sinequan(R), 2004).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category B (Prod Info Zonalon(R) cream, 1997) (All Trimesters)

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

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

3) Crosses Placenta: Unknown

4) Clinical Management

a) Due to reported teratogenic effects with other tricyclic antidepressants, use of doxepin during pregnancy should be avoided if possible, especially during the first trimester. The dangers of failure to treat major depression, however, are obvious, and in each case these dangers must be weighed against the potential for teratogenic effects.

5) Literature Reports

a) Based on data collected through the Motherisk Program for a very small number of patients, there appear to be no differences in cognitive function, temperament and general behavior in children exposed to doxepin throughout gestation as compared to controls (Nulman et al, 2002). However, among infants who were exposed to either fluoxetine or tricyclic antidepressants thoughout gestation, those born to mothers with uncontrolled depressive symptoms showed lower cognitive and language achievements than those born to mothers who were well-controlled (Nulman et al, 2002).

b) Poor sucking and swallowing, muscle hypotonia, drowsiness, vomiting, and jaundice occurred in a neonate whose mother used doxepin in her third trimester and during the postpartum period. The doxepin dose had been 75 mg/day, but was tapered in the last weeks of pregnancy and was 35 mg/day at parturition (Frey et al, 1999).

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 has been demonstrated.

a) Evidence and/or expert consensus has demonstrated harmful infant effects when used during breastfeeding. An alternative to this drug should be prescribed or patients should be advised to discontinue breastfeeding.

3) Clinical Management

a) Both doxepin and its active metabolite have been found in breast milk, and the active metabolite has been found in infant serum at a concentration similar to therapeutic concentrations in adults. Sedation and respiratory depression has been reported in a breastfeeding infant (Matheson et al, 1985), therefore breastfeeding is not recommended during maternal doxepin therapy. Alternatively, available data suggest that clomipramine is a safer agent for use during breastfeeding, and clomipramine is considered compatible

with breastfeeding by the American Academy of Pediatrics.

4) Literature Reports

a) Doxepin and desmethyldoxepin levels were measured in the milk of a mother being treated with doxepin 150 mg daily for major depressive disorder (Kemp et al, 1985). The milk to plasma ratio averaged 1.46 for both doxepin and desmethyldoxepin. With an average maternal serum level of 46 mcg/L for doxepin and 90 mcg/L for desmethyldoxepin, a nursing infant would consume a dose of 237 mcg in 1.2 L of milk per day.

b) Respiratory depression occurred in an 8-week-old breastfed girl whose mother was receiving doxepin 25 mg TID. In the infant's serum, the level of doxepin was almost undetectable (3 mcg/mL); therefore, the respiratory depression was attributed to the high concentrations of N-desmethyldoxepin (58 and 66 mcg/mL) which were similar to the levels in the mother (Matheson et al, 1985). After discontinuing breastfeeding, the infant's respiration normalized within 24 hours.

c) Poor sucking and swallowing, muscle hypotonia, drowsiness, vomiting, and jaundice occurred in a neonate whose mother used doxepin in her third trimester and during the postpartum period. The doxepin dose had been 75 mg/day, but was tapered in the last weeks of pregnancy and was 35 mg/day at parturition. The amount of doxepin and desmethyldoxepin (active metabolite) ingested by the nursing infant was estimated at 10 to 20 mcg/kg/day (2.5% of the weight-adjusted dose of the mother) (Frey et al, 1999a).

5) Drug Levels in Breastmilk

a) Parent Drug

1) Milk to Maternal Plasma Ratio

a) 1.08-1.66 (Kemp et al, 1985)

b) Active Metabolites

1) DESMETHYLDOXEPIN (Bennett, 1996)

a) Milk to Maternal Plasma Ratio

1) 1.02-1.53 (Kemp et al, 1985)

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Food Combinations

3.5.1 Drug-Drug Combinations

Acecainide

Acenocoumarol

Ajmaline

Amiodarone

Amisulpride

Amobarbital

Amphetamine

Amprenavir

Anisindione

Aprobarbital

Arbutamine

Arformoterol

Arsenic Trioxide

Astemizole

Atomoxetine

Azimilide

Baclofen

Belladonna

Belladonna Alkaloids

Bepridil

Bethanidine

Bretylium

Butabarbital

Butalbital

Cannabis

Carbamazepine

Chloroquine

Chlorotrianisene

Cimetidine

Cisapride

Clarithromycin

Clonidine

Clorgyline

Conjugated Estrogens

Dexfenfluramine

Dexmethylphenidate

Dextroamphetamine

Dicumarol

Dienestrol

Diethylpropion

Diethylstilbestrol

Disopyramide

Dofetilide

Dolasetron

Droperidol

Duloxetine

Enflurane

Epinephrine

Erythromycin

Esterified Estrogens

Estradiol

Estriol

Estrone

Estropipate

Eterobarb

Ethinyl Estradiol

Etilefrine

Fenfluramine

Fluconazole

Fluoxetine

Formoterol

Fosamprenavir

Foscarnet

Fosphenytoin

Gatifloxacin

Gemifloxacin

Grepafloxacin

Guanadrel

Guanethidine

Halofantrine

Haloperidol

Halothane

Heptabarbital

Hexobarbital

Hydroquinidine

Ibutilide

Iproniazid

Isocarboxazid

Isoflurane

Isradipine

Levomethadyl

Linezolid

Lisdexamfetamine

Mazindol

Mephentermine

Mephobarbital

Mesoridazine

Mestranol

Methamphetamine

Methohexital

Methoxamine

Methylphenidate

Midodrine

Moclobemide

Moxifloxacin

Nefopam

Nialamide

Norepinephrine

Octreotide

Oxilofrine

Pargyline

Paroxetine

Pemoline

Pentamidine

Pentobarbital

Phendimetrazine

Phenelzine

Phenindione

Phenmetrazine

Phenobarbital

Phenprocoumon

Phentermine

Phenylephrine

Phenytoin

Pimozide

Pirmenol

Prajmaline

Primidone

Procainamide

Procarbazine

Prochlorperazine

Propafenone

Propoxyphene

Propylhexedrine

Quetiapine

Quinestrol

Quinidine

Quinidine

Rasagiline

Risperidone

S-Adenosylmethionine

Salmeterol

Secobarbital

Selegiline

Sematilide

Sertindole

Sertraline

Sotalol

Sparfloxacin

Spiramycin

St John's Wort

Sulfamethoxazole

Sultopride

Tapentadol

Tedisamil

Telithromycin

Terfenadine

Thiopental

Thioridazine

Tibolone

Toloxatone

Tramadol

Tranylcypromine

Trifluoperazine

Trimethoprim

Vasopressin

Venlafaxine

Warfarin

Ziprasidone

Zolmitriptan

Zotepine

3.5.1.A Acecainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cases of QTc prolongation and/or torsades de pointes have been reported with all Class III antiarrhythmic agents, including acecainide (Chow et al, 1984), amiodarone (Faggiano et al, 1996), azimilide (Corey et al, 1999), bretylium (Gilman et al, 1985a), ibutilide (Rodriguez et al, 2001), sematilide (Singh, 1996), dofetilide (Allen et al, 2002), and sotalol (Marill & Runge, 2001). Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Yamreudeewong et al, 2003a; Prod Info Corvert(R), 2000).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepressant (TCA) is not recommended.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flattened T waves (Marshall & Forker, 1982y).
b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as tricyclic antidepressants, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003).

3.5.1.B Acenocoumarol

1) Interaction Effect: increased risk of bleeding
2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants (Vesell et al, 1970i; Williams et al, 1976i). Considerable interindividual differences may be found (Pond et al, 1975i).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: In patients receiving tricyclic antidepressants and oral anticoagulant therapy, the prothrombin time ratio or INR (international normalized ratio) should be closely monitored with the addition and withdrawal of the antidepressant, and should be periodically reassessed during concurrent therapy. Achieving a stable drug regimen which produces the desired level of anticoagulation may be difficult in patients on this combination, and frequent adjustments of the anticoagulant dose may be required.
7) Probable Mechanism: decreased acenocoumarol metabolism; increased acenocoumarol absorption
8) Literature Reports
a) In a study of healthy volunteers, the concurrent use of nortriptyline or amitriptyline resulted in an increase of dicumarol levels and an increase in the plasma half-life of dicumarol, although the effect was not consistent in all subjects (Pond et al, 1975h). This effect was not observed with warfarin.
b) A single oral dose of bishydroxycoumarin after 8 days of nortriptyline resulted in a significantly prolonged half-life and decreased volume of distribution of the coumarin anticoagulant in 6 healthy volunteers (Vesell et al, 1970h). The mechanism of action was suggested to be reduced bishydroxycoumarin metabolism and/or altered coumarin absorption.

c) Drug dosing was studied in 16 patients on long-term anticoagulant therapy who used concurrent TCAs (Williams et al, 1976h). TCAs affected the stability of anticoagulant control leading to frequent changes in the doses of anticoagulants. Inhibition of coumarin metabolism was the postulated mechanism.

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 and tricyclic antidepressants 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 Class Ia antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Prod Info Elavil(R), 1999g; Prod Info Quinaglute(R), 1999; Marshall & Forker, 1982m).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic agent and a tricyclic antidepressant is not recommended.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) Quinidine is an inhibitor of the cytochrome P450 isoenzyme responsible for the 2-hydroxylation of imipramine and desipramine (Brosen & Gram, 1989). Inhibition of this enzyme system can result in a 35% decrease in imipramine clearance and 85% decrease in desipramine clearance. Demethylation of imipramine by the cytochrome P450 system is unaffected by this interaction. Until more information is available all patients having quinidine added to drug regimen containing imipramine or desipramine should be monitored for increased antidepressant serum concentrations and potential toxicity.

b) An increased incidence in sudden death was observed in six out of 53 patients with cardiac disease receiving amitriptyline, compared to 0 out of 53 in the control group. It was recommended that amitriptyline be avoided in patients with underlying cardiac disease except when depression was debilitating and no other drugs were helpful (Moir et al, 1972; Coull et al, 1970).

c) In a placebo controlled study, imipramine 3.5 mg/kg was administered daily for seven patients with severe depression and titrated doses to obtain therapeutic plasma concentrations. Two patients displayed premature atrial depolarizations and premature ventricular depolarizations before therapy. On patient had 33 premature atrial depolarizations (PAD) and 30 premature ventricular depolarizations (PVD) per hour, which decreased to 0.4 PAC and zero PVC per hour on imipramine. The other patient had 12 PAD and 169 PVD per hour before treatment and 1.8 PAD and 28.1 PVD per hour on imipramine. The authors also cautioned that the incidence of cardiotoxicity may increase if tricyclic antidepressants are administered with Type I antiarrhythmics. It was also recommended that quinidine and procainamide not be used to treat the arrhythmias of a tricyclic overdose. The similarities between these agents may exacerbate the cardiotoxicity (Kantor et al, 1978).

3.5.1.D Amiodarone

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Cases of QTc prolongation and/or torsades de pointes have been reported with all Class III antiarrhythmic agents, including acecainide (Chow et al, 1984), amiodarone (Faggiano et al, 1996), azimilide (Corey et al, 1999), bretylium (Gilman et al, 1985a), ibutilide (Rodriguez et al, 2001), sematilide (Singh, 1996), dofetilide (Allen et al, 2002), and sotalol (Marill & Runge, 2001). Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Yamreudeewong et al, 2003a; Prod Info Corvert(R), 2000).

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepressant (TCA) is not recommended.

7) Probable Mechanism: additive QT prolongation

8) Literature Reports

a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flattened T waves (Marshall & Forker, 1982y).

b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as tricyclic antidepressants, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003).

3.5.1.E Amisulpride

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac

arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), quetiapine (Owens, 2001b), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marshall & Forker, 1982p).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999).

3.5.1.F Amobarbital
1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.G Amphetamine
1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

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

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

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

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

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.H Amprenavir

1) Interaction Effect: increased tricyclic serum concentrations and potential toxicity (anticholinergic effects, sedation, confusion, cardiac arrhythmias)

2) Summary: Coadministered amprenavir may increase serum concentrations of tricyclic antidepressants, causing a potential risk of arrhythmias or other serious adverse effects. Currently no interaction study has been conducted. Amprenavir is metabolized by cytochrome P450 3A4 enzymes in addition to being a CYP3A4 inhibitor, and tricyclics may partially depend on this pathway for metabolism. Plasma concentrations of the tricyclic should be closely monitored and dose adjustments made accordingly in patients also receiving amprenavir (Prod Info Agenerase(R), 2000).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: If concomitant therapy with amprenavir and a tricyclic antidepressant is unavoidable, plasma concentrations of the tricyclic should be closely monitored and dose adjustments made accordingly. Also monitor patients for signs and symptoms of tricyclic toxicity (anticholinergic effects, sedation, confusion, cardiac arrhythmias).

7) Probable Mechanism: inhibition of cytochrome P450-mediated tricyclic metabolism

3.5.1.I Anisindione

1) Interaction Effect: increased risk of bleeding

2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants (Vesell et al, 1970c; Williams et al, 1976c). Considerable interindividual differences may be found (Pond et al, 1975c).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: In patients receiving tricyclic antidepressants and oral anticoagulant therapy, the prothrombin time ratio or INR (international normalized ratio) should be closely monitored with the addition and withdrawal of the antidepressant, and should be periodically reassessed during concurrent therapy. Achieving a stable drug regimen which produces the desired level of anticoagulation may be difficult in patients on this combination, and frequent adjustments of the anticoagulant dose may be required.

7) Probable Mechanism: decreased anisindione metabolism; increased anisindione absorption

8) Literature Reports

a) In a study of healthy volunteers, the concurrent use of nortriptyline or amitriptyline resulted in an increase of dicumarol levels and an increase in the plasma half-life of dicumarol, although the effect was not consistent in all subjects (Pond et al, 1975b). This effect was not observed with warfarin.

b) A single oral dose of bishydroxycoumarin after 8 days of nortriptyline resulted in a significantly prolonged half-life and decreased volume of distribution of the coumarin anticoagulant in 6 healthy volunteers (Vesell et al, 1970b). The mechanism of action was suggested to be reduced bishydroxycoumarin metabolism and/or altered coumarin absorption.

c) Drug dosing was studied in 16 patients on long-term anticoagulant therapy who used concurrent TCAs (Williams et al, 1976b). TCAs affected the stability of anticoagulant control leading to frequent changes in the doses of anticoagulants. Inhibition of coumarin metabolism was the postulated

mechanism.

3.5.1.J Aprobarbital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects

2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.

7) Probable Mechanism: increased tricyclic antidepressant metabolism

8) Literature Reports

a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.K Arbutamine

1) Interaction Effect: unreliable arbutamine test results

2) Summary: Because tricyclic antidepressants may affect heart rate, arbutamine should not be administered to a patient receiving a tricyclic antidepressant, since arbutamine test results may be unreliable (Prod Info GenESA(R), 1997).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Arbutamine should not be administered to a patient receiving tricyclic antidepressant therapy.

7) Probable Mechanism: alteration of heart rate by the tricyclic antidepressant

3.5.1.L Arformoterol

1) Interaction Effect: an increased risk of cardiovascular excitation

2) Summary: Concurrent administration of arformoterol with a tricyclic antidepressant (TCA) may lead to potentiation of arformoterol's adrenergic effects on the cardiovascular system. Therefore, extreme caution is advised if arformoterol is administered to patients who are being treated with a TCA (Prod Info BROVANA (TM) inhalation solution, 2006). Monitor patients closely for adverse cardiovascular effects.

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Extreme caution and close observation for adverse cardiovascular effects are warranted when arformoterol is administered concurrently with a tricyclic antidepressant (TCA) as the cardiovascular effects of arformoterol can be potentiated by TCAs (Prod Info BROVANA(TM) inhalation solution, 2006).

7) Probable Mechanism: potentiation of cardiovascular effects

3.5.1.M Arsenic Trioxide

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 arsenic trioxide. Possible pharmacodynamic interactions can occur between arsenic trioxide and potentially arrhythmogenic agents such as tricyclic antidepressants that prolong the QT interval (Prod Info Trisenox(R), 2000a). Even though no formal drug interaction studies have been done, the coadministration of arsenic trioxide and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Prod Info Elavil(R), 1999k; Marshall & Forker, 1982af).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of arsenic trioxide and other drugs that may prolong

the QTc interval, such as tricyclic antidepressants is not recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) An increased incidence in sudden death was observed in six out of 53 patients with cardiac disease receiving amitriptyline, compared to zero out of 53 in the control group using a hospital based information system. The authors recommended that amitriptyline not be used in patients with underlying cardiac disease except when depression was debilitating and no other drugs were helpful (Moir et al, 1972a; Coull et al, 1970a).
b) 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), 2000).

3.5.1.N Astemizole
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants 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 astemizole and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Prod Info Elavil(R), 1999l; Prod Info Hismanal(R), 1996).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of astemizole and agents that prolong the QT interval, such as tricyclic antidepressants, is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) A comprehensive discussion of the cardiovascular effects of tricyclic antidepressants has been presented (Marshall & Forker, 1982ag). Electrocardiogram effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flattened T waves.

3.5.1.O Atomoxetine
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as doxepin. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with doxepin, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with doxepin.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by doxepin

3.5.1.P Azimilide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cases of QTc prolongation and/or torsades de pointes have been reported with all Class III antiarrhythmic agents, including acecainide (Chow et al, 1984), amiodarone (Faggiano et al, 1996), azimilide (Corey et al, 1999), bretylium (Gilman et al, 1985a), ibutilide (Rodriguez et al, 2001), sematilide (Singh, 1996), dofetilide (Allen et al, 2002), and sotalol (Marill & Runge, 2001). Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Yamreudeewong et al, 2003a; Prod Info Corvert(R), 2000).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepressant (TCA) is not recommended.
7) Probable Mechanism: additive QT prolongation

8) Literature Reports

a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flattened T waves (Marshall & Forker, 1982y).

b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as tricyclic antidepressants, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003).

3.5.1.Q Baclofen

1) Interaction Effect: memory loss, loss of muscle tone

2) Summary: Baclofen when administered with antidepressants, specifically imipramine, amitriptyline, and clomipramine, has induced short term memory loss (Sandyk & Gillman, 1985a). In addition, concomitant imipramine and baclofen may result in additive muscle relaxant effects (Silverglat, 1981a).

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Due to the additive effects of both drugs, monitor for excess anticholinergic activity and muscle relaxant effects with concomitant therapy.

7) Probable Mechanism: unknown

8) Literature Reports

a) Baclofen when administered with antidepressants, specifically imipramine, amitriptyline, and clomipramine, has induced short-term memory loss in three patients. Specifically, the patients could not remember names of persons or places familiar to them. The interaction is believed to be caused by baclofen enhancing the anticholinergic effects of antidepressants, which may be partially reversed by piracetam (Sandyk & Gillman, 1985).

b) Concomitant imipramine and baclofen therapy has been reported to result in an additive muscle relaxant effect. A 54-year-old male with a 12-year history of multiple sclerosis and a two-year history of depression was maintained on baclofen 10 mg four times daily. The patient experienced good relief of spasticity with this regimen and maintained sufficient muscle tone to stand. Nortriptyline 50 mg nightly was added to relieve depression. On the sixth day of therapy, the patient was no longer able to stand. Nortriptyline was withdrawn and muscle tone returned within 48 hours. Two weeks later, imipramine 75 mg daily was given to the patient for treatment of depression, however, the patient again experienced loss of muscle tone. Muscle tone returned within two days of imipramine discontinuation. The additive effect between baclofen and the tricyclic antidepressants is attributed to an interaction affecting the neurotransmitters at the presynaptic membrane (Silverglat, 1981).

3.5.1.R Belladonna

1) Interaction Effect: excessive anticholinergic activity (severe dry mouth, constipation, decreased urination, excessive sedation, blurred vision)

2) Summary: The anticholinergic activity of the active alkaloids present in belladonna may predispose the patient to excessive anticholinergic activity if taken with tricyclic antidepressants. Belladonna contains L-hyoscyamine, atropine, and scopolamine with a total alkaloid content of at least 0.3% in the leaves and 0.5% in the roots (Blumenthal et al, 1998). Because belladonna is typically available as a homeopathic preparation, the clinical severity of the interaction with tricyclic antidepressants is unknown. Caution is advised.

3) Severity: minor

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Excessive anticholinergic activity may be manifested by dry mouth, constipation, urinary retention, tachycardia, decreased sweating, mydriasis, blurred vision, elevated temperature, muscular weakness, and sedation. If such effects are noted, belladonna should be discontinued immediately. In severe cases, paralytic ileus, confusion, psychoses, agitation, delusions, delirium, and paranoia may be encountered as well as tachycardia, dysrhythmia, and hypertension. In severe cases, immediate medical attention should be obtained.

7) Probable Mechanism: additive anticholinergic effect

3.5.1.S Belladonna Alkaloids

1) Interaction Effect: excessive anticholinergic activity (severe dry mouth, constipation, decreased urination, excessive sedation, blurred vision)

2) Summary: The anticholinergic activity of the active alkaloids present in belladonna may predispose the patient to excessive anticholinergic activity if taken with tricyclic antidepressants. Belladonna contains L-hyoscyamine, atropine, and scopolamine with a total alkaloid content of at least 0.3% in the leaves and 0.5% in the roots (Blumenthal et al, 1998). Because belladonna is typically available as a homeopathic preparation, the clinical severity of the interaction with tricyclic antidepressants is unknown. Caution is advised.

3) Severity: minor

4) Onset: rapid

5) Substantiation: theoretical
6) Clinical Management: Excessive anticholinergic activity may be manifested by dry mouth, constipation, urinary retention, tachycardia, decreased sweating, mydriasis, blurred vision, elevated temperature, muscular weakness, and sedation. If such effects are noted, belladonna should be discontinued immediately. In severe cases, paralytic ileus, confusion, psychoses, agitation, delusions, delirium, and paranoia may be encountered as well as tachycardia, dysrhythmia, and hypertension. In severe cases, immediate medical attention should be obtained.
7) Probable Mechanism: additive anticholinergic effect

3.5.1.T Bepridil

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: In US clinical trials, the QT and QTc intervals were commonly prolonged by bepridil in a dose-related fashion (Prod Info Vascor(R), 2000). Tricyclic antidepressants (TCAs) have been shown to prolong the QTc interval at the recommended therapeutic dose (Marshall & Forker, 1982t).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of bepridil and other drugs which may prolong the QTc interval, including tricyclic antidepressants, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.U Bethanidine

1) Interaction Effect: decreased antihypertensive effectiveness
2) Summary: Tricyclic antidepressants inhibit the uptake of bethanidine at its site of action in the adrenergic neuron. The antagonism may last for several days after discontinuation of the antidepressant. The interaction with doxepin is dose related (Oates et al, 1969; Fann et al, 1971); doxepin in doses less than 150 mg daily may be used with bethanidine, but the antidepressant effect may be insufficient at such a low dose (Skinner et al, 1969a; Avery, 1973; Feagin et al, 1969).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The combination of bethanidine and doxepin, as well as other tricyclic antidepressant agents, should be avoided. An alternative antihypertensive should be considered.
7) Probable Mechanism: decreased uptake of bethanidine into adrenergic neurons
8) Literature Reports
a) Adequate control of hypertension was reported in only two of eight adult hypertensive patients who received bethanidine or debrisoquine concurrently with a tricyclic antidepressant. In 24 control patients given the same drugs without antidepressants, blood pressure control was achieved in 18. Withdrawal of hypotension that necessitated a reduction in dosage of bethanidine or debrisoquine (Skinner et al, 1969).

3.5.1.V Bretylium

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cases of QTc prolongation and/or torsades de pointes have been reported with all Class III antiarrhythmic agents, including acecainide (Chow et al, 1984), amiodarone (Faggiano et al, 1996), azimilide (Corey et al, 1999), bretylium (Gilman et al, 1985a), ibutilide (Rodriguez et al, 2001), sematilide (Singh, 1996), dofetilide (Allen et al, 2002), and sotalol (Marill & Runge, 2001). Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Yamreudeewong et al, 2003a; Prod Info Corvert(R), 2000).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepressant (TCA) is not recommended.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flattened T waves (Marshall & Forker, 1982y).
b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as tricyclic antidepressants, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003).

3.5.1.W Butabarbital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.X Butalbital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.Y Cannabis

1) Interaction Effect: tachycardia and delirium
2) Summary: Concomitant tetrahydrocannabinol and tricyclic antidepressant therapy has increased the heart rate and cause delirium beyond that expected with either drug alone (Wilens et al, 1997a; Hillard & Vieweg, 1983a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Caution is advised if patients use cannabis with a tricyclic antidepressant. Monitor heart rate changes closely.
7) Probable Mechanism: possibly due to beta-adrenergic effect of cannabis coupled with the anticholinergic effect of tricyclic antidepressants
8) Literature Reports
a) A 21-year-old female receiving oral nortriptyline 30 milligrams at bedtime for 9 months developed marked sinus tachycardia (160 beats/minute) within 30 minutes of smoking a cannabis cigarette. The patient's heart rate was about 90 beats/minute before smoking the cannabis. She had used cannabis many times before starting the nortriptyline without ill effects (Hillard & Vieweg, 1983).

b) Four cases of tachycardia, cognitive changes, and delirium have been reported in adolescent males treated with tricyclic antidepressants who smoked marijuana. One of the four cases was evaluated by a physician, the others were later accounts of the event. The toxic effects were considered by the reporters to have resulted from a drug interaction because they occurred with lower doses of marijuana than are common in other reports of marijuana toxicity (usually greater than 20 mg). In case 1, a 16-year-old male taking nortriptyline 75 mg/day presented with tachycardia (130 beats/minute), delirium, confusion, and short-term memory loss 30 minutes after smoking one marijuana cigarette. Symptoms resolved spontaneously after 24 hours. In case 2, and 18-year-old male taking desipramine 200 mg/day presented 12 hours after smoking marijuana with symptoms of edginess, severe dry mouth, lightheadedness, confusion, short-term memory impairment, and tachycardia (110 beats/minute). Symptoms resolved within 48 hours. Case 3, a 15-year-old male taking desipramine 150 mg/day and sertraline 50 mg/day, reported mood lability, irritability, and a racing heart after smoking 2 marijuana cigarettes which resolved after 16 hours. Case 4, a 16-year-old male taking desipramine and clonidine reported hallucinations, confusion, mild shortness of breath, and elevated heart rate after smoking marijuana. This was different than the effect he experienced prior to taking desipramine (Wilens et al, 1997).

3.5.1.Z Carbamazepine

1) Interaction Effect: decreased doxepin effectiveness and possibly increased carbamazepine toxicity (diplopia, blurred vision, dizziness, tremor)
2) Summary: The concomitant use of carbamazepine and antidepressants has been reported to decrease doxepin levels (Leinonen et al, 1991a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for clinical efficacy of the doxepin therapy and for any signs of toxicity of carbamazepine. Serum levels of both agents should be considered when either agent is added or discontinued, with appropriate dosage adjustments made accordingly.
7) Probable Mechanism: increased doxepin metabolism
8) Literature Reports
a) The effect of carbamazepine on doxepin levels were examined in 17 psychiatric inpatients who were stabilized for a minimum of 7 days prior to measurement of baseline antidepressant concentrations. The average daily doxepin dosage was 201.5 mg. Carbamazepine was added in a mean dose of 593 mg and continued over a 4-week period. Serum doxepin concentrations were decreased to 46% in patients receiving combination therapy compared to patients receiving doxepin alone (Leinonen et al, 1991).

3.5.1.AA Chloroquine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Chloroquine can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Because tricyclic antidepressants may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of chloroquine and tricyclic antidepressants is not recommended (Prod Info Aralen(R), 1999; Marshall & Forker, 1982v).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of chloroquine and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AB Chlorotrianisene

1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973i), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972i). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972i) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984i).
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic
8) Literature Reports
a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten

patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mcg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972h).

b) A case reported demonstrated an interaction in a 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg (Khurana, 1972h). The patient developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side-effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973h).

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973e).

d) The effects of oral contraceptives on clomipramine were studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980d).

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984h).

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984d).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980d). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983d).

3.5.1.AC Cimetidine

1) Interaction Effect: doxepin toxicity (dry mouth, blurred vision, urinary retention)

2) Summary: Concomitant administration of doxepin 50 mg daily and cimetidine 600 mg twice daily was reported to result in significant increases in doxepin concentration and elimination half-life (Sutherland et al, 1987; Curry et al, 1987; Wells et al, 1986).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor serum tricyclic antidepressant levels within the first few days of starting or discontinuing cimetidine. An H2 blocker that does not impair the metabolism of the tricyclic agents, such as ranitidine or famotidine, may be an alternative.

7) Probable Mechanism: decreased doxepin metabolism

3.5.1.AD 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 tricyclic antidepressant agents 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: theoretical
6) Clinical Management: The concurrent use of cisapride and tricyclic antidepressants is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AE Clarithromycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and clarithromycin have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Biaxin(R), 2002; Marshall & Forker, 1982n). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as clarithromycin, is not recommended (Prod Info Elavil(R), 1999h).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of tricyclic antidepressants and agents that prolong the QT interval, such as clarithromycin, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AF Clonidine

1) Interaction Effect: decreased antihypertensive effectiveness
2) Summary: Concomitant clonidine and tricyclic antidepressant (TCA) therapy may impair the antihypertensive effects of clonidine (Prod Info Catapres(R), 1996). Tricyclic antidepressants increase the release of noradrenaline, presumably through re-uptake blockade. Clonidine reduces the release of noradrenaline by stimulating pre-synaptic alpha-2 adrenoreceptors, whose function is to inhibit noradrenaline release (Briant et al, 1973a; Hicks et al, 1981; Hui, 1983; Glass et al, 1982a). Mianserin, a tetracyclic antidepressant, was not shown to exhibit the impairment of clonidine's antihypertensive effects seen with tricyclic antidepressants (Elliott et al, 1981; Elliott et al, 1983).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Blood pressure should be monitored for an appropriate clinical response. Higher doses of clonidine may be required. An alternative class of antihypertensive agents or an alternative class of antidepressants might be considered.
7) Probable Mechanism: pharmacological antagonism at central alpha-2 receptors
8) Literature Reports

a) The interaction between clonidine and desipramine was studied in five hypertensive patients. The results of this double-blind placebo controlled study showed that the introduction of the tricyclic antidepressant led to the loss of blood pressure control in four of the five subjects within two weeks. The rise in the arterial pressure was more prominent in the supine position than in the erect. The average blood pressure increase in the desipramine period compared to the placebo period was 22/15 mm Hg in the lying position and 12/11 mm Hg standing (Briant et al, 1973).

b) Eleven drug-free patients who met the Research Diagnostic Criteria for Major Depressive Disorder enrolled in a study to determine the effects of desipramine on central adrenergic function. Patients were given a clonidine infusion after 0, 1 and 3 weeks of treatment with desipramine. Results showed that the sedative and hypotensive effects of clonidine were significantly inhibited after three weeks of treatment with desipramine. This interaction was also seen at one week, but did not reach clinical significance. The authors concluded that the effects that were observed during the study were due to an acute drug effect, rather than to a chronic adaptive change (Glass et al, 1982).

c) One case report describes a 65-year-old man who was experiencing perineal pain following the excision of a carcinoma. Pain management of amitriptyline 75 mg nightly and sodium valproate 500 mg three times daily was initiated after slow-release morphine only had a limited effect. A clonidine spinal intrathecal injection of 75 micrograms was given when it was felt that the patient had become tolerant to opioid treatment. Within five minutes, the patient was found to be in severe pain, which resolved within 30 minutes after diamorphine was given. Two mechanisms for this interaction were postulated. In the first, the pain could have been the result of a clonidine-cholinergic interaction. In the second, the tricyclic augmentation of serotoninergic transmission may have unmasked an effect of clonidine at central receptors to enhance nociception (Hardy & Wells, 1988).

3.5.1.AG Clorgyline

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

2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982e; Spigset et al, 1993f; Brodribb et al, 1994e; Neuvonen et al, 1993b). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991c). If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971g; White & Simpson, 1984e).

3) Severity: major

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of a tricyclic antidepressant, such as doxepin, and a monoamine oxidase inhibitor (MAOI), such as clorgyline, should be done only with close monitoring and where the clinical benefit outweighs the potential risk. Other antidepressant therapy should first be considered. If deemed clinically necessary, avoid large doses and use agents other than imipramine, clomipramine, desipramine, and tranylcypromine. If doxepin is replacing treatment with clorgyline, a minimum of 14 days should elapse after clorgyline is discontinued before doxepin therapy begins (Prod Info SINEQUAN(R) capsule, oral concentrate, 2005). There is no specific washout period for replacing doxepin treatment with clorgyline. However, it is advisable to gradually taper the tricyclic antidepressant dosage before starting treatment with the MAOI (Remick, 2002).

7) Probable Mechanism: altered catecholamine uptake and metabolism

8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers. Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965c; Brachfeld et al, 1963b; Winston, 1971c; Schuckit et al, 1971f; Sargent, 1965b; Spiker & Pugh, 1976c). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965c).

b) Administration of a TCA after MAOI therapy may result in the development of serotonin syndrome. In a double-blind, crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-compulsive disorder, two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipramine therapy. After taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with clomipramine without adverse effects (Insel et al, 1982d).

c) A drug interaction occurred in a 76-year old woman who had been taking clomipramine 50 mg daily for several months prior to switching to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fever which then progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days later after discontinuing all antidepressant medications (Spigset et al, 1993e).

d) A 39-year old woman with bipolar disorder developed serotonin syndrome after imipramine was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when imipramine was started at 50 mg daily, followed by two dosage increases of imipramine to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in imipramine to 200 mg per day, the patient developed symptoms of serotonin syndrome, including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated with chlorpromazine and symptoms resolved over the next few days without further complications (Brodribb et al, 1994d).

e) Three patients with bipolar disorder developed manic symptoms while undergoing concurrent therapy with isocarboxazid and amitriptyline. In all three cases the patients had been given MAOIs and TCAs alone without complications. It was only when the drugs were used in combination that symptoms of mania emerged, suggesting a synergistic effect (de la Fuente et al, 1986a).

f) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a physically healthy 34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulation and eventual death (Tackley & Tregaskis, 1987c).

g) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 150 mg amitriptyline or its equivalent, 45 mg phenelzine, or 60 mg isocarboxazid) b) oral administration c) avoidance of clomipramine, imipramine, desipramine, and tranylcypromine in any combination, and d) close monitoring of patients (Kline, 1974a; Winston, 1971c;

Schuckit et al, 1971f; White & Simpson, 1984d; Rom & Benner, 1972a). The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991b). Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some sources suggest that the combination of amitriptyline and isocarboxazid is preferred (Perry et al, 1991b). Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs (Ponto et al, 1977c; Schuckit et al, 1971f; Ashcroft, 1975b).

3.5.1.AH Conjugated Estrogens

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973a), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972a). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972a) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984a).

3) Severity: minor

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.

7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant

8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972).

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973; Khurana, 1972).

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973).

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980).

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed

amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984).

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983).

3.5.1.AI Dexfenfluramine

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

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

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

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

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

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

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.AJ Dexmethylphenidate

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

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine

analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

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

DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.AL Dicumarol

1) Interaction Effect: increased risk of bleeding
2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants (Vesell et al, 1970k; Williams et al, 1976k). Considerable interindividual differences may be found (Pond et al, 1975k).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: In patients receiving oral anticoagulant therapy, the prothrombin time ratio or international normalized ratio (INR) should be closely monitored with the addition and withdrawal of treatment with doxepin, and should be reassessed periodically during concurrent therapy. Adjustments of the dicumarol dose may be necessary in order to maintain the desired level of anticoagulation.
7) Probable Mechanism: decreased dicumarol metabolism; increased dicumarol absorption
8) Literature Reports
a) In a study of healthy volunteers, the concurrent use of nortriptyline or amitriptyline resulted in an increase of dicumarol levels and an increase in the plasma half-life of dicumarol, although the effect was not consistent in all subjects (Pond et al, 1975j). This effect was not observed with warfarin.
b) A single oral dose of bishydroxycoumarin after eight days of nortriptyline resulted in a significantly prolonged half-life and decreased volume of distribution of the coumarin anticoagulant in six healthy volunteers (Vesell et al, 1970j). The mechanism of action was suggested to be reduced bishydroxycoumarin metabolism and/or altered coumarin absorption.
c) Drug dosing was studied in 16 patients on long-term anticoagulant therapy who used concurrent TCAs (Williams et al, 1976j). TCAs affected the stability of anticoagulant control leading to frequent changes in the doses of anticoagulants. Inhibition of coumarin metabolism was the postulated mechanism.

3.5.1.AM Dienestrol

1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973g), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972g). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972g) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984g).
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic
8) Literature Reports
a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received imipramine (150 milligrams/day) and placebo, 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (50 micrograms/day), while 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (25 micrograms/day). The 10 patients that received placebo did not improve over the 6 weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after 2 weeks, the 5 patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The

only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received imipramine 150 milligrams and ethinyl estradiol 50 micrograms daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972f).

b) A case reported by (Khurana, 1972f) demonstrated an interaction in a 32-year-old female taking conjugated estrogens 2.5 milligrams and imipramine 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side-effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973f).

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973c).

d) The effect of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 milligrams at bedtime while 19 took clomipramine 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimental group (2 due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980c).

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 milligrams/day for anorexia nervosa and conjugated estrogens 1.25 milligrams/day for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogens 1.25 milligrams/day who was prescribed amitriptyline 50 milligrams/day for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. Positive rechallenge at one week with doxepin 100 milligrams, with resolution following discontinuation of doxepin. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogens 1.25 milligrams/day and amitriptyline 50 milligrams/day. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984f).

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 micrograms or less of ethinyl estradiol) from 27 to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984c).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980c). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983c).

3.5.1.AN Diethylpropion

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

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation

(Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

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

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

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

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

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.AO Diethylstilbestrol

1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973e), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972e). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972e) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984e).

3) Severity: minor

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.

7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic

8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received imipramine (150 milligrams/day) and placebo, 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (50 micrograms/day), while 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (25 micrograms/day). The 10 patients that received placebo did not improve over the 6 weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after 2 weeks, the 5 patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received imipramine 150 milligrams and ethinyl estradiol 50 micrograms daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972d).

b) A case reported by (Khurana, 1972d) demonstrated an interaction in a 32-year-old female taking conjugated estrogens 2.5 milligrams and imipramine 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side-effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana,

1973d).
c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973b).
d) The effect of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 milligrams at bedtime while 19 took clomipramine 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimental group (2 due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980b).
e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 milligrams/day for anorexia nervosa and conjugated estrogens 1.25 milligrams/day for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogens 1.25 milligrams/day who was prescribed amitriptyline 50 milligrams/day for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. Positive rechallenge at one week with doxepin 100 milligrams, with resolution following discontinuation of doxepin. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogens 1.25 milligrams/day and amitriptyline 50 milligrams/day. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984d).
f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 micrograms or less of ethinyl estradiol) from 27 to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984b).
g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980b). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983b).

3.5.1.AP Disopyramide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class Ia antiarrhythmics and tricyclic antidepressants 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 Class Ia antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Prod Info Elavil(R), 1999g; Prod Info Quinaglute(R), 1999; Marshall & Forker, 1982m).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic agent and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Quinidine is an inhibitor of the cytochrome P450 isoenzyme responsible for the 2-hydroxylation of imipramine and desipramine (Brosen & Gram, 1989). Inhibition of this enzyme system can result in a 35% decrease in imipramine clearance and 85% decrease in desipramine clearance. Demethylation of imipramine by the cytochrome P450 system is unaffected by this interaction. Until more information is available all patients having quinidine added to drug regimen containing imipramine or desipramine should be monitored for increased antidepressant serum concentrations and potential toxicity.
b) An increased incidence in sudden death was observed in six out of 53 patients with cardiac disease receiving amitriptyline, compared to 0 out of 53 in the control group. It was recommended that amitriptyline be avoided in patients with underlying cardiac disease except when depression was debilitating and no other drugs were helpful (Moir et al, 1972; Coull et al, 1970).
c) In a placebo controlled study, imipramine 3.5 mg/kg was administered daily for seven patients with severe depression and titrated doses to obtain therapeutic plasma concentrations. Two patients displayed premature atrial depolarizations and premature ventricular depolarizations before therapy. On patient had 33 premature atrial depolarizations (PAD) and 30 premature ventricular depolarizations (PVD) per hour, which decreased to 0.4 PAC and zero PVC per hour on imipramine. The other patient had 12 PAD and 169 PVD per hour before treatment and 1.8 PAD and 28.1 PVD per hour on

imipramine. The authors also cautioned that the incidence of cardiotoxicity may increase if tricyclic antidepressants are administered with Type I antiarrhythmics. It was also recommended that quinidine and procainamide not be used to treat the arrhythmias of a tricyclic overdose. The similarities between these agents may exacerbate the cardiotoxicity (Kantor et al, 1978).

3.5.1.AQ Dofetilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cases of QTc prolongation and/or torsades de pointes have been reported with all Class III antiarrhythmic agents, including acecainide (Chow et al, 1984), amiodarone (Faggiano et al, 1996), azimilide (Corey et al, 1999), bretylium (Gilman et al, 1985a), ibutilide (Rodriguez et al, 2001), sematilide (Singh, 1996), dofetilide (Allen et al, 2002), and sotalol (Marill & Runge, 2001). Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Yamreudeewong et al, 2003a; Prod Info Corvert(R), 2000).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepressant (TCA) is not recommended.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flattened T waves (Marshall & Forker, 1982y).
b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as tricyclic antidepressants, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003).

3.5.1.AR Dolasetron

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and dolasetron have been shown to prolong the QTc interval at the recommended therapeutic dose (Marshall & Forker, 1982c). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as dolasetron, is not recommended (Prod Info Elavil(R), 1999b; Prod Info Anzemet (R), 1997).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of dolasetron with other agents that may prolong the QTc interval, such as tricyclic antidepressants, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AS Droperidol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Droperidol has 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 droperidol and other drugs known to prolong the QTc interval, including tricylclic antidepressants is not recommended (Prod Info Inapsine(R), 2002; Marshall & Forker, 1982aa).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of droperidol and tricyclic antidepressants is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.AT Duloxetine

1) Interaction Effect: increased tricyclic antidepressant serum concentrations and potential toxicity (anticholinergic effects, sedation, confusion, cardiac arrhythmias)
2) Summary: The coadministration of duloxetine with a tricyclic antidepressant is likely to increase bioavailability of the tricyclic agent, increasing the risk of adverse events. Duloxetine is a moderately potent inhibitor of CYP2D6. When a single dose of the CYP2D6 substrate desipramine 50 mg and duloxetine 60 mg twice daily were coadministered, the desipramine AUC increased 3-fold over baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified

5) Substantiation: theoretical
6) Clinical Management: Use caution with the combined use of duloxetine with tricyclic antidepressants (TCAs). If concomitant therapy with duloxetine and a TCA is unavoidable, plasma concentrations of the tricyclic should be closely monitored and dose adjustments made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008). Also, monitor patients for signs and symptoms of TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrhythmias).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyclic agent metabolism

3.5.1.AU Enflurane
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest) and an increased risk of seizure activity
2) Summary: Enflurane may prolong the QT interval in some patients (Owens, 2001). Because tricyclic antidepressants may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of enflurane and tricyclic antidepressants is not recommended (Marshall & Forker, 1982a). Concomitant administration of amitriptyline and enflurane anesthesia has been reported to result in seizures in two cases (Sprague & Wolf, 1982a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Avoid concurrent use of enflurane and tricyclic antidepressants, particularly in patients with a history of seizure activity or when hyperventilation or high concentrations of enflurane will be required.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Two case reports of patients on amitriptyline therapy who experienced seizure activity while receiving enflurane anesthesia have been documented (Sprague & Wolf, 1982). The first patient, a 42-year old female, was taking amitriptyline 100 mg daily. Anesthesia was induced with fentanyl, enflurane, and nitrous oxide. Approximately three hours after anesthesia was induced, clonic movements of the patient's right hand and forearm were noted. Enflurane concentration was 1% at the time. Changes in ventilation did not affect the involuntary movements, so enflurane was discontinued and replaced with halothane 1%. The movements decreased in frequency and amplitude and subsequently disappeared in approximately one minute. The second case report involved a 39-year old male who was taking amitriptyline 150 mg daily. Anesthesia was maintained with enflurane 1% to 2%, and intermittent clonic movements started in the right arm and leg approximately one hour into the surgery. Enflurane was discontinued and halothane was instituted, which caused the involuntary movements to disappear in approximately two minutes. No further movements were seen during the remaining three hours of anesthesia.

3.5.1.AV Epinephrine
1) Interaction Effect: hypertension, cardiac arrhythmias, and tachycardia
2) Summary: Clinical trials have demonstrated a 2- to 8-fold increase in the effects of intravenous infusions of alpha adrenergic drugs to volunteers on tricyclic antidepressants. Arrhythmias and other severe adverse effects have also been reported (Ghose, 1980; Avery, 1973a; Boakes et al, 1973a; Boakes, 1973; Mitchell et al, 1970; Stone et al, 1964). Local use (e.g., dental anesthesia) of epinephrine in concentrations of 1:100,000 or less is less likely to precipitate clinically significant hemodynamic changes (Steinberg & Block, 1971).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The vasoconstriction and other alpha-adrenergic effects of sympathomimetic drugs are substantially enhanced in the presence of tricyclic antidepressants (TCAs). Concomitant use should be avoided. If these drugs are given together, careful monitoring and a dose reduction of the sympathomimetic is required. Patients should be instructed to inform their doctor or dentist that they are taking a tricyclic antidepressant prior to any surgery or procedure.
7) Probable Mechanism: inhibition of norepinephrine reuptake
8) Literature Reports
a) Four healthy volunteers received intravenous infusions of various sympathomimetic amines (epinephrine, norepinephrine, phenylephrine, and isoproterenol) before and after imipramine (25 mg three times daily for five days). They showed an increased pressor response to epinephrine (2- to 4-fold), norepinephrine (4- to 8-fold), and phenylephrine (2- to 3-fold) after imipramine, but no difference was observed in the response to isoproterenol. Thus, the increased pressor response appeared to occur only for alpha adrenergic effects. All four subjects demonstrated changes in cardiac rhythm with epinephrine and imipramine consisting of sinus arrhythmia in three subjects and multiple ectopic beats and a nodal rhythm in the fourth subject (Boakes et al, 1973).
b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found that 15 patients receiving a local anesthetic with norepinephrine (1:25,000) had severe reactions (severe headaches, chest tightness, subarachnoid hemorrhage). The drug history was incomplete, but at least three had been taking a tricyclic antidepressant at the time (Anon, 1972).

3.5.1.AW 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, 1995a). Erythromycin has demonstrated QTc prolongation in combination with other drugs that prolong the QT interval (Prod Info PCE(R), 1997). Tricyclic antidepressants have been shown to prolong the QTc interval at the recommended therapeutic dose (Marshall & Forker, 1982g). Caution is advised with coadministration of drugs that potentially prolong the QTc interval.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Caution is advised if erythromycin and tricyclic antidepressants are used concomitantly. Monitor QT interval at baseline and periodically during treatment.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) Erythromycin did not significantly affect the metabolism of tricyclic antidepressants in a study of 8 patients. Patients were maintained on desipramine (n equal to 5), imipramine (n equal to 1), doxepin (n equal to 1), or doxepin (n equal to 1). All patients received erythromycin stearate 250 mg four times daily for six days while maintaining their usual tricyclic regimen. No change in the antidepressant or active metabolite concentrations was seen during coadministration with erythromycin (Amsterdam & Maislin, 1991).

b) Tricyclic antidepressants have been shown to prolong the QTc interval at the recommended therapeutic dose (Marshall & Forker, 1982f).

c) Erythromycin significantly increased the QTc interval compared with baseline in a retrospective study of 49 patients. The erythromycin dose was 500 milligrams or 1 gram four times daily, with a mean of 15 doses received. Patients (n equal to 9) who received 60 mg/kg/day or more all developed increases in QT interval of 15% or greater. For all patients, the mean QTc interval increased from 432 milliseconds (msec) at baseline to 483 msec (p less than 0.01). In patients with delayed repolarization at baseline (n equal to 9), the QTc interval increased from 473 msec to 525 msec (p less than 0.01). In patients with heart disease (n equal to 30), all experienced an increase in QTc interval (mean of 15%), compared with an increase of 8% in patients without heart disease (p less than 0.05). In 5 patients (10%), the QTc interval was severely prolonged. One patient developed torsades de pointes attributed to erythromycin. Of 16 patients receiving cotrimoxazole concomitantly, 8 developed QT prolongation of 15% or greater (Oberg & Bauman, 1995).

3.5.1.AX Esterified Estrogens

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973a), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972a). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972a) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984a).

3) Severity: minor

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.

7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant

8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic

hypotension (Prange, 1972).
b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973; Khurana, 1972).
c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973).
d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980).
e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984).
f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984).
g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983).

3.5.1.AY Estradiol
1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973a), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972a). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972a) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984a).
3) Severity: minor
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant
8) Literature Reports
a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect

reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972).

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973; Khurana, 1972).

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973).

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980).

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984).

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983).

3.5.1.AZ Estriol

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973a), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972a). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972a) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984a).

3) Severity: minor

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.

7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant

8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received

imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972).

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973; Khurana, 1972).

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973).

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980).

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984).

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983).

3.5.1.BA Estrone

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973a), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972a). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972a) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984a).

3) Severity: minor

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or

resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant
8) Literature Reports
a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972).
b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973; Khurana, 1972).
c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973).
d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980).
e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984).
f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984).
g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983).

3.5.1.BB Estropipate
1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973a), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972a). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972a) and may be of clinical importance primarily in patients previously

stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984a).
3) Severity: minor
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant
8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972).

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973; Khurana, 1972).

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973).

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980).

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984).

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983).

3.5.1.BC Eterobarb

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.BD Ethinyl Estradiol

1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973k), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972k). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972k) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984k).
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic
8) Literature Reports
a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received imipramine (150 milligrams/day) and placebo, 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (50 micrograms/day), while 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (25 micrograms/day). The 10 patients that received placebo did not improve over the 6 weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after 2 weeks, the 5 patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received imipramine 150 milligrams and ethinyl estradiol 50 micrograms daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972j).
b) A case reported by (Khurana, 1972j) demonstrated an interaction in a 32-year-old female taking conjugated estrogens 2.5 milligrams and imipramine 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side-effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973j).
c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No

significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973f).

d) The effect of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 milligrams at bedtime while 19 took clomipramine 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimental group (2 due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980e).

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 milligrams/day for anorexia nervosa and conjugated estrogens 1.25 milligrams/day for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogens 1.25 milligrams/day who was prescribed amitriptyline 50 milligrams/day for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. Positive rechallenge at one week with doxepin 100 milligrams, with resolution following discontinuation of doxepin. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogens 1.25 milligrams/day and amitriptyline 50 milligrams/day. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984j).

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 micrograms or less of ethinyl estradiol) from 27 to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984e).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980e). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983e).

3.5.1.BE Etilefrine

1) Interaction Effect: hypertension, cardiac arrhythmias, and tachycardia

2) Summary: Clinical trials have demonstrated a 2- to 8-fold increase in the effects of intravenous infusions of alpha adrenergic drugs to volunteers on tricyclic antidepressants. Arrhythmias and other severe adverse effects have also been reported (Ghose, 1980; Avery, 1973a; Boakes et al, 1973a; Boakes, 1973; Mitchell et al, 1970; Stone et al, 1964). Local use (e.g., dental anesthesia) of epinephrine in concentrations of 1:100,000 or less is less likely to precipitate clinically significant hemodynamic changes (Steinberg & Block, 1971).

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: The vasoconstriction and other alpha-adrenergic effects of sympathomimetic drugs are substantially enhanced in the presence of tricyclic antidepressants (TCAs). Concomitant use should be avoided. If these drugs are given together, careful monitoring and a dose reduction of the sympathomimetic is required. Patients should be instructed to inform their doctor or dentist that they are taking a tricyclic antidepressant prior to any surgery or procedure.

7) Probable Mechanism: inhibition of norepinephrine reuptake

8) Literature Reports

a) Four healthy volunteers received intravenous infusions of various sympathomimetic amines (epinephrine, norepinephrine, phenylephrine, and isoproterenol) before and after imipramine (25 mg three times daily for five days). They showed an increased pressor response to epinephrine (2- to 4-fold), norepinephrine (4- to 8-fold), and phenylephrine (2- to 3-fold) after imipramine, but no difference was observed in the response to isoproterenol. Thus, the increased pressor response appeared to occur only for alpha adrenergic effects. All four subjects demonstrated changes in cardiac rhythm with epinephrine and imipramine consisting of sinus arrhythmia in three subjects and multiple ectopic beats and a nodal rhythm in the fourth subject (Boakes et al, 1973).

b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found that 15 patients receiving a local anesthetic with norepinephrine (1:25,000) had severe reactions (severe headaches, chest tightness, subarachnoid hemorrhage). The drug history was incomplete, but at least three had been taking a tricyclic antidepressant at the time (Anon, 1972).

3.5.1.BF Fenfluramine

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

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d;

Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.BG Fluconazole
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Case reports have described QT prolongation and torsades de points associated with fluconazole (Wassmann et al, 1999). Several tricyclic antidepressants (TCAs) have been shown to prolong the QTc interval at the recommended therapeutic dose (Marshall & Forker, 1982u). 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: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluconazole and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BH Fluoxetine
1) Interaction Effect: tricyclic antidepressant toxicity (dry mouth, urinary retention, sedation) and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001; Marshall & Forker, 1982h). Even though no formal drug interaction studies have been done which demonstrate QT prolongation, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as fluoxetine, is not recommended (Prod Info Elavil(R), 1999d). In addition, concurrent use of fluoxetine and TCAs such as desipramine, nortriptyline, and imipramine has resulted in significant increases in TCA concentrations (Preskorn et al, 1994a; Preskorn et al, 1994a; Aranow et al, 1989a; Downs et al, 1989a; Goodnick, 1989a; Bell & Cole, 1988a).

3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: decreased tricyclic antidepressant metabolism; additive effects on QT prolongation
8) Literature Reports
a) Fluoxetine increased the level of tricyclic antidepressants (nortriptyline, imipramine, desipramine) in 4 patients. After the addition of fluoxetine, the ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients developed clinical symptoms (anticholinergic effects, constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels (Aranow et al, 1989).
b) Fluoxetine statistically and clinically significantly increased desipramine concentrations in 18 healthy subjects. When fluoxetine (20 mg daily) was added to desipramine (50 mg daily), the mean maximum concentration of desipramine increased by 278% and the area under the concentration-time curve increased by 342%. Desipramine trough concentrations continued to be 198% above baseline three weeks after fluoxetine was discontinued. The same study compared pharmacokinetics of desipramine when combined with sertraline. The impact of sertraline was modest, resulting in small and short-term increases in desipramine plasma concentrations (Preskorn et al, 1994).
c) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations when fluoxetine was added. Desipramine serum levels ranged from 109 to 150 ng/mL with oral doses of 300 mg at bedtime prior to fluoxetine therapy. Following the addition of oral fluoxetine 20 mg daily to the regimen, the desipramine serum level increased to 212 ng/mL within five days. The fluoxetine dose was increased to 40 mg/day three days later, and the desipramine serum level was 419 ng/mL after four days. A worsening of depression and severe fatigue coincided with the increases in desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose to 200 mg daily reduced the desipramine serum level to 231 ng/mL within two weeks (Bell & Cole, 1988).
d) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with alertness and memory while receiving fluoxetine 40 mg daily and desipramine 150 mg daily for five weeks; fluoxetine was discontinued and the blood levels of desipramine decreased from 938 to 48 ng/mL with resolution of clinical symptoms (Goodnick, 1989).
e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant fluoxetine therapy. Prior to fluoxetine therapy, the patient's measured levels of desipramine had ranged from 148 to 160 ng/mL on a regimen of 300 mg daily. Five weeks after the addition of fluoxetine 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a desipramine level of 527 ng/mL. The desipramine dose was lowered to 200 mg/day; eleven days later, the level was 244 ng/mL; the patient reported decreased energy, impaired short-term memory, and some "garbled" speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced to 50 mg/day; the adverse effects resolved in six days. Eight days later, the desipramine level was 122 ng/mL (Downs et al, 1989).
f) Concomitant administration of fluoxetine and desipramine was reported to result in an increased desipramine level and new onset of delirium in a 69-year-old male within 10 days of the addition of fluoxetine to the patient's regimen (Preskorn et al, 1990).

3.5.1.BI Formoterol

1) Interaction Effect: an increased risk of cardiovascular excitation
2) Summary: Concurrent administration of formoterol with a tricyclic antidepressant (TCA) may lead to potentiation of formoterol's adrenergic effects on the cardiovascular system. Therefore, extreme caution is advised if formoterol is administered to patients who are being treated with a TCA (Prod Info FORADIL(R) AEROLIZER(R) inhalation powder, 2006). Monitor patients closely for adverse cardiovascular effects.
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Extreme caution and close observation for adverse cardiovascular effects are warranted when formoterol is administered concurrently with a tricyclic antidepressant (TCA) as the cardiovascular effects of formoterol can be potentiated by TCAs (Prod Info FORADIL(R) AEROLIZER(R) inhalation powder, 2006).
7) Probable Mechanism: potentiation of cardiovascular effects

3.5.1.BJ Fosamprenavir

1) Interaction Effect: increased tricyclic agent serum concentrations and potential toxicity (anticholinergic effects, sedation, confusion, cardiac arrhythmias)
2) Summary: Coadministration of fosamprenavir with a tricyclic antidepressant may provoke increased serum concentrations of the tricyclic antidepressant, causing a potential risk of arrhythmias or other serious adverse effects. Fosamprenavir is a prodrug of amprenavir, an inhibitor of the CYP3A4 isoenzyme in addition to being a CYP3A4 substrate. Tricyclic agents may partially depend on the CYP3A4 pathway for metabolism. Plasma concentrations of the tricyclic agent should be closely monitored in patients also receiving fosamprenavir (Prod Info LEXIVA(R) oral solution, oral tablets, 2009).

3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: If concomitant therapy with fosamprenavir and a tricyclic antidepressant is unavoidable, plasma concentrations of the tricyclic agent should be closely monitored. Also monitor patients for signs and symptoms of tricyclic toxicity (anticholinergic effects, sedation, confusion, cardiac arrhythmias) (Prod Info LEXIVA(R) oral solution, oral tablets, 2009).
7) Probable Mechanism: inhibition of CYP3A4-mediated tricyclic agent metabolism

3.5.1.BK 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. Because tricyclic antidepressants may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of foscarnet and tricyclic antidepressants is not recommended (Prod Info Foscavir(R), 1998; Marshall & Forker, 1982r).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of foscarnet and tricyclic antidepressants is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.BL Fosphenytoin
1) Interaction Effect: an increased risk of phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremor)
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). A few case reports have indicated that imipramine inhibits phenytoin metabolism resulting in increased serum phenytoin concentration (Petti & Campbell, 1975; Perucca & Richens, 1977). Tricyclic antidepressants (TCAs) may lower the seizure threshold in epileptic patients stabilized on anticonvulsants. Theoretically, because phenytoin is an enzyme inducer, the metabolism of antidepressants may be increased resulting in reduced TCA serum levels.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Consider monitoring phenytoin serum levels if a tricyclic antidepressant is added to therapy or if the patient begins to exhibit signs of toxicity (tremor, nystagmus, ataxia, hyperreflexia); lower doses of phenytoin may be required. If phenytoin is added to tricyclic antidepressant therapy, monitor for clinical efficacy of the tricyclic agent.
7) Probable Mechanism: inhibition of phenytoin metabolism

3.5.1.BM 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. Although pharmacokinetic studies between gatifloxacin and other drugs which prolong the QT interval have not been performed, an additive effect cannot be excluded. Therefore, the concurrent administration of gatifloxacin and a tricyclic antidepressant is not recommended (Prod Info Tequin(TM), 1999).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of gatifloxacin and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BN Gemifloxacin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although pharmacokinetic studies between gemifloxacin and drugs that prolong the QT interval, such as tricyclic antidepressants, have not been performed, gemifloxacin should be used cautiously when given concurrently with tricyclic antidepressants (Prod Info Factive(R), 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of two drugs that prolong the QT interval, such as gemifloxacin and tricyclic antidepressants, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BO 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 tricyclic antidepressants. 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 tricyclic antidepressants is contraindicated unless appropriate cardiac monitoring can be assured, such as in the hospitalized patient.
7) Probable Mechanism: additive cardiac effects

3.5.1.BP Guanadrel

1) Interaction Effect: decreased antihypertensive effectiveness
2) Summary: Tricyclic antidepressants inhibit the uptake of guanethidine, and possibly guanadrel into the adrenergic neuron, resulting in an inhibition of its antihypertensive effect (Mitchell et al, 1967; Ober & Wang, 1973). When a patient is on concomitant tricyclic antidepressant and guanadrel therapy, caution should be exercised when the tricyclic antidepressant is discontinued, since an exaggerated effect of guanadrel may be seen (Prod Info Hylorel(R), 1995).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Blood pressure should be monitored for an appropriate clinical response; higher doses of guanadrel may be required. An alternative class of antihypertensive agents, such as an angiotensin-converting enzyme inhibitor might be considered.
7) Probable Mechanism: decreased uptake of guanadrel into adrenergic neurons

3.5.1.BQ Guanethidine

1) Interaction Effect: decreased antihypertensive effectiveness
2) Summary: Tricyclic antidepressants inhibit the uptake of guanethidine, and possibly guanadrel, into the adrenergic neuron, resulting in a inhibition of the antihypertensive effect (Meyer et al, 1970; Pinder et al, 1977).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Blood pressure should be monitored for an appropriate clinical response; higher doses of guanethidine may be required. An alternative class of antihypertensive agents, such as an angiotensin-converting enzyme inhibitor, might be considered.
7) Probable Mechanism: decreased uptake of guanethidine into adrenergic neurons
8) Literature Reports
a) Doses of doxepin of 200 mg daily or more progressively produce blockade of the effects of guanethidine (Fann et al, 1971a; Oates et al, 1969a). Antagonism of the effects of guanethidine developed slowly in one patient (over two to four days), even when given in a dose of 300 mg daily doxepin. Two other patients experienced reversal of the hypotensive effects of guanethidine at doses of doxepin 200 to 300 mg daily. In all cases, the antagonism of antihypertensive effects was less than that of desipramine (Fann et al, 1971a).
b) No antagonism of guanethidine was reported in two patients receiving doxepin 200 mg (Ayd, 1975). However, antagonism was observed at 300 mg doses (Ayd, 1971). A single case report describes a hypertensive crisis in a patient receiving guanethidine and chlorpromazine upon initiation of doxepin therapy less than 200 mg (Poe et al, 1979). Doses of 300 mg a day or more will usually completely reverse the hypotensive effects of guanethidine (Ayd, 1973).

3.5.1.BR 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. Because tricyclic antidepressants may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of halofantrine and tricyclic antidepressants is not recommended (Prod Info Halfan(R), 1998; Marshall & Forker, 1982x).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The concurrent administration of halofantrine and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.BS Haloperidol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), quetiapine (Owens, 2001b), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marshall & Forker, 1982p).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999).

3.5.1.BT Halothane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Halothane may prolong the QT interval in some patients (Owens, 2001a). Because tricyclic antidepressants may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of halothane and tricyclic antidepressants is not recommended (Marshall & Forker, 1982o).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Because of the potential for additive QT interval prolongation, the concurrent administration of halothane and tricyclic antidepressants is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BU Heptabarbital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects

2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.

7) Probable Mechanism: increased tricyclic antidepressant metabolism

8) Literature Reports

a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.BV Hexobarbital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects

2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of

TCAs in the presence of a barbiturate (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.BW Hydroquinidine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class Ia antiarrhythmics and tricyclic antidepressants 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 Class Ia antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Prod Info Elavil(R), 1999g; Prod Info Quinaglute(R), 1999; Marshall & Forker, 1982m).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic agent and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Quinidine is an inhibitor of the cytochrome P450 isoenzyme responsible for the 2-hydroxylation of imipramine and desipramine (Brosen & Gram, 1989). Inhibition of this enzyme system can result in a 35% decrease in imipramine clearance and 85% decrease in desipramine clearance. Demethylation of imipramine by the cytochrome P450 system is unaffected by this interaction. Until more information is available all patients having quinidine added to drug regimen containing imipramine or desipramine should be monitored for increased antidepressant serum concentrations and potential toxicity.
b) An increased incidence in sudden death was observed in six out of 53 patients with cardiac disease receiving amitriptyline, compared to 0 out of 53 in the control group. It was recommended that amitriptyline be avoided in patients with underlying cardiac disease except when depression was debilitating and no other drugs were helpful (Moir et al, 1972; Coull et al, 1970).
c) In a placebo controlled study, imipramine 3.5 mg/kg was administered daily for seven patients with severe depression and titrated doses to obtain therapeutic plasma concentrations. Two patients displayed premature atrial depolarizations and premature ventricular depolarizations before therapy. On patient had 33 premature atrial depolarizations (PAD) and 30 premature ventricular depolarizations (PVD) per hour, which decreased to 0.4 PAC and zero PVC per hour on imipramine. The other patient had 12 PAD and 169 PVD per hour before treatment and 1.8 PAD and 28.1 PVD per hour on imipramine. The authors also cautioned that the incidence of cardiotoxicity may increase if tricyclic antidepressants are administered with Type I antiarrhythmics. It was also recommended that quinidine and procainamide not be used to treat the arrhythmias of a tricyclic overdose. The similarities between these agents may exacerbate the cardiotoxicity (Kantor et al, 1978).

3.5.1.BX Ibutilide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cases of QTc prolongation and/or torsades de pointes have been reported with all Class III antiarrhythmic agents, including acecainide (Chow et al, 1984), amiodarone (Faggiano et al, 1996), azimilide (Corey et al, 1999), bretylium (Gilman et al, 1985a), ibutilide (Rodriguez et al, 2001), sematilide (Singh, 1996), dofetilide (Allen et al, 2002), and sotalol (Marill & Runge, 2001). Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Yamreudeewong et al, 2003a; Prod Info Corvert(R), 2000).
3) Severity: major

4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepressant (TCA) is not recommended.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flattened T waves (Marshall & Forker, 1982y).
b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as tricyclic antidepressants, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003).

3.5.1.BY Iproniazid
1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982o; Spigset et al, 1993p; Brodribb et al, 1994m; Neuvonen et al, 1993g). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991h). If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971q; White & Simpson, 1984m).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of a tricyclic antidepressant (TCA) and a monoamine oxidase inhibitor (MAOI) should be done only with close monitoring and where the clinical benefit outweighs the potential risk. Other antidepressant therapy should first be considered. Consider using a 14 day washout period between treatment with both medicines. If deemed clinically necessary, avoid large doses and use agents other than imipramine, clomipramine, desipramine, and tranylcypromine.
7) Probable Mechanism: altered catecholamine uptake and metabolism
8) Literature Reports
a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past. Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965h; Winston, 1971h; Schuckit et al, 1971p; Spiker & Pugh, 1976h). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965h).
b) Administration of a TCA after MAOI therapy may result in the development of serotonin syndrome. In a double-blind, crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-compulsive disorder, two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipramine therapy. After taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with clomipramine without adverse effects (Insel et al, 1982n).
c) A drug interaction occurred in a 76-year old woman who had been taking clomipramine 50 mg daily for several months prior to switching to moclobemide 300 mg daily. The patient experienced somnolescence, confusion, and fever which then progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days later after discontinuing all antidepressant medications (Spigset et al, 1993o).
d) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a physically healthy 34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulation and eventual death (Tackley & Tregaskis, 1987h).
e) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991g). Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs (Ponto et al, 1977h; Schuckit et al, 1971p; Ashcroft, 1975g).

3.5.1.BZ Isocarboxazid

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

2) Summary: The concurrent administration of isocarboxazid and doxepin is contraindicated (Prod Info Marplan(R), 1998). Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982r; Spigset et al, 1993s; Brodribb et al, 1994q; Neuvonen et al, 1993i). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991j). If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971u; White & Simpson, 1984p).

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: The concurrent use of doxepin and isocarboxazid is contraindicated. In patients being transferred to isocarboxazid therapy from a dibenzazepine-related entity, allow at least a one-week medication-free interval and then initiate isocarboxazid at one-half of the normal dose for at least the first week of therapy. Also allow one week to elapse between the discontinuation of isocarboxazid and the administration of another MAO inhibitor or dibenzazepine-related entity.

7) Probable Mechanism: altered catecholamine uptake and metabolism

8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOI) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers. Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965j; Brachfeld et al, 1963f; Winston, 1971j; Schuckit et al, 1971t; Sargent, 1965f; Spiker & Pugh, 1976j). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965j).

b) The development of serotonin syndrome was first reported due to administration of a TCA after MAOI therapy. In a double-blind, crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-compulsive disorder, two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipramine therapy. After taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with clomipramine without adverse effects (Insel et al, 1982q).

c) A drug interaction was reported when a 76-year old woman who had been taking clomipramine 50 mg daily for several months was switched to moclobemide 300 mg daily. The patient experienced somnolescence, confusion, and fever which then progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days later after discontinuing all antidepressant medications (Spigset et al, 1993r).

d) A 39-year old woman with bipolar disorder developed serotonin syndrome after imipramine was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when imipramine was started at 50 mg daily, followed by two dosage increases of imipramine to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in imipramine to 200 mg per day, the patient developed symptoms of serotonin syndrome, including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated with chlorpromazine and symptoms resolved over the next few days without further complications (Brodribb et al, 1994p).

e) Three patients with bipolar disorder developed manic symptoms while undergoing concurrent therapy with isocarboxazid and amitriptyline. In all three cases the patients had been given MAOIs and TCAs alone without complications. It was only when the drugs were used in combination that symptoms of mania emerged, suggesting a synergistic effect (de la Fuente et al, 1986e).

f) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a physically healthy 34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulation and eventual death (Tackley & Tregaskis, 1987i).

g) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 150 mg amitriptyline or its equivalent, 45 mg phenelzine, or 60 mg isocarboxazid) b) oral administration c) avoidance of clomipramine, imipramine, desipramine, and tranylcypromine in any combination, and d) close monitoring of patients (Kline, 1974e; Winston, 1971j; Schuckit et al, 1971t; White & Simpson, 1984o; Rom & Benner, 1972e). The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants

(five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991i). Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some sources suggest that the combination of amitriptyline and isocarboxazid is preferred (Perry et al, 1991i). Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs (Ponto et al, 1977j; Schuckit et al, 1971t; Ashcroft, 1975i).

3.5.1.CA Isoflurane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Isoflurane may prolong the QT interval in some patients (Owens, 2001c). Because tricyclic antidepressants may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of isoflurane and tricyclic antidepressants is not recommended (Marshall & Forker, 1982s).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Because of the potential for additive QT interval prolongation, the concurrent administration of isoflurane and a tricyclic antidepressants is not recommended.
7) Probable Mechanism: additive effect on QT prolongation

3.5.1.CB 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. Because tricyclic antidepressants may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of isradipine with a tricyclic antidepressant is not recommended (Prod Info DynaCirc(R), 2000; Marshall & Forker, 1982w).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of isradipine and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.CC Levomethadyl

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Levomethadyl can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Because doxepin may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of levomethadyl with doxepin is contraindicated (Prod Info Orlaam(R), 2001; Giardina et al, 1987).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of levomethadyl and doxepin is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.CD Linezolid

1) Interaction Effect: increased risk of serotonin syndrome (hyperthermia, hyperreflexia, myoclonus, mental status changes)
2) Summary: Concomitant use of linezolid and a tricyclic antidepressant, such as doxepin, is contraindicated in the absence of monitoring for serotonin syndrome. If symptoms occur, consider discontinuation of either one or both of the drugs. Linezolid is a reversible, nonselective inhibitor of monoamine oxidase and may therefore interact with tricyclic antidepressants. Spontaneous reports of serotonin syndrome associated with the co-administration of linezolid and serotonergic agents have been reported (Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension, 2008).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of linezolid and tricyclic antidepressants, such as doxepin, is contraindicated unless patient is closely observed for signs and/or symptoms of serotonin syndrome. If concomitant use is clinically warranted, monitor for signs and 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; Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension, 2008).

7) Probable Mechanism: linezolid inhibition of monoamine oxidase resulting in an increased concentration of serotonin

3.5.1.CE Lisdexamfetamine

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

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

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

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

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

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

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.CF Mazindol

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

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such

therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

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

treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.CH Mephobarbital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects

2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.

7) Probable Mechanism: increased tricyclic antidepressant metabolism

8) Literature Reports

a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.CI Mesoridazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Although citing no data, the manufacturer of mesoridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Serentil(R), 2001). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Marshall & Forker, 1982e).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent administration of a tricyclic antidepressant and mesoridazine is contraindicated.

7) Probable Mechanism: additive effect on QT interval

3.5.1.CJ Mestranol

1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973k), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972k). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972k) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984k).

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.

7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic

8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received imipramine (150 milligrams/day) and placebo, 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (50 micrograms/day), while 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (25 micrograms/day). The 10 patients that received placebo did not improve over the 6 weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after 2 weeks, the 5 patients that received imipramine and high-dose

estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received imipramine 150 milligrams and ethinyl estradiol 50 micrograms daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972j).

b) A case reported by (Khurana, 1972j) demonstrated an interaction in a 32-year-old female taking conjugated estrogens 2.5 milligrams and imipramine 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side-effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973j).

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973f).

d) The effect of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 milligrams at bedtime while 19 took clomipramine 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimental group (2 due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980e).

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 milligrams/day for anorexia nervosa and conjugated estrogens 1.25 milligrams/day for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogens 1.25 milligrams/day who was prescribed amitriptyline 50 milligrams/day for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. Positive rechallenge at one week with doxepin 100 milligrams, with resolution following discontinuation of doxepin. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogens 1.25 milligrams/day and amitriptyline 50 milligrams/day. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984j).

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 micrograms or less of ethinyl estradiol) from 27 to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984e).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980e). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983e).

3.5.1.CK Methamphetamine

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

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other

sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.CL Methohexital
1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.CM Methoxamine
1) Interaction Effect: hypertension, cardiac arrhythmias, and tachycardia
2) Summary: Clinical trials have demonstrated a 2- to 8-fold increase in the effects of intravenous infusions of alpha adrenergic drugs to volunteers on tricyclic antidepressants. Arrhythmias and other severe adverse effects have also been reported (Ghose, 1980; Avery, 1973a; Boakes et al, 1973a; Boakes, 1973; Mitchell et al, 1970; Stone et al, 1964). Local use (e.g., dental anesthesia) of epinephrine in concentrations of 1:100,000 or less is less likely to precipitate clinically significant hemodynamic changes (Steinberg & Block, 1971).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The vasoconstriction and other alpha-adrenergic effects of sympathomimetic drugs

are substantially enhanced in the presence of tricyclic antidepressants (TCAs). Concomitant use should be avoided. If these drugs are given together, careful monitoring and a dose reduction of the sympathomimetic is required. Patients should be instructed to inform their doctor or dentist that they are taking a tricyclic antidepressant prior to any surgery or procedure.

7) Probable Mechanism: inhibition of norepinephrine reuptake

8) Literature Reports

a) Four healthy volunteers received intravenous infusions of various sympathomimetic amines (epinephrine, norepinephrine, phenylephrine, and isoproterenol) before and after imipramine (25 mg three times daily for five days). They showed an increased pressor response to epinephrine (2- to 4-fold), norepinephrine (4- to 8-fold), and phenylephrine (2- to 3-fold) after imipramine, but no difference was observed in the response to isoproterenol. Thus, the increased pressor response appeared to occur only for alpha adrenergic effects. All four subjects demonstrated changes in cardiac rhythm with epinephrine and imipramine consisting of sinus arrhythmia in three subjects and multiple ectopic beats and a nodal rhythm in the fourth subject (Boakes et al, 1973).

b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found that 15 patients receiving a local anesthetic with norepinephrine (1:25,000) had severe reactions (severe headaches, chest tightness, subarachnoid hemorrhage). The drug history was incomplete, but at least three had been taking a tricyclic antidepressant at the time (Anon, 1972).

3.5.1.CN Methylphenidate

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

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

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

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

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

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

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.CO Midodrine

1) Interaction Effect: hypertension, cardiac arrhythmias, and tachycardia

2) Summary: Clinical trials have demonstrated a 2- to 8-fold increase in the effects of intravenous infusions

of alpha adrenergic drugs to volunteers on tricyclic antidepressants. Arrhythmias and other severe adverse effects have also been reported (Ghose, 1980; Avery, 1973a; Boakes et al, 1973a; Boakes, 1973; Mitchell et al, 1970; Stone et al, 1964). Local use (e.g., dental anesthesia) of epinephrine in concentrations of 1:100,000 or less is less likely to precipitate clinically significant hemodynamic changes (Steinberg & Block, 1971).

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: The vasoconstriction and other alpha-adrenergic effects of sympathomimetic drugs are substantially enhanced in the presence of tricyclic antidepressants (TCAs). Concomitant use should be avoided. If these drugs are given together, careful monitoring and a dose reduction of the sympathomimetic is required. Patients should be instructed to inform their doctor or dentist that they are taking a tricyclic antidepressant prior to any surgery or procedure.

7) Probable Mechanism: inhibition of norepinephrine reuptake

8) Literature Reports

a) Four healthy volunteers received intravenous infusions of various sympathomimetic amines (epinephrine, norepinephrine, phenylephrine, and isoproterenol) before and after imipramine (25 mg three times daily for five days). They showed an increased pressor response to epinephrine (2- to 4-fold), norepinephrine (4- to 8-fold), and phenylephrine (2- to 3-fold) after imipramine, but no difference was observed in the response to isoproterenol. Thus, the increased pressor response appeared to occur only for alpha adrenergic effects. All four subjects demonstrated changes in cardiac rhythm with epinephrine and imipramine consisting of sinus arrhythmia in three subjects and multiple ectopic beats and a nodal rhythm in the fourth subject (Boakes et al, 1973).

b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found that 15 patients receiving a local anesthetic with norepinephrine (1:25,000) had severe reactions (severe headaches, chest tightness, subarachnoid hemorrhage). The drug history was incomplete, but at least three had been taking a tricyclic antidepressant at the time (Anon, 1972).

3.5.1.CP Moclobemide

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

2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982c; Spigset et al, 1993c; Brodribb et al, 1994b; Neuvonen et al, 1993a). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991b). Consequently, coadministration of TCAs and MAOIs is contraindicated in most cases. If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971e; White & Simpson, 1984c).

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of moclobemide and a tricyclic antidepressant, such as doxepin, is contraindicated. If doxepin is replacing treatment with moclobemide, a minimum of two days should elapse after moclobemide is discontinued and doxepin therapy is begun (Prod Info Manerix(R), 2001). However, the manufacturer of doxepin recommends that the monoamine oxidase inhibitor (MAOI) be discontinued for at least 14 days before treatment with doxepin is initiated (Prod Info SINEQUAN(R) oral capsule, 2005). There is no specific washout period for replacing doxepin treatment with moclobemide. However, it is advisable to gradually taper the tricyclic antidepressant dosage before starting treatment with and MAOI (Remick, 2002).

7) Probable Mechanism: altered catecholamine uptake and metabolism

8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers (Prod Info Manerix(R), 2001). Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965b; Brachfeld et al, 1963a; Winston, 1971b; Schuckit et al, 1971d; Sargent, 1965a; Spiker & Pugh, 1976b). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965b).

b) A clinical study designed to detect an interaction between moclobemide and a tricyclic antidepressant (clomipramine) resulted in severe adverse effects, and the study was terminated. Information about interactions with moclobemide and other tricyclic antidepressants is limited (Prod Info Manerix(R), 2001).

c) A drug interaction occurred in which a 76-year old woman who had been taking clomipramine 50 mg daily for several months prior to switching to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fever which then progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days later after discontinuing all

antidepressant medications (Spigset et al, 1993b).
d) Administration of a TCA after MAOI therapy may result in the development of serotonin syndrome. In a double-blind, crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-compulsive disorder, two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipramine therapy. After taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with clomipramine without adverse effects (Insel et al, 1982b).
e) A 39-year old woman with bipolar disorder developed serotonin syndrome after imipramine was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when imipramine was started at 50 mg daily, followed by two dosage increases of imipramine to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in imipramine to 200 mg per day, the patient developed symptoms of serotonin syndrome, including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated with chlorpromazine and symptoms resolved over the next few days without further complications (Brodribb et al, 1994a).
f) Three patients with bipolar disorder developed manic symptoms while undergoing concurrent therapy with isocarboxazid and amitriptyline. In all three cases the patients had been given MAOIs and TCAs alone without complications. It was only when the drugs were used in combination that symptoms of mania emerged, suggesting a synergistic effect (de la Fuente et al, 1986).
g) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a physically healthy 34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulation and eventual death (Tackley & Tregaskis, 1987a).
h) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 150 mg amitriptyline or its equivalent, 45 mg phenelzine, or 60 mg isocarboxazid) b) oral administration c) avoidance of clomipramine, imipramine, desipramine, and tranylcypromine in any combination, and d) close monitoring of patients (Kline, 1974; Winston, 1971b; Schuckit et al, 1971d; White & Simpson, 1984b; Rom & Benner, 1972). The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991a). Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some sources suggest that the combination of amitriptyline and isocarboxazid is preferred (Perry et al, 1991a). Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs (Ponto et al, 1977b; Schuckit et al, 1971d; Ashcroft, 1975a).

3.5.1.CQ Moxifloxacin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Moxifloxacin has been shown to prolong the QT interval in some patients and should be avoided in those patients receiving agents that also prolong the QT interval, such as tricyclic antidepressants. Although pharmacokinetic studies between moxifloxacin and other drugs which prolong the QT interval have not been performed, an additive effect cannot be excluded. Therefore, moxifloxacin should be used with caution when given concurrently with a tricyclic antidepressant (Prod Info Avelox(TM), 2000).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Moxifloxacin should be used with caution when given concurrently with a tricyclic antidepressant.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CR Nefopam
1) Interaction Effect: an increased risk of seizures
2) Summary: Nefopam inhibits the neuronal uptake of norepinephrine and serotonin and increases the risk of seizures, especially in patients with a history of a convulsive disorder. Tricyclic antidepressants also lower the seizure threshold. Therefore, the manufacturer of nefopam advises caution in patients on concurrent tricyclic antidepressant therapy (Pillans & Woods, 1995).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Because of the increased risk of seizures, extreme caution should be exercised in patients receiving nefopam and a tricyclic antidepressant. An alternative analgesic may be considered.
7) Probable Mechanism: additive lowering of seizure threshold

3.5.1.CS Nialamide

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

2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982m; Spigset et al, 1993n; Brodribb et al, 1994l; Neuvonen et al, 1993f). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991g). If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971o; White & Simpson, 1984l).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concomitant use of a tricyclic antidepressant (TCA) and a monoamine oxidase inhibitor (MAOI) should be done only with close monitoring and where the clinical benefit outweighs the potential risk. Other antidepressant therapy should first be considered. If deemed clinically necessary, avoid large doses and use agents other than imipramine, clomipramine, desipramine, and tranylcypromine.

7) Probable Mechanism: altered catecholamine uptake and metabolism

8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past. Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965g; Winston, 1971g; Schuckit et al, 1971n; Spiker & Pugh, 1976g). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965g).

b) In a double-blind, crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-compulsive disorder, two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipramine therapy. After taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with clomipramine without adverse effects (Insel et al, 1982l).

c) A drug interaction occurred in a 76-year old woman who had been taking clomipramine 50 mg daily for several months prior to switching to moclobemide 300 mg daily. The patient experienced somnolescence, confusion, and fever which then progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days later after discontinuing all antidepressant medications (Spigset et al, 1993m).

d) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a physically healthy 34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulation and eventual death (Tackley & Tregaskis, 1987g).

e) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991f). Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs (Ponto et al, 1977g; Schuckit et al, 1971n; Ashcroft, 1975f).

3.5.1.CT Norepinephrine

1) Interaction Effect: hypertension, cardiac arrhythmias, and tachycardia

2) Summary: Clinical trials have demonstrated a 2- to 8-fold increase in the effects of intravenous infusions of alpha adrenergic drugs to volunteers on tricyclic antidepressants. Arrhythmias and other severe adverse effects have also been reported (Ghose, 1980; Avery, 1973a; Boakes et al, 1973a; Boakes, 1973; Mitchell et al, 1970; Stone et al, 1964). Local use (e.g., dental anesthesia) of epinephrine in concentrations of 1:100,000 or less is less likely to precipitate clinically significant hemodynamic changes (Steinberg & Block, 1971).

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: The vasoconstriction and other alpha-adrenergic effects of sympathomimetic drugs are substantially enhanced in the presence of tricyclic antidepressants (TCAs). Concomitant use should be avoided. If these drugs are given together, careful monitoring and a dose reduction of the sympathomimetic is required. Patients should be instructed to inform their doctor or dentist that they are taking a tricyclic

antidepressant prior to any surgery or procedure.
7) Probable Mechanism: inhibition of norepinephrine reuptake
8) Literature Reports
a) Four healthy volunteers received intravenous infusions of various sympathomimetic amines (epinephrine, norepinephrine, phenylephrine, and isoproterenol) before and after imipramine (25 mg three times daily for five days). They showed an increased pressor response to epinephrine (2- to 4-fold), norepinephrine (4- to 8-fold), and phenylephrine (2- to 3-fold) after imipramine, but no difference was observed in the response to isoproterenol. Thus, the increased pressor response appeared to occur only for alpha adrenergic effects. All four subjects demonstrated changes in cardiac rhythm with epinephrine and imipramine consisting of sinus arrhythmia in three subjects and multiple ectopic beats and a nodal rhythm in the fourth subject (Boakes et al, 1973).
b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found that 15 patients receiving a local anesthetic with norepinephrine (1:25,000) had severe reactions (severe headaches, chest tightness, subarachnoid hemorrhage). The drug history was incomplete, but at least three had been taking a tricyclic antidepressant at the time (Anon, 1972).

3.5.1.CU Octreotide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and octreotide have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Sandostatin(R), 1999; Marshall & Forker, 1982). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as octreotide, is not recommended (Prod Info Elavil (R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of octreotide and tricyclic antidepressants is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CV Oxilofrine
1) Interaction Effect: hypertension, cardiac arrhythmias, and tachycardia
2) Summary: Clinical trials have demonstrated a 2- to 8-fold increase in the effects of intravenous infusions of alpha adrenergic drugs to volunteers on tricyclic antidepressants. Arrhythmias and other severe adverse effects have also been reported (Ghose, 1980; Avery, 1973a; Boakes et al, 1973a; Boakes, 1973; Mitchell et al, 1970; Stone et al, 1964). Local use (e.g., dental anesthesia) of epinephrine in concentrations of 1:100,000 or less is less likely to precipitate clinically significant hemodynamic changes (Steinberg & Block, 1971).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The vasoconstriction and other alpha-adrenergic effects of sympathomimetic drugs are substantially enhanced in the presence of tricyclic antidepressants (TCAs). Concomitant use should be avoided. If these drugs are given together, careful monitoring and a dose reduction of the sympathomimetic is required. Patients should be instructed to inform their doctor or dentist that they are taking a tricyclic antidepressant prior to any surgery or procedure.
7) Probable Mechanism: inhibition of norepinephrine reuptake
8) Literature Reports
a) Four healthy volunteers received intravenous infusions of various sympathomimetic amines (epinephrine, norepinephrine, phenylephrine, and isoproterenol) before and after imipramine (25 mg three times daily for five days). They showed an increased pressor response to epinephrine (2- to 4-fold), norepinephrine (4- to 8-fold), and phenylephrine (2- to 3-fold) after imipramine, but no difference was observed in the response to isoproterenol. Thus, the increased pressor response appeared to occur only for alpha adrenergic effects. All four subjects demonstrated changes in cardiac rhythm with epinephrine and imipramine consisting of sinus arrhythmia in three subjects and multiple ectopic beats and a nodal rhythm in the fourth subject (Boakes et al, 1973).
b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found that 15 patients receiving a local anesthetic with norepinephrine (1:25,000) had severe reactions (severe headaches, chest tightness, subarachnoid hemorrhage). The drug history was incomplete, but at least three had been taking a tricyclic antidepressant at the time (Anon, 1972).

3.5.1.CW Pargyline
1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982a; Spigset et al, 1993a; Brodribb et al, 1994; Neuvonen et al, 1993). Serotonin

syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991a). If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971a; White & Simpson, 1984).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of a tricyclic antidepressant (TCA) and a monoamine oxidase inhibitor (MAOI) should be done only with close monitoring and where the clinical benefit outweighs the potential risk. Other antidepressant therapy should first be considered. If deemed clinically necessary, avoid large doses and use agents other than imipramine, clomipramine, desipramine, and tranylcypromine.
7) Probable Mechanism: altered catecholamine uptake and metabolism
8) Literature Reports
a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past. Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965; Winston, 1971; Schuckit et al, 1971; Spiker & Pugh, 1976). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965).
b) Administration of a TCA after MAOI therapy may result in the development of serotonin syndrome. In a double-blind, crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-compulsive disorder, two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipramine therapy. After taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with clomipramine without adverse effects (Insel et al, 1982).
c) A drug interaction occurred in a 76-year old woman who had been taking clomipramine 50 mg daily for several months prior to switching to moclobemide 300 mg daily. The patient experienced somnolescence, confusion, and fever which then progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days later after discontinuing all antidepressant medications (Spigset et al, 1993).
d) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a physically healthy 34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulation and eventual death (Tackley & Tregaskis, 1987).
e) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991). Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs (Ponto et al, 1977; Schuckit et al, 1971; Ashcroft, 1975).

3.5.1.CX Paroxetine
1) Interaction Effect: doxepin toxicity (dry mouth, sedation, urinary retention)
2) Summary: Paroxetine coadministered with desipramine or imipramine produced higher serum concentrations of the tricyclic antidepressant (TCA) in some patients (Hartter et al, 1994; Brosen et al, 1993a). Although not reported specifically with doxepin, a similar interaction could be expected to occur. Paroxetine's effect on TCAs may resemble that of fluoxetine (another selective serotonin reuptake inhibitor), which is known to inhibit TCA metabolism (Aranow et al, 1989b; Vaughan, 1988; Goodnick, 1989b). With coadministration, monitor patients for doxepin toxicity. Doxepin doses may need to be reduced (Prod Info Paxil CR(TM), 2003).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When doxepin is coadministered with paroxetine, monitor patients for signs and symptoms of doxepin toxicity (dry mouth, sedation, urinary retention, blurred vision). Doxepin doses may need to be reduced.
7) Probable Mechanism: decreased doxepin metabolism
8) Literature Reports
a) The effect of paroxetine on desipramine metabolism was studied in 9 extensive metabolizers (EM) and 8 poor metabolizers (PM) of desipramine. Subjects took a single oral dose of desipramine before starting paroxetine and a second dose after 11 days of paroxetine use. After the addition of paroxetine,

EMs experienced a 5-fold decrease in clearance of desipramine, indicating that paroxetine inhibits oxidation reactions catalyzed by CYP2D6. PMs had a slight increase in clearance of desipramine with paroxetine. With concurrent administration of desipramine and paroxetine, interaction of the two drugs may result in a need for dosage adjustments, especially in extensive metabolizers of desipramine (Brosen et al, 1993).

3.5.1.CY Pemoline

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

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

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

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

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

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.CZ Pentamidine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and pentamidine have been shown to prolong the QTc interval at the recommended therapeutic dose (Lindsay et al, 1990; Marshall & Forker, 1982i). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as pentamidine, is not recommended (Prod Info Elavil (R), 1999e).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pentamidine and tricyclic antidepressants is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.DA Pentobarbital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

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

advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.DC Phenelzine

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

2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982k; Spigset et al, 1993l; Brodribb et al, 1994k; Neuvonen et al, 1993e). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991f). If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971m; White & Simpson, 1984k).

3) Severity: major

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of a tricyclic antidepressant, such as doxepin, and a monoamine oxidase inhibitor (MAOI), such as phenelzine, should be done only with close monitoring and where the clinical benefit outweighs the potential risk. Other antidepressant therapy should first be considered. If deemed clinically necessary, avoid large doses and use agents other than imipramine, clomipramine, desipramine, and tranylcypromine. If doxepin is replacing treatment with phenelzine, a minimum of 14 days should elapse after phenelzine is discontinued before doxepin therapy begins (Prod Info SINEQUAN(R) capsule, oral concentrate, 2005). The manufacturer of phenelzine recommends a minimum of 10 days should elapse between discontinuing the tricyclic antidepressant therapy and initiating treatment with phenelzine (Prod Info NARDIL(R) Tablets, USP, 2005).

7) Probable Mechanism: altered catecholamine uptake and metabolism

8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers. Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965f; Brachfeld et al, 1963e; Winston, 1971f; Schuckit et al, 1971l; Sargent, 1965e; Spiker & Pugh, 1976f). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965f).

b) Administration of a TCA after MAOI therapy may result in the development of serotonin syndrome. In a double-blind, crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-compulsive disorder, two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipramine therapy. After taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with clomipramine without adverse effects (Insel et al, 1982j).

c) A drug interaction occurred in a 76-year old woman who had been taking clomipramine 50 mg daily for several months prior to switching to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fever which then progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days later after discontinuing all antidepressant medications (Spigset et al, 1993k).

d) A 39-year old woman with bipolar disorder developed serotonin syndrome after imipramine was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when imipramine was started at 50 mg daily, followed by two dosage increases of imipramine to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in imipramine to 200 mg per day, the patient developed symptoms of serotonin syndrome, including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated with chlorpromazine and symptoms resolved over the next few days without further complications (Brodribb et al, 1994j).

e) Three patients with bipolar disorder developed manic symptoms while undergoing concurrent therapy with isocarboxazid and amitriptyline. In all three cases the patients had been given MAOIs and TCAs alone without complications. It was only when the drugs were used in combination that symptoms of mania emerged, suggesting a synergistic effect (de la Fuente et al, 1986d).

f) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a physically healthy 34-year old man. After taking several doses, the patient developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulation and eventual death (Tackley & Tregaskis, 1987f).

g) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. A few precautions must be followed including: a) avoidance of

large doses (no more than 150 mg amitriptyline or its equivalent, 45 mg phenelzine, or 60 mg isocarboxazid) b) oral administration c) avoidance of clomipramine, imipramine, desipramine, and tranylcypromine in any combination, and d) close monitoring of patients (Kline, 1974d; Winston, 1971f; Schuckit et al, 1971l; White & Simpson, 1984j; Rom & Benner, 1972d). The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991e). Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some sources suggest that the combination of amitriptyline and isocarboxazid is preferred (Perry et al, 1991e). Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs (Ponto et al, 1977f; Schuckit et al, 1971l; Ashcroft, 1975e).

3.5.1.DD Phenindione

1) Interaction Effect: increased risk of bleeding
2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants (Vesell et al, 1970e; Williams et al, 1976e). Considerable interindividual differences may be found (Pond et al, 1975e).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: In patients receiving tricyclic antidepressants and oral anticoagulant therapy, the prothrombin time ratio or INR (international normalized ratio) should be closely monitored with the addition and withdrawal of the antidepressant, and should be periodically reassessed during concurrent therapy. Achieving a stable drug regimen which produces the desired level of anticoagulation may be difficult in patients on this combination, and frequent adjustments of the anticoagulant dose may be required.
7) Probable Mechanism: decreased phenindione metabolism; increased phenindione absorption
8) Literature Reports

a) In a study of healthy volunteers, the concurrent use of nortriptyline or amitriptyline resulted in an increase of dicumarol levels and an increase in the plasma half-life of dicumarol, although the effect was not consistent in all subjects (Pond et al, 1975d). This effect was not observed with warfarin.
b) A single oral dose of bishydroxycoumarin after 8 days of nortriptyline resulted in a significantly prolonged half-life and decreased volume of distribution of the coumarin anticoagulant in 6 healthy volunteers (Vesell et al, 1970d). The mechanism of action was suggested to be reduced bishydroxycoumarin metabolism and/or altered coumarin absorption.
c) Drug dosing was studied in 16 patients on long-term anticoagulant therapy who used concurrent TCAs (Williams et al, 1976d). TCAs affected the stability of anticoagulant control leading to frequent changes in the doses of anticoagulants. Inhibition of coumarin metabolism was the postulated mechanism.

3.5.1.DE Phenmetrazine

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

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info

DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.DF Phenobarbital
1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.DG Phenprocoumon
1) Interaction Effect: increased risk of bleeding
2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants (Vesell et al, 1970g; Williams et al, 1976g). Considerable interindividual differences may be found (Pond et al, 1975g).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: In patients receiving tricyclic antidepressants and oral anticoagulant therapy, the prothrombin time ratio or INR (international normalized ratio) should be closely monitored with the addition and withdrawal of the antidepressant, and should be periodically reassessed during concurrent therapy. Achieving a stable drug regimen which produces the desired level of anticoagulation may be difficult in patients on this combination, and frequent adjustments of the anticoagulant dose may be required.
7) Probable Mechanism: decreased phenprocoumon metabolism; increased phenprocoumon absorption
8) Literature Reports
a) In a study of healthy volunteers, the concurrent use of nortriptyline or amitriptyline resulted in an increase of dicumarol levels and an increase in the plasma half-life of dicumarol, although the effect was not consistent in all subjects (Pond et al, 1975f). This effect was not observed with warfarin.
b) A single oral dose of bishydroxycoumarin after 8 days of nortriptyline resulted in a significantly prolonged half-life and decreased volume of distribution of the coumarin anticoagulant in 6 healthy volunteers (Vesell et al, 1970f). The mechanism of action was suggested to be reduced bishydroxycoumarin metabolism and/or altered coumarin absorption.
c) Drug dosing was studied in 16 patients on long-term anticoagulant therapy who used concurrent TCAs (Williams et al, 1976f). TCAs affected the stability of anticoagulant control leading to frequent changes in the doses of anticoagulants. Inhibition of coumarin metabolism was the postulated

mechanism.

3.5.1.DH Phentermine

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

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

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

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

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

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

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.DI Phenylephrine

1) Interaction Effect: hypertension, cardiac arrhythmias, and tachycardia

2) Summary: Clinical trials have demonstrated a 2- to 8-fold increase in the effects of intravenous infusions of alpha adrenergic drugs to volunteers on tricyclic antidepressants. Arrhythmias and other severe adverse effects have also been reported (Ghose, 1980; Avery, 1973a; Boakes et al, 1973a; Boakes, 1973; Mitchell et al, 1970; Stone et al, 1964). Local use (e.g., dental anesthesia) of epinephrine in concentrations of 1:100,000 or less is less likely to precipitate clinically significant hemodynamic changes (Steinberg & Block, 1971).

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: The vasoconstriction and other alpha-adrenergic effects of sympathomimetic drugs are substantially enhanced in the presence of tricyclic antidepressants (TCAs). Concomitant use should be avoided. If these drugs are given together, careful monitoring and a dose reduction of the sympathomimetic is required. Patients should be instructed to inform their doctor or dentist that they are taking a tricyclic antidepressant prior to any surgery or procedure.

7) Probable Mechanism: inhibition of norepinephrine reuptake

8) Literature Reports

a) Four healthy volunteers received intravenous infusions of various sympathomimetic amines (epinephrine, norepinephrine, phenylephrine, and isoproterenol) before and after imipramine (25 mg

three times daily for five days). They showed an increased pressor response to epinephrine (2- to 4-fold), norepinephrine (4- to 8-fold), and phenylephrine (2- to 3-fold) after imipramine, but no difference was observed in the response to isoproterenol. Thus, the increased pressor response appeared to occur only for alpha adrenergic effects. All four subjects demonstrated changes in cardiac rhythm with epinephrine and imipramine consisting of sinus arrhythmia in three subjects and multiple ectopic beats and a nodal rhythm in the fourth subject (Boakes et al, 1973).

b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found that 15 patients receiving a local anesthetic with norepinephrine (1:25,000) had severe reactions (severe headaches, chest tightness, subarachnoid hemorrhage). The drug history was incomplete, but at least three had been taking a tricyclic antidepressant at the time (Anon, 1972).

3.5.1.DJ Phenytoin

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

2) Summary: A few case reports have indicated that imipramine inhibits phenytoin metabolism resulting in increased serum phenytoin. Tricyclic antidepressants (TCAs) may lower the seizure threshold in epileptic patients stabilized on anticonvulsants. Theoretically, because phenytoin is an enzyme inducer, the metabolism of antidepressants may be increased resulting in reduced TCA serum levels (Petti & Campbell, 1975a; Perucca & Richens, 1977a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor therapeutic efficacy of doxepin; an increased dose may be required. Serum phenytoin levels should be obtained when tricyclic antidepressant agents are added to therapy due to the potential for impaired phenytoin metabolism.

7) Probable Mechanism: inhibition of phenytoin metabolism

3.5.1.DK 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 pimozide states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Orap(R), 1999a). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Prod Info Norpramin(R), 2000; Marshall & Forker, 1982z).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Because of the potential to prolong the QT interval, concurrent administration of a tricyclic antidepressant and pimozide is contraindicated.

7) Probable Mechanism: additive effects on QT interval

8) Literature Reports

a) Electrocardiogram (ECG) changes seen during clinical trials of pimozide in Tourette's syndrome and schizophrenia patients include prolongation of the QT interval, flattening, notching, and inversion of the T wave, and the appearance of U waves. Sudden, unexpected deaths have occurred at doses greater than 20 milligrams/day (Prod Info Orap(R) pimozide, 1999).

3.5.1.DL Pirmenol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Class Ia antiarrhythmics and tricyclic antidepressants 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 Class Ia antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Prod Info Elavil(R), 1999g; Prod Info Quinaglute(R), 1999; Marshall & Forker, 1982m).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic agent and a tricyclic antidepressant is not recommended.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) Quinidine is an inhibitor of the cytochrome P450 isoenzyme responsible for the 2-hydroxylation of imipramine and desipramine (Brosen & Gram, 1989). Inhibition of this enzyme system can result in a 35% decrease in imipramine clearance and 85% decrease in desipramine clearance. Demethylation of imipramine by the cytochrome P450 system is unaffected by this interaction. Until more information is available all patients having quinidine added to drug regimen containing imipramine or desipramine should be monitored for increased antidepressant serum concentrations and potential toxicity.

b) An increased incidence in sudden death was observed in six out of 53 patients with cardiac disease receiving amitriptyline, compared to 0 out of 53 in the control group. It was recommended that

amitriptyline be avoided in patients with underlying cardiac disease except when depression was debilitating and no other drugs were helpful (Moir et al, 1972; Coull et al, 1970).
c) In a placebo controlled study, imipramine 3.5 mg/kg was administered daily for seven patients with severe depression and titrated doses to obtain therapeutic plasma concentrations. Two patients displayed premature atrial depolarizations and premature ventricular depolarizations before therapy. On patient had 33 premature atrial depolarizations (PAD) and 30 premature ventricular depolarizations (PVD) per hour, which decreased to 0.4 PAC and zero PVC per hour on imipramine. The other patient had 12 PAD and 169 PVD per hour before treatment and 1.8 PAD and 28.1 PVD per hour on imipramine. The authors also cautioned that the incidence of cardiotoxicity may increase if tricyclic antidepressants are administered with Type I antiarrhythmics. It was also recommended that quinidine and procainamide not be used to treat the arrhythmias of a tricyclic overdose. The similarities between these agents may exacerbate the cardiotoxicity (Kantor et al, 1978).

3.5.1.DM Prajmaline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class Ia antiarrhythmics and tricyclic antidepressants 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 Class Ia antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Prod Info Elavil(R), 1999g; Prod Info Quinaglute(R), 1999; Marshall & Forker, 1982m).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic agent and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Quinidine is an inhibitor of the cytochrome P450 isoenzyme responsible for the 2-hydroxylation of imipramine and desipramine (Brosen & Gram, 1989). Inhibition of this enzyme system can result in a 35% decrease in imipramine clearance and 85% decrease in desipramine clearance. Demethylation of imipramine by the cytochrome P450 system is unaffected by this interaction. Until more information is available all patients having quinidine added to drug regimen containing imipramine or desipramine should be monitored for increased antidepressant serum concentrations and potential toxicity.
b) An increased incidence in sudden death was observed in six out of 53 patients with cardiac disease receiving amitriptyline, compared to 0 out of 53 in the control group. It was recommended that amitriptyline be avoided in patients with underlying cardiac disease except when depression was debilitating and no other drugs were helpful (Moir et al, 1972; Coull et al, 1970).
c) In a placebo controlled study, imipramine 3.5 mg/kg was administered daily for seven patients with severe depression and titrated doses to obtain therapeutic plasma concentrations. Two patients displayed premature atrial depolarizations and premature ventricular depolarizations before therapy. On patient had 33 premature atrial depolarizations (PAD) and 30 premature ventricular depolarizations (PVD) per hour, which decreased to 0.4 PAC and zero PVC per hour on imipramine. The other patient had 12 PAD and 169 PVD per hour before treatment and 1.8 PAD and 28.1 PVD per hour on imipramine. The authors also cautioned that the incidence of cardiotoxicity may increase if tricyclic antidepressants are administered with Type I antiarrhythmics. It was also recommended that quinidine and procainamide not be used to treat the arrhythmias of a tricyclic overdose. The similarities between these agents may exacerbate the cardiotoxicity (Kantor et al, 1978).

3.5.1.DN Primidone

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-

related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.DO Procainamide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Class Ia antiarrhythmics and tricyclic antidepressants 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 Class Ia antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Prod Info Elavil(R), 1999g; Prod Info Quinaglute(R), 1999; Marshall & Forker, 1982m).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic agent and a tricyclic antidepressant is not recommended.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) Quinidine is an inhibitor of the cytochrome P450 isoenzyme responsible for the 2-hydroxylation of imipramine and desipramine (Brosen & Gram, 1989). Inhibition of this enzyme system can result in a 35% decrease in imipramine clearance and 85% decrease in desipramine clearance. Demethylation of imipramine by the cytochrome P450 system is unaffected by this interaction. Until more information is available all patients having quinidine added to drug regimen containing imipramine or desipramine should be monitored for increased antidepressant serum concentrations and potential toxicity.

b) An increased incidence in sudden death was observed in six out of 53 patients with cardiac disease receiving amitriptyline, compared to 0 out of 53 in the control group. It was recommended that amitriptyline be avoided in patients with underlying cardiac disease except when depression was debilitating and no other drugs were helpful (Moir et al, 1972; Coull et al, 1970).

c) In a placebo controlled study, imipramine 3.5 mg/kg was administered daily for seven patients with severe depression and titrated doses to obtain therapeutic plasma concentrations. Two patients displayed premature atrial depolarizations and premature ventricular depolarizations before therapy. On patient had 33 premature atrial depolarizations (PAD) and 30 premature ventricular depolarizations (PVD) per hour, which decreased to 0.4 PAC and zero PVC per hour on imipramine. The other patient had 12 PAD and 169 PVD per hour before treatment and 1.8 PAD and 28.1 PVD per hour on imipramine. The authors also cautioned that the incidence of cardiotoxicity may increase if tricyclic antidepressants are administered with Type I antiarrhythmics. It was also recommended that quinidine and procainamide not be used to treat the arrhythmias of a tricyclic overdose. The similarities between these agents may exacerbate the cardiotoxicity (Kantor et al, 1978).

3.5.1.DP Procarbazine

1) Interaction Effect: neurotoxicity, seizures

2) Summary: Concomitant tricyclic antidepressant and more potent MAOI use has resulted in hyperpyrexia, convulsions, and death. Procarbazine has relatively weak MAOI actions, so while the potential for drug interactions between tricyclic antidepressants and procarbazine exists, clinical data are lacking at this time (Schuckit et al, 1971c; White & Simpson, 1984a). Concurrent use is not recommended (Prod Info Matulane (R), 1997).

3) Severity: major

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Concomitant use is not recommended and should probably be initiated only under close medical supervision, and then only if other antidepressant class agents have proven unsuccessful. With more potent MAOIs, recommendations for concurrent use of TCAs have included avoiding large doses of the TCA, using only oral tricyclics, and avoiding imipramine, clomipramine, and desipramine. Procarbazine therapy should not begin until seven days following discontinuation of tricyclic antidepressants and 14 days following the discontinuation of other MAO inhibitors.

7) Probable Mechanism: altered catecholamine uptake and metabolism

8) Literature Reports

a) Procarbazine is primarily used as an antineoplastic agent, but was originally investigated as a monoamine oxidase inhibitor (Gilman et al, 1985). Animal studies have indicated that procarbazine is a monoamine oxidase inhibitor (MAOI) (DeVita et al, 1965) but appears to be a relatively weak MAOI in man (Gilman et al, 1985). Hypertensive reactions may still result from concomitant administration of tricyclic antidepressants, sympathomimetics, and tyramine containing foods (Gilman et al, 1985; Ponto et al, 1977a).

b) Concomitant administration of monoamine oxidase (MAO) inhibitors with tricyclic antidepressants

has been considered an absolute contraindication in the past and still is listed as such by the manufacturers. Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965a; Brachfeld et al, 1963; Winston, 1971a; Schuckit et al, 1971b; Sargent, 1965; Spiker & Pugh, 1976a). Careful examination of such reports indicate unusual circumstances in most cases such as parenteral administration of a tricyclic. The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965a).

c) Procarbazine therapy should not begin until 7 days following discontinuation of tricyclic antidepressants and 14 days following the discontinuation of other MAO inhibitors (AMA Department of Drugs, 1992; Gilman et al, 1985).

3.5.1.DQ Prochlorperazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002; Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, though no reports are available. Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Marshall & Forker, 1982ad). Case reports have described increased plasma levels and adverse effects when phenothiazines and tricyclic antidepressants were taken together, likely due to inhibition of their metabolism (Ghaemi & Kirkwood, 1998; Geller et al, 1985; Siris et al, 1982; Loga et al, 1981).

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent administration of a phenothiazine and a tricyclic antidepressant is not recommended.

7) Probable Mechanism: additive effect on QT interval

3.5.1.DR Propafenone

1) Interaction Effect: doxepin toxicity (sedation, dry mouth)

2) Summary: A single case was reported in which coadministration of propafenone and desipramine in an elderly patient resulted in desipramine toxicity at a desipramine dosage which had previously produced levels in the therapeutic range (Katz, 1991a). Although not reported for doxepin, caution should be used with concomitant use of propafenone.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Monitor for symptoms of tricyclic antidepressant toxicity.

7) Probable Mechanism: decreased doxepin metabolism

8) Literature Reports

a) A 68-year-old man suffering from agitated major depression was started on a dose of desipramine 125 mg daily which produced a subtherapeutic serum level of 442 nmol/L (therapeutic range 500 to 1000 nmol/L). An increased dose of 175 mg daily produced excellent clinical response with no side effects. He developed atrial fibrillation and flutter. Digoxin 0.25 mg daily was added to his therapy, and desipramine was discontinued. His arrhythmia was suppressed with the addition of propafenone 150 mg twice daily and 300 mg at bedtime. Desipramine 150 mg daily was again begun, at which point he experienced dry mouth, sedation, and shakiness; the desipramine serum level was measured at 2092 nmol/L. The desipramine was discontinued for five days, the side effects ceased, and desipramine therapy was resumed at 75 mg daily. The desipramine serum level was measured at 1130 nmol/L (Katz, 1991).

3.5.1.DS Propoxyphene

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

2) Summary: Concomitant therapy with propoxyphene and doxepin has been reported to double steady state doxepin and desmethyldoxepin plasma concentrations and decrease cognitive function. This interaction is most likely related to inhibition of hepatic microsomal enzymes by propoxyphene (Abernethy et al, 1982).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for symptoms of tricyclic antidepressant toxicity such as sedation, dry mouth, and urinary retention. Serum doxepin levels may also be of value in predicting toxicity. An alternative analgesic agent such as acetaminophen with codeine might be considered if clinically appropriate.

7) Probable Mechanism: decreased doxepin metabolism

3.5.1.DT Propylhexedrine

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

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been

reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

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

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

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

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

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.DU Quetiapine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), quetiapine (Owens, 2001b), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marshall & Forker, 1982p).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999).

3.5.1.DV Quinestrol

1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension,

akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973c), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972c). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972c) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984c).
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic
8) Literature Reports
a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mcg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor, and systolic hypotension (Prange, 1972b).
b) A case reported by (Khurana, 1972b) demonstrated an interaction in a 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg. The patient developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side-effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973b).
c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973a).
d) The effect of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980a).
e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984b).
f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984a).
g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980a). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation

of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983a).

3.5.1.DW Quinidine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Class Ia antiarrhythmics and tricyclic antidepressants 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 Class Ia antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Prod Info Elavil(R), 1999g; Prod Info Quinaglute(R), 1999; Marshall & Forker, 1982m).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic agent and a tricyclic antidepressant is not recommended.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) Quinidine is an inhibitor of the cytochrome P450 isoenzyme responsible for the 2-hydroxylation of imipramine and desipramine (Brosen & Gram, 1989). Inhibition of this enzyme system can result in a 35% decrease in imipramine clearance and 85% decrease in desipramine clearance. Demethylation of imipramine by the cytochrome P450 system is unaffected by this interaction. Until more information is available all patients having quinidine added to drug regimen containing imipramine or desipramine should be monitored for increased antidepressant serum concentrations and potential toxicity.

b) An increased incidence in sudden death was observed in six out of 53 patients with cardiac disease receiving amitriptyline, compared to 0 out of 53 in the control group. It was recommended that amitriptyline be avoided in patients with underlying cardiac disease except when depression was debilitating and no other drugs were helpful (Moir et al, 1972; Coull et al, 1970).

c) In a placebo controlled study, imipramine 3.5 mg/kg was administered daily for seven patients with severe depression and titrated doses to obtain therapeutic plasma concentrations. Two patients displayed premature atrial depolarizations and premature ventricular depolarizations before therapy. On patient had 33 premature atrial depolarizations (PAD) and 30 premature ventricular depolarizations (PVD) per hour, which decreased to 0.4 PAC and zero PVC per hour on imipramine. The other patient had 12 PAD and 169 PVD per hour before treatment and 1.8 PAD and 28.1 PVD per hour on imipramine. The authors also cautioned that the incidence of cardiotoxicity may increase if tricyclic antidepressants are administered with Type I antiarrhythmics. It was also recommended that quinidine and procainamide not be used to treat the arrhythmias of a tricyclic overdose. The similarities between these agents may exacerbate the cardiotoxicity (Kantor et al, 1978).

3.5.1.DX Quinidine

1) Interaction Effect: doxepin toxicity (sedation, dry mouth, urinary retention) and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Two studies have demonstrated that concomitant use of quinidine and imipramine or desipramine results in increased serum concentrations of these antidepressants (Brosen & Gram, 1989b; Steiner et al, 1987). A similar interaction may occur with other tricyclic antidepressants including doxepin. Due to their similar cardiac effects, the incidence of cardiotoxicity (increased PR interval, QRS complex, and QTc interval) may also be increased if tricyclic antidepressants are administered with Type I antiarrhythmics (Kantor et al, 1978b; Bigger et al, 1977).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concurrent use of quinidine and doxepin is not recommended. Monitor for symptoms of tricyclic antidepressant toxicity; a decrease in doxepin dosage may be required. Also monitor the patient for signs and symptoms of additive cardiac effects, including any changes in the EKG.

7) Probable Mechanism: decreased doxepin metabolism, additive cardiac effects

8) Literature Reports

a) Quinidine is an inhibitor of the cytochrome P450 isoenzyme responsible for the 2-hydroxylation of imipramine and desipramine (Brosen & Gram, 1989a). Inhibition of this enzyme system can result in a 35% decrease in imipramine clearance and 85% decrease in desipramine clearance. Demethylation of imipramine by the cytochrome P450 system is unaffected by this interaction. Until more information is available, all patients having quinidine added to drug regimen containing imipramine or desipramine should be monitored for increased antidepressant serum concentrations and potential toxicity.

b) In a placebo controlled study, (Kantor et al, 1978a) administered imipramine 3.5 mg/kg daily for seven patients with severe depression and titrated doses to obtain therapeutic plasma concentrations. Two patients displayed premature atrial depolarizations and premature ventricular depolarizations before therapy. On patient had 33 premature atrial depolarizations (PAD) and 30 premature ventricular depolarizations (PVD) per hour, which decreased to 0.4 PAC and zero PVC per hour on imipramine.

The other patient had 12 PAD and 169 PVD per hour before treatment and 1.8 PAD and 28.1 PVD per hour on imipramine. The authors also cautioned that the incidence of cardiotoxicity may increase if tricyclic antidepressants are administered with Type I antiarrhythmics. It was also recommended that quinidine and procainamide not be used to treat the arrhythmias of a tricyclic overdose. The similarities between these agents may exacerbate the cardiotoxicity.

3.5.1.DY Rasagiline

1) Interaction Effect: severe CNS toxicity
2) Summary: Concomitant use of rasagiline and tricyclic antidepressants should be avoided. Concurrent administration or overlapping therapy with tricyclic antidepressants and non-selective MAOIs has been reported to cause serious, sometimes fatal, reactions; the mechanisms of these reactions are not fully understood. Signs and symptoms include severe CNS toxicity (behavioral and mental status changes, diaphoresis, muscular rigidity, hypertension, and syncope) associated with hyperpyrexia and death. Data from clinical studies, where rasagiline-treated patients (n=115) were concomitantly exposed to tricyclic antidepressants, are insufficient to rule out an interaction. At least 14 days should elapse after discontinuing rasagiline before initiating therapy with a tricyclic antidepressant (Prod Info AZILECT(R) oral tablets, 2006).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of rasagiline and a tricyclic antidepressant is not recommended. Wait at least 14 days after discontinuing rasagiline before initiating therapy with a tricyclic antidepressant (Prod Info AZILECT(R) oral tablets, 2006).
7) Probable Mechanism: unknown

3.5.1.DZ Risperidone

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), quetiapine (Owens, 2001b), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marshall & Forker, 1982p).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999).

3.5.1.EA S-Adenosylmethionine

1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: A single case has been reported of serotonin syndrome likely resulting from the combination of S-adenosylmethionine (SAMe) and clomipramine (Iruela et al, 1993a). SAMe was shown to hasten the onset of therapeutic response of imipramine in a clinical trial involving 40 patients, without serotonergic side effects (Berlanga et al, 1992). If therapy is initiated with SAMe and a tricyclic antidepressant, the patient should be monitored closely for early signs of serotonin syndrome. 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, 1991).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: S-adenosylmethionine (SAMe) used concomitantly with imipramine was found to decrease depressive symptoms sooner than imipramine alone (Berlanga et al, 1992). One case has been reported of serotonin syndrome likely resulting from concomitant use of SAMe and clomipramine (Iruela et al, 1993). If SAMe and a tricyclic antidepressant are used together, use low doses of each and titrate upward slowly, while monitoring closely for early signs of serotonin syndrome such as increasing anxiety, confusion, and disorientation.
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

8) Literature Reports

a) A 71 year-old female was hospitalized with anxiety, agitation, confusion, and symptoms of serotonin syndrome. She had been taking S-adenosylmethionine 100 milligrams (mg) intramuscularly daily and clomipramine 25 mg daily for 10 days, which was then increased to 75 mg/day. Within 48-72 hours of the increased clomipramine dosage, she became progressively anxious, agitated, and confused. On admission she was verbally unresponsive and stuporous, with heart rate 130 beats/minute, respiratory rate 30 breaths/minute, temperature 40.5 degrees Celsius, diarrhea, myoclonus, generalized tremors, rigidity, hyperreflexia, shivering, diaphoresis, and dehydration. Temperature increased to 43 degrees Celsius during her hospital stay, with no documented infection. White blood cell count (WBC) was 13,040 mm3, lactic dehydrogenase was 662 units/liter (U/L), creatine phosphokinase was 8920 U/L, serum potassium 2.7 milliequivalents/liter (mEq/L), creatinine 1.1 mg/100 milliliter (mL) (laboratory reference values were not provided). A cranial computed tomography (CT) scan was normal. The patient was not taking neuroleptics. Serum benzodiazepine and tricyclic antidepressant levels were normal. Symptoms resolved gradually with 4 days of hydration and supportive care. The interaction was proposed to be a result of synergistic activity of S-adenosylmethionine and clomipramine (Iruela et al, 1993).

3.5.1.EB Salmeterol

1) Interaction Effect: an increased risk of cardiovascular excitation

2) Summary: Salmeterol should be administered with extreme caution to patients who are being treated with a tricyclic antidepressant, or within two weeks of the discontinuation of a tricyclic antidepressant (Prod Info SEREVENT(R) DISKUS(R) inhalation powder, 2006). Clinically significant changes in systolic and diastolic blood pressure, pulse rate, and electrocardiograms have been seen with the use of salmeterol, and these changes may be exacerbated by the use of a tricyclic antidepressant.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Close observation for adverse cardiovascular effects is warranted when these agents are administered concurrently or if salmeterol is given within two weeks of discontinuation of a tricyclic antidepressant.

7) Probable Mechanism: potentiation of vascular effects

3.5.1.EC Secobarbital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects

2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.

7) Probable Mechanism: increased tricyclic antidepressant metabolism

8) Literature Reports

a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.ED Selegiline

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

2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982i; Spigset et al, 1993j; Brodribb et al, 1994i; Neuvonen et al, 1993d). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991e). If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971k; White & Simpson,

1984i).
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of a tricyclic antidepressant, such as doxepin, and a monoamine oxidase inhibitor (MAOI), such as selegiline, should be done only with close monitoring and where the clinical benefit outweighs the potential risk. Other antidepressant therapy should first be considered. If deemed clinically necessary, avoid large doses and use agents other than imipramine, clomipramine, desipramine, and tranylcypromine. A minimum of 14 days should elapse after selegiline is discontinued before doxepin therapy begins (Prod Info SINEQUAN(R) capsule, oral concentrate, 2005). There is no specific washout period for doxepin when beginning treatment with selegiline. However, it is advisable to gradually taper the tricyclic antidepressant dosage before starting treatment with the MAOI (Remick, 2002).
7) Probable Mechanism: altered catecholamine uptake and metabolism
8) Literature Reports
a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers. Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965e; Brachfeld et al, 1963d; Winston, 1971e; Schuckit et al, 1971j; Sargent, 1965d; Spiker & Pugh, 1976e). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965e).
b) Administration of a TCA after MAOI therapy may result in the development of serotonin syndrome. In a double-blind, crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-compulsive disorder, two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipramine therapy. After taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with clomipramine without adverse effects (Insel et al, 1982h).
c) A drug interaction occurred in a 76-year old woman who had been taking clomipramine 50 mg daily for several months prior to switching to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fever which then progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days later after discontinuing all antidepressant medications (Spigset et al, 1993i).
d) A 39-year old woman with bipolar disorder developed serotonin syndrome after imipramine was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when imipramine was started at 50 mg daily, followed by two dosage increases of imipramine to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in imipramine to 200 mg per day, the patient developed symptoms of serotonin syndrome, including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated with chlorpromazine and symptoms resolved over the next few days without further complications (Brodribb et al, 1994h).
e) Three patients with bipolar disorder developed manic symptoms while undergoing concurrent therapy with isocarboxazid and amitriptyline. In all three cases the patients had been given MAOIs and TCAs alone without complications. It was only when the drugs were used in combination that symptoms of mania emerged, suggesting a synergistic effect (de la Fuente et al, 1986c).
f) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a physically healthy 34-year old man. After taking several doses, the patient developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulation and eventual death (Tackley & Tregaskis, 1987e).
g) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 150 mg amitriptyline or its equivalent, 45 mg phenelzine, or 60 mg isocarboxazid) b) oral administration c) avoidance of clomipramine, imipramine, desipramine, and tranylcypromine in any combination, and d) close monitoring of patients (Kline, 1974c; Winston, 1971e; Schuckit et al, 1971j; White & Simpson, 1984h; Rom & Benner, 1972c). The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991d). Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some sources suggest that the combination of amitriptyline and isocarboxazid is preferred (Perry et al, 1991d). Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs (Ponto et al, 1977e; Schuckit et al, 1971j; Ashcroft, 1975d).

3.5.1.EE Sematilide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac

arrest)
2) Summary: Cases of QTc prolongation and/or torsades de pointes have been reported with all Class III antiarrhythmic agents, including acecainide (Chow et al, 1984), amiodarone (Faggiano et al, 1996), azimilide (Corey et al, 1999), bretylium (Gilman et al, 1985a), ibutilide (Rodriguez et al, 2001), sematilide (Singh, 1996), dofetilide (Allen et al, 2002), and sotalol (Marill & Runge, 2001). Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Yamreudeewong et al, 2003a; Prod Info Corvert(R), 2000).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepressant (TCA) is not recommended.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flattened T waves (Marshall & Forker, 1982y).
b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as tricyclic antidepressants, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003).

3.5.1.EF Sertindole
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), quetiapine (Owens, 2001b), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marshall & Forker, 1982p).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999).

3.5.1.EG Sertraline
1) Interaction Effect: modest elevations in doxepin serum levels or possible serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: There is limited evidence suggesting that sertraline may inhibit tricyclic antidepressant (TCA) metabolism resulting in higher TCA serum concentrations. Sertraline inhibits cytochrome P450 2D6 enzyme activity and may increase the plasma concentrations of coadministered drugs that are metabolized by this pathway, including the tricyclic antidepressants (Prod Info Zoloft(R), 2002; Preskorn et al, 1994c; Lydiard et al, 1993). Effects of the interaction may have little or no clinical impact, however. Increases in TCA serum levels associated with sertraline coadministration were modest compared with those found when fluoxetine (another selective serotonin reuptake inhibitor) was combined with desipramine (von Moltke et al, 1994). Monitor patients on doxepin-sertraline therapy for TCA toxicity (dry mouth, urinary retention, CNS depression). Doxepin doses may need to be reduced.
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The combined use of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) may result in the inhibition of the TCA metabolism. A few cases of serotonin syndrome have also been reported with concurrent TCA and SSRI therapy. Caution should be observed when drugs in these two classes are used together.
7) Probable Mechanism: inhibition of doxepin metabolism
8) Literature Reports
a) Desipramine pharmacokinetics was studied in 18 healthy male volunteers. Study subjects received

only desipramine (50 mg daily) for 7 days followed by desipramine with sertraline (50 mg daily) for 21 days. When sertraline was added to desipramine therapy, the mean maximum concentration of desipramine increased by 34% and the area under the concentration-time curve increased by 26%. Trough concentrations of desipramine were close to baseline one week after sertraline was discontinued. The changes in desipramine concentrations were modest and the interaction may not be clinically significant (Preskorn et al, 1994b).

3.5.1.EH Sotalol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Cases of QTc prolongation and/or torsades de pointes have been reported with all Class III antiarrhythmic agents, including acecainide (Chow et al, 1984), amiodarone (Faggiano et al, 1996), azimilide (Corey et al, 1999), bretylium (Gilman et al, 1985a), ibutilide (Rodriguez et al, 2001), sematilide (Singh, 1996), dofetilide (Allen et al, 2002), and sotalol (Marill & Runge, 2001). Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Yamreudeewong et al, 2003a; Prod Info Corvert(R), 2000).

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepressant (TCA) is not recommended.

7) Probable Mechanism: additive QT prolongation

8) Literature Reports

a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flattened T waves (Marshall & Forker, 1982y).

b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as tricyclic antidepressants, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003).

3.5.1.EI 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 tricyclic antidepressants. Sparfloxacin is also contraindicated in persons with known QTc prolongation (Prod Info Zagam(R), 1998a).

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), 1998).

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.EJ Spiramycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Tricyclic antidepressants (TCAs) and spiramycin have been shown to prolong the QTc interval at the recommended therapeutic dose (Stramba-Badiale et al, 1997; Marshall & Forker, 1982b). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as spiramycin, is not recommended (Prod Info Elavil(R), 1999a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of spiramycin and tricyclic antidepressants is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.EK St John's Wort
1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Theoretically, since 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), serotonin syndrome could result when St. John's Wort is taken along with a tricyclic antidepressant. This theoretical risk of serotonin syndrome is also based on case reports of serotonin syndrome resulting from concomitant use of selective serotonin reuptake inhibitors with tricyclic antidepressants (Alderman & Lee, 1996), as well as concomitant use of monoamine oxidase inhibitors with tricyclic antidepressants (Brodribb et al, 1994c; Spigset et al, 1993d; Tackley & Tregaskis, 1987b). Coadministration of amitriptyline and St. John's Wort decreased the area under the concentration-time curve of amitriptyline and its metabolite nortriptyline (Roots et al, 2000); if other tricyclic antidepressants are similarly affected by St. John's Wort, the risk of serotonin syndrome may be reduced, yet effectiveness of the tricyclic antidepressant may also be reduced. To maintain maximal effectiveness of the tricyclic antidepressant, as well as avoid any potential risk of serotonin syndrome, avoid concomitant use of St. John's Wort and tricyclic antidepressants.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of St. John's Wort with tricyclic antidepressants.
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.EL Sulfamethoxazole
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and cotrimoxazole have been shown to prolong the QTc interval at the recommended therapeutic dose (Lopez et al, 1987; Marshall & Forker, 1982q). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as cotrimoxazole, is not recommended (Prod Info Elavil (R), 1999i).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of cotrimoxazole and tricyclic antidepressants is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.EM Sultopride
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), quetiapine (Owens, 2001b), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marshall & Forker, 1982p).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is

prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999).

3.5.1.EN Tapentadol

1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent use of tapentadol and a tricyclic antidepressant 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 a tricyclic antidepressant 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.EO Tedisamil

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cases of QTc prolongation and/or torsades de pointes have been reported with all Class III antiarrhythmic agents, including acecainide (Chow et al, 1984), amiodarone (Faggiano et al, 1996), azimilide (Corey et al, 1999), bretylium (Gilman et al, 1985a), ibutilide (Rodriguez et al, 2001), sematilide (Singh, 1996), dofetilide (Allen et al, 2002), and sotalol (Marill & Runge, 2001). Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Yamreudeewong et al, 2003a; Prod Info Corvert(R), 2000).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class III antiarrhythmic and a tricyclic antidepressant (TCA) is not recommended.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increased heart rate, prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flattened T waves (Marshall & Forker, 1982y).
b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as tricyclic antidepressants, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003).

3.5.1.EP Telithromycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Telithromycin may prolong the QT interval in some patients (Owens, 2001d). Because tricyclic antidepressants may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of telithromycin and tricyclic antidepressants is not recommended (Marshall & Forker, 1982ac).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Because of the potential for additive QT interval prolongation, the concurrent administration of telithromycin and a tricyclic antidepressants is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.EQ Terfenadine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) have been shown to prolong the QTc interval at the recommended therapeutic dose (Marshall & Forker, 1982ab). Even though no formal drug interaction studies have been done, the coadministration of terfenadine and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is contraindicated (Prod Info Elavil(R), 1999j; Anon, 1997).
3) Severity: contraindicated

4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of terfenadine with any drug that prolongs the QT interval, such as tricyclic antidepressants, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.ER Thiopental

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.ES Thioridazine

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, 1982k).
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.ET Tibolone

1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973m), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972m). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972m) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984m).
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic
8) Literature Reports
a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received imipramine (150 milligrams/day) and placebo, 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (50 micrograms/day), while 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (25 micrograms/day). The 10 patients that received placebo did not improve over the 6 weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients

taking imipramine alone. However, after 2 weeks, the 5 patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received imipramine 150 milligrams and ethinyl estradiol 50 micrograms daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972l).

b) A case reported by (Khurana, 1972l) demonstrated an interaction in a 32-year-old female taking conjugated estrogens 2.5 milligrams and imipramine 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side-effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973l).

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973g).

d) The effect of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 milligrams at bedtime while 19 took clomipramine 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimental group (2 due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980f).

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 milligrams/day for anorexia nervosa and conjugated estrogens 1.25 milligrams/day for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogens 1.25 milligrams/day who was prescribed amitriptyline 50 milligrams/day for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. Positive rechallenge at one week with doxepin 100 milligrams, with resolution following discontinuation of doxepin. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogens 1.25 milligrams/day and amitriptyline 50 milligrams/day. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984l).

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 micrograms or less of ethinyl estradiol) from 27 to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984f).

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980f). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983f).

3.5.1.EU Toloxatone

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

2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982p; Spigset et al, 1993q; Brodribb et al, 1994o; Neuvonen et al, 1993h). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991i). If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971s; White & Simpson, 1984n).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concomitant use of a tricyclic antidepressant (TCA) and a monoamine oxidase

inhibitor (MAOI) should be done only with close monitoring and where the clinical benefit outweighs the potential risk. Other antidepressant therapy should first be considered. If deemed clinically necessary, avoid large doses and use agents other than imipramine, clomipramine, desipramine, and tranylcypromine.
7) Probable Mechanism: altered catecholamine uptake and metabolism
8) Literature Reports
a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past. Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965i; Winston, 1971i; Schuckit et al, 1971r; Spiker & Pugh, 1976i). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965i).
b) There is minimal risk of a clinically significant pharmacokinetic interaction between amitriptyline and toloxatone, a MAOI-A (Vandel et al, 1993). Seventeen inpatients being treated for major depressive illness were administered amitriptyline 125 mg once daily for two weeks, and the following two weeks they received amitriptyline 125 mg daily and toloxatone 600 mg daily. With combined therapy there was a small, nonsignificant increase in amitriptyline plasma levels. The availability and urinary excretion of amitriptyline and its metabolites were not significantly affected.
c) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991h). Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs (Ponto et al, 1977i; Schuckit et al, 1971r; Ashcroft, 1975h).
d) Serotonin syndrome has been reported with the use of moclobemide, a reversible inhibitor of monoamine oxidase, and a TCA. A 39-year old woman with bipolar disorder developed serotonin syndrome after imipramine was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when imipramine was started at 50 mg daily, followed by two dosage increases of imipramine to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in imipramine to 200 mg per day, the patient developed symptoms of serotonin syndrome, including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated with chlorpromazine and symptoms resolved over the next few days without further complications (Brodribb et al, 1994n).

3.5.1.EV Tramadol
1) Interaction Effect: an increased risk of seizures
2) Summary: Seizures have been reported in patients using tramadol. Some medications, including tricyclic antidepressants (TCAs), are known to reduce the seizure threshold. The risk of seizures may be enhanced when doxepin and tramadol therapy are combined (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 concomitant TCA therapy. If possible, avoid this combination, especially in patients with underlying conditions that might predispose to seizures.
7) Probable Mechanism: unknown

3.5.1.EW Tranylcypromine
1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982g; Spigset et al, 1993h; Brodribb et al, 1994g; Neuvonen et al, 1993c). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991d). Consequently, coadministration of TCAs and MAOIs is contraindicated in most cases. If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971i; White & Simpson, 1984g).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of doxepin with a monoamine oxidase inhibitor (MAOI), such as tranylcypromine is contraindicated (Prod Info Parnate(R), 2001). If doxepin is replacing treatment with tranylcypromine, a minimum of 14 days should elapse after tranylcypromine is discontinued before therapy with doxepin begins (Prod Info SINEQUAN(R) capsule, oral concentrate, 2005). The manufacturer of tranylcypromine recommends that at least 7 days should elapse before tranylcypromine therapy is replaced by doxepin. Similarly, if doxepin therapy is substituted by tranylcypromine, there should be a 7 day washout period. Tranylcypromine should then be given using half the normal starting dosage for, minimally, the first

week of therapy (Prod Info Parnate(R), 2001).
7) Probable Mechanism: altered catecholamine uptake and metabolism
8) Literature Reports
a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers (Prod Info Parnate(R), 2001). Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965d; Brachfeld et al, 1963c; Winston, 1971d; Schuckit et al, 1971h; Sargent, 1965c; Spiker & Pugh, 1976d). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965d).
b) Administration of a TCA after MAOI therapy may result in the development of serotonin syndrome. In a double-blind, crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-compulsive disorder, two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipramine therapy. After taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with clomipramine without adverse effects (Insel et al, 1982f).
c) A drug interaction occurred in a 76-year old woman who had been taking clomipramine 50 mg daily for several months prior to switching to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fever which then progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days later after discontinuing all antidepressant medications (Spigset et al, 1993g).
d) A 39-year old woman with bipolar disorder developed serotonin syndrome after imipramine was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when imipramine was started at 50 mg daily, followed by two dosage increases of imipramine to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in imipramine to 200 mg per day, the patient developed symptoms of serotonin syndrome, including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated with chlorpromazine and symptoms resolved over the next few days without further complications (Brodribb et al, 1994f).
e) Three patients with bipolar disorder developed manic symptoms while undergoing concurrent therapy with isocarboxazid and amitriptyline. In all three cases the patients had been given MAOIs and TCAs alone without complications. It was only when the drugs were used in combination that symptoms of mania emerged, suggesting a synergistic effect (de la Fuente et al, 1986b).
f) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a physically healthy 34-year old man. After taking several doses, the patient developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulation and eventual death (Tackley & Tregaskis, 1987d).
g) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 150 mg amitriptyline or its equivalent, 45 mg phenelzine, or 60 mg isocarboxazid) b) oral administration c) avoidance of clomipramine, imipramine, desipramine, and tranylcypromine in any combination, and d) close monitoring of patients (Kline, 1974b; Winston, 1971d; Schuckit et al, 1971h; White & Simpson, 1984f; Rom & Benner, 1972b). The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991c). Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some sources suggest that the combination of amitriptyline and isocarboxazid is preferred (Perry et al, 1991c). Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs (Ponto et al, 1977d; Schuckit et al, 1971h; Ashcroft, 1975c).

3.5.1.EX Trifluoperazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002; Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, though no reports are available. Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Marshall & Forker, 1982ad). Case reports have described increased plasma levels and adverse effects when phenothiazines and tricyclic antidepressants were taken together, likely due to inhibition of their metabolism (Ghaemi & Kirkwood, 1998; Geller et al, 1985; Siris et al, 1982; Loga et al, 1981).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable

6) Clinical Management: Concurrent administration of a phenothiazine and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: additive effect on QT interval

3.5.1.EY Trimethoprim
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and cotrimoxazole have been shown to prolong the QTc interval at the recommended therapeutic dose (Lopez et al, 1987; Marshall & Forker, 1982q). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as cotrimoxazole, is not recommended (Prod Info Elavil (R), 1999i).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of cotrimoxazole and tricyclic antidepressants is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.EZ Vasopressin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants and vasopressin have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Vivactil(R), 1999; McCue et al, 1989; Munger & Effron, 1988; Mauro et al, 1988; Marshall & Forker, 1982j; Goldstein & Claghorn, 1980; Buckhardt et al, 1978; Pinder et al, 1977a; Thorstrand, 1976; Singh, 1972). 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: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of drugs that prolong the QT interval, such as tricyclic antidepressants and vasopressin, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.FA Venlafaxine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest) and adverse effects of both drugs
2) Summary: Tricyclic antidepressants (TCAs) and venlafaxine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Effexor(R) XR, 2003; Marshall & Forker, 1982d). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as venlafaxine, is not recommended (Prod Info Elavil(R), 1999c). In addition, venlafaxine and tricyclic antidepressants (TCAs) may competitively inhibit each other's metabolism which may increase side effects of both drugs (Perry, 2000; Prod Info Effexor(R) XR, 2003; Ellingrod & Perry, 1994). Venlafaxine increased the AUC, Cmax, and Cmin of desipramine by approximately 35%. The AUCs of 2-OH-desipramine increased by 2.5 and 4.5 fold when administered with venlafaxine 37.5 mg and 75 mg every 12 hours, respectively. The pharmacokinetics of imipramine and the 2-hydroxy metabolite were not affected (Prod Info venlafaxine extended release oral tablets, 2008).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administration of venlafaxine and tricyclic antidepressants is not recommended.
7) Probable Mechanism: decreased TCA and venlafaxine metabolism; additive effects on QT prolongation
8) Literature Reports
a) When administered with imipramine, the pharmacokinetics of imipramine and the 2-hydroxy metabolite were not affected. Venlafaxine increased the area under the concentration-time curve (AUC), maximum concentration (Cmax), and minimum concentration (Cmin) of desipramine by approximately 35%. The 2-OH-desipramine AUCs increased by 2.5-fold (venlafaxine 37.5 mg every 12 hours) and by 4.5-fold (venlafaxine 75 mg every 12 hours). The clinical significance of this finding is unknown (Prod Info venlafaxine extended release oral tablets, 2008).

3.5.1.FB Warfarin
1) Interaction Effect: an increased risk of bleeding
2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagulants (Vesell et al, 1970a; Williams et al, 1976a). Considerable interindividual differences may be found (Pond et al, 1975a).
3) Severity: moderate

4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: In patients receiving doxepin and warfarin concurrently, the prothrombin time ratio or international normalized ratio (INR) should be closely monitored for stability of the anticoagulant response. Adjustment of the warfarin dosage may be required to maintain the desired level of anticoagulation.
7) Probable Mechanism: decreased warfarin metabolism; increased warfarin absorption
8) Literature Reports
a) In a study of healthy volunteers, the concurrent use of nortriptyline or amitriptyline resulted in an increase of dicumarol levels and an increase in the plasma half-life of dicumarol, although the effect was not consistent in all subjects (Pond et al, 1975). This effect was not observed with warfarin.
b) A single oral dose of bishydroxycoumarin after eight days of nortriptyline resulted in a significantly prolonged half-life and decreased volume of distribution of the coumarin anticoagulant in six healthy volunteers (Vesell et al, 1970). The mechanism of action was suggested to be reduced bishydroxycoumarin metabolism and/or altered coumarin absorption.
c) Drug dosing was studied in 16 patients on long-term anticoagulant therapy who used concurrent TCAs (Williams et al, 1976). TCAs affected the stability of anticoagulant control leading to frequent changes in the doses of anticoagulants. Inhibition of coumarin metabolism was the postulated mechanism.

3.5.1.FC Ziprasidone
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Ziprasidone use is associated with dose-related prolongation of the QTc interval. Even though no formal drug interaction studies have been done, it is recommended that concurrent use with other agents that may prolong QTc interval be avoided (Prod Info GEODON(R) oral capsules, IM injection, 2007; Marshall & Forker, 1982ae).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive QTc interval prolongation, avoid the concurrent administration of ziprasidone and agents that can prolong the QTc interval (Prod Info GEODON(R) oral capsules, IM injection, 2007).
7) Probable Mechanism: additive cardiac effects

3.5.1.FD Zolmitriptan
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and zolmitriptan have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Zomig(R), 2001; Marshall & Forker, 1982l). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as zolmitriptan, is not recommended (Prod Info Elavil(R), 1999f).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of zolmitriptan and tricyclic antidepressants is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.FE Zotepine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), quetiapine (Owens, 2001b), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marshall & Forker, 1982p).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the

appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999).

3.5.2 Drug-Food Combinations

3.5.2.A Ethanol

1) Interaction Effect: enhanced drowsiness; impairment of motor skills
2) Summary: Ethanol in combination with antidepressants may alter behavior, with the predominant effect being enhanced impairment in psychomotor performance. Almost all studies to date have evaluated the effects of the combination on motor skills, driving behavior and psychomotor skills (Landauer et al, 1969; Patman et al, 1969; Milner & Landauer, 1973a; Seppala et al, 1975; Seppala, 1977). There are no studies evaluating respiratory response with the combination.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Encourage abstention from alcohol during at least the first few weeks of tricyclic administration to allow patient accommodation to potential CNS depressant effects of the tricyclic.
7) Probable Mechanism: additive CNS depressant activity; impaired hepatic metabolism of the tricyclic antidepressant
8) Literature Reports
a) The studies available indicate that the interaction between amitriptyline (and other antidepressants) in combination with ethanol is unpredictable. They indicate that antidepressants may enhance, prevent, or not affect the CNS depressant actions of ethanol. The most significant effect reported is enhanced CNS depression. However, there are reports that tricyclic antidepressants may actually antagonize the sedative effects of ethanol (Milner & Landauer, 1973).
b) The propensity for interaction may be related to the inherent CNS depressant action of the tricyclic antidepressant, listed in one series in descending order as amitriptyline, doxepin, imipramine, nortriptyline, desipramine, and protriptyline (Marco & Randels, 1981).
c) Imipramine and amitriptyline are the best documented examples of disruptions of metabolism. Clearance of imipramine was 3-fold higher in alcoholics compared with healthy volunteers (Ciraulo et al, 1988).
d) Individual case reports have documented "blackouts" following modest amounts of alcohol in combination with either amitriptyline or imipramine (Hudson, 1981), and reversible extrapyramidal effects (parkinsonian effects, akathisia) with amoxapine (Shen, 1984).

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) Doxepin Hydrochloride
1) Therapeutic
a) Laboratory Parameters
1) Urinary MHPG
a) Elevations of urinary MHPG (3-methoxy-4-hydroxyphenethylene glycol) before treatment were reported to correlate with pain relief with doxepin treatment, but not improvement in depression (Ward et al, 1983).
b) Physical Findings
1) Relief of symptoms of depression
2) Improvement of mood
3) Relief of anxiety
a) ANXIETY AND DEPRESSION ASSOCIATED WITH ALCOHOLISM

1) Reduction or resolution of palpitations, tachycardia, chest pain or tightness, shortness of breath, hyperventilation, or depressed mood.

b) ANOREXIA NERVOSA

1) Reduction and resolution of signs/symptoms associated with anorexia nervosa (ie, calorie restriction, excess energy or exercise, disturbed sleep, sense of personal ineffectiveness, amenorrhea, social withdrawal, emaciated appearance, dry-cracked skin, fine downy hair, vomiting, malnutrition, and associated medical complications.

c) DEPRESSION

1) The following target symptoms should be monitored (depressed mood, suicidal thoughts or intent, change in appetite (increased/decreased), lack of energy, change in sleep patterns (hypersomnia/insomnia), lack of pleasure/interest in usual activities, feeling of excessive guilt/worthlessness, psychomotor retardation or agitation, difficulties in thinking/concentration/memory).

d) DETRUSOR OVERACTIVITY

1) Reduction or resolution of nocturnal micturition and incontinence.

e) INSOMNIA

1) Patients should be monitored for improvement in the signs/symptoms consistent with insomnia (delay in sleep onset, frequent nocturnal awakenings, the subjective feeling of not feeling rested, and disturbances in daytime functioning, such as decreased concentration, fatigue, myalgias).

f) CHRONIC PAIN

1) Reduction or resolution of pain perception, depression, sleep disturbances, anxiety, and irritability.

2) Improve or maintain patient's level of functioning, decreasing the rate of physical deterioration, improve sense of well being, improve family and social relationships.

g) PREMENSTRUAL SYNDROME

1) Reduction or resolution of signs/symptoms associated with premenstrual syndrome (ie, tension, irritability, dysphoria, fatigue, anxiety, crying, depression, restlessness, cravings for sweet/salty foods, binge eating, headache).

h) POSTTRAUMATIC STRESS DISORDER

1) Reduction or resolution of flashbacks, recollections, and dreams associated with a traumatic event.

2) Reduction or resolution of sleep disturbances, outbursts of anger, hypervigilance, emotional numbing, guilt, inability to concentrate, and the physiological reaction (ie, sweating) upon re-exposure to the event (ie, nightmare).

i) TOBACCO CESSATION

1) Reduction or resolution of irritability, craving, anxiety/nervousness, difficulty with concentration, restlessness, headaches, drowsiness, changes in sleep patterns, increase in appetite and weight, and gastrointestinal upset.

j) URTICARIA

1) Reduction or resolution of erythema, wheal, swelling, angioedema, itching, and lesions.

2) Toxic

a) Laboratory Parameters

1) Complete blood cell count

2) Liver function tests

b) Physical Findings

1) Blood pressure for hypotension and pulse

2) Seizures have developed during therapy

3) Sexual dysfunction (ejaculatory dysfunction) or priapism

4) 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 (ie, daily observation) of patients and communication with the prescriber (Anon, 2004).

5) 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 (Anon, 2004).

4.2 Patient Instructions

A) Doxepin (By mouth)

Doxepin

Treats depression, anxiety, and sleep disorders. This medicine is a tricyclic antidepressant.

When This Medicine Should Not Be Used:
You should not use this medicine if you have ever had an allergic reaction to doxepin or other tricyclic antidepressants (such as Elavil® or Tofranil®), maprotiline (Ludiomil®), or trazodone (Desyrel®). Do not use this medicine if you have glaucoma or if you are unable to pass urine.

How to Use This Medicine:
Capsule, Liquid, Tablet
Your doctor will tell you how much of this medicine to use and how often. 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.
Measure the oral liquid with a marked dropper that comes with the medicine.
The oral liquid must be mixed with one-half glass of water, milk, or fruit juice before you drink it. Do not use grape juice or carbonated beverages (soda pop). Mix the medicine just before taking the dose. Do not prepare ahead of time.
If you are using this medicine once a day, you may take it at bedtime.
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.
If you use only one dose at bedtime, skip the missed dose. Wait until the next night. You should not use two doses at the same time.

How to Store and Dispose of This Medicine:
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after you have finished your treatment. You will also need to throw away old medicine after the expiration date has passed.
Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.
Make sure your doctor knows if you are using disulfiram (Antabuse®), cimetidine (Tagamet®), tolazamide (Tolinase®), or certain medicine for heart rhythm problems (such as flecainide, propafenone, quinidine, Cardioquin®, Quinaglute®, Rythmol®, or Tambocor®).
You must wait at least 5 weeks between using this medicine and other medicine to treat depression (such as citalopram, escitalopram, fluoxetine, paroxetine, sertraline, Celexa®, Lexapro™, Paxil®, Prozac®, or Zoloft®). Do not use this medicine if you have used an MAO inhibitor (MAOI) such as Eldepryl®, Marplan®, Nardil®, or Parnate® within the past 14 days.
Do not drink alcohol while you are using this medicine.
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and allergy medicine, narcotic pain relievers, and sedatives.

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant or breastfeeding, or if you have heart disease, epilepsy, or stomach problems.
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.
If you are using this medicine for depression, it may take 2 to 3 weeks before you start to feel better.
Do not stop using this medicine suddenly without asking your doctor. You may need to slowly decrease your dose before stopping it completely.
This medicine may make you drowsy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert.

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.

Changes in behavior, or thoughts of hurting yourself or others.
Fast or uneven heartbeat.
Feeling nervous, restless, anxious, agitated, or excited for no reason.
Jerky muscle movement you cannot control (often in your face, tongue, or jaw).
Lightheadedness or fainting.
Numbness, tingling, or burning pain in your hands, arms, legs, or feet.
Problems with balance or walking.
Problems with urination.
Ringing, buzzing, or other unexplained noise in ears.
Seizures or tremors.
Severe confusion, or seeing or hearing things that are not there.
Swelling in your hands, ankles, or feet.
Trouble sleeping.
Twitching or muscle movements you cannot control.
Unexplained fever, chills, or sweating.
Unusual bleeding or bruising.
Unusual tiredness or weakness.
Yellowing of your skin or the whites of your eyes.

If you notice these less serious side effects, talk with your doctor:
Blurred vision.
Change in taste.
Constipation, diarrhea, nausea, vomiting, or upset stomach.
Drowsiness or dizziness.
Dry mouth or mouth sores.
Hair loss.
Headache.
Problems having sex.
Sensitivity to sunlight.
Skin rash or itching.
Swelling in scrotum or testicles.
Swelling of the breasts or breast soreness in both females and males.
Warmth or redness in your face, neck, arms, or upper chest.

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

B) Doxepin (On the skin)

Doxepin

Reduces itching caused by skin diseases such as atopic dermatitis or lichen simplex chronicus.

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to doxepin, or if you have glaucoma or problems urinating.

How to Use This Medicine:
Cream
Apply a thin layer to the affected area. Rub it in gently.
Apply a thin layer of this medicine each time you use it.
Wash your hands with soap and water before and after using this medicine.
Do not cover the treated area with a bandage unless your doctor has told you to.

If a Dose is Missed:
If you miss a dose or forget to use your medicine, apply it as soon as you can. If it is almost time for your next dose, wait until then to apply the medicine and skip the missed dose. Do not apply 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 the used medicine container and any leftover medicine after you have finished your treatment. You will also need to throw away old medicine after the expiration date has passed.
Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.
Make sure your doctor knows if you are using MAO inhibitors such as Eldepryl®, Marplan®, Nardil®, or Parnate®, or allergy medicines.

Make sure your doctor knows if you are using medicine for depression such as trazadone, Clexa®, Prozac®, Paxil®, or Zoloft®, or amitriptyline, Norpramin®, or Vivactil®.
There are many other drugs that can interact with doxepin. Make sure your doctor knows about all other medicines you are using.
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and allergy medicine, narcotic pain relievers, and sedatives.
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant or breast feeding.
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.

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.
Confusion, hallucinations, severe weakness, vomiting, muscle stiffness.
Drowsiness or lightheadedness or fainting.
Irregular heartbeat
Swelling in your feet, arms, or body.

If you notice these less serious side effects, talk with your doctor:
Burning or stinging of your skin where the medicine in applied.
Change in taste or dryness of your mouth.
Headache or tiredness.
Nervousness, anxiety.
Numbness in your tongue.
Redness, pain, swelling, or itching on site of cream application.
Worsening of you skin condition.

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

4.3 Place In Therapy

A) Depression is a complicated disorder and consequently treatment regimens are diverse. The two most prevalent diagnostic syndromes among affective disorders are major depression and bipolar disorders. The tricyclic antidepressants (TCAs) serotonin reuptake inhibitors (SSRIs) and the monoamine oxidase inhibitors (MAOIs) are considered the most effective agents for treating major depression. For treating bipolar disorders, lithium is considered the standard of therapy over TCAs, MAOIs, SSRIs, and other agents such as carbamazepine or levothyroxine.

B) Doxepin is effective for the treatment of endogenous or typical depression. Doxepin has similar efficacy and adverse effects as the other TCAs, but possesses some distinguishing characteristics. Doxepin inhibits histamine release and has been used topically to treat pruritus and systemically for peptic ulcer disease. Doxepin has also been used for treating anxiety-depression states and depression-induced insomnia. Cardiac effects of doxepin are considered mild compared to those of the other TCAs.

C) Doxepin does have a place in therapy for the treatment of unipolar depression, but should be considered secondary to imipramine and amitriptyline. Because of anxiolytic properties, antihistamine action, sedative effects and fewer cardiac effects, doxepin may be useful for treating depressed patients with coanxiety, peptic ulcer disease, associated insomnia, or who are elderly. Doxepin should be considered an alternative agent and formulary considerations should be based primarily on cost.

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) Doxepin has similar pharmacologic properties to other tricyclic antidepressants (amitriptyline and imipramine). Doxepin has a pronounced sedative effect similar to amitriptyline but probably less than that of imipramine. Doxepin is particularly effective in depression associated with anxiety or in mixed anxiety depression syndromes (Pinder et al, 1977b).

2) Doxepin may be more effective than imipramine in patients with depression associated with sleep disturbances but it is not superior to other tricyclic antidepressants for severe endogenous depression (Pinder et al, 1977b).

3) Doxepin has been shown to exert a significant antihistamine effect. In 8 subjects administered a dose of 25 mg, the amount of histamine required to cause an urticarial reaction increased 82-fold (Sullivan, 1982).

B) REVIEW ARTICLES

1) A review of the other uses of antidepressant agents, including enuresis, bulimia, anorexia nervosa, panic disorder, chronic pain, migraine headache, and peptic ulcer disease is available (Orsulak & Waller, 1989).

2) Drug-interactions of antidepressants are reviewed in German language (Zapotoczky & Simhandl, 1995).

4.5 Therapeutic Uses

Doxepin

Doxepin Hydrochloride

4.5.A Doxepin

4.5.A.1 Anorexia nervosa

See Drug Consult reference: ANOREXIA NERVOSA - DRUG THERAPY

4.5.B Doxepin Hydrochloride

Alcoholism - Anxiety - Depression

Anxiety - Depression

Anxiety - Depression - Psychoneurotic personality disorder

Cancer pain; Adjunct

Chronic pain

Cocaine-induced anxiety disorder

Complex regional pain syndrome

Cyclical vomiting syndrome

Depression - Opioid dependence

Detrusor instability of bladder

Disorder of gastrointestinal tract

Disorder of oral mucous membrane - Pain

Insomnia

Nicotine dependence

Peptic ulcer disease

Post-prandial hypoglycemia

Posttraumatic stress disorder

Pruritus (Moderate), Due to atopic dermatitis or lichen simplex chronicus

Psychogenic headache

Urticaria

4.5.B.1 Alcoholism - Anxiety - Depression

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (12 years and older)
Efficacy: Adult, Effective

Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Indicated for controlling the anxiety and/or depression associated with alcoholism

c) Adult:

1) GENERAL INFORMATION

a) The most effective dose of DOXEPIN for mild-to-moderate anxiety or depression ranges between 75 and 150 milligrams/day. A starting dose of DOXEPIN 25 milligrams 3 times daily is recommended, but the entire daily dose up to 150 milligrams may be administered at bedtime without altering efficacy. For more severe anxiety and depression, DOXEPIN 50 milligrams 3 times daily may be administered and the dose increased to a maximum of 300 milligrams/day. The antidepressant effect of DOXEPIN may take 2 or 3 weeks to achieve, but the antianxiety effect usually occurs rapidly (Prod Info Adapin(R), 1995a).

4.5.B.2 Anxiety - Depression

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (12 years and older)
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:

Indicated for the treatment of depression and/or anxiety associated with organic disease
Also indicated for PSYCHOTIC DEPRESSIVE DISORDERS with associated anxiety including involutional depression and manic-depressive disorders

c) Adult:

1) GENERAL INFORMATION

a) DOXEPIN is an effective agent in the treatment of ENDOGENOUS DEPRESSION (Grof et al, 1974; Burrows et al, 1972; Bianchi et al, 1971a) and NEUROTIC DEPRESSION (Mendels & Schless, 1975; Solis et al, 1970a). Clinical trials have shown that DOXEPIN has less marked mood elevating activities than IMIPRAMINE but similar to that of AMITRIPTYLINE. DOXEPIN has been shown to be most effective in agitated depressed patients and less effective in retarded depressive patients. In addition, DOXEPIN is shown to be more effective than IMIPRAMINE in neurotic-type depression and less effective than IMIPRAMINE in endogenous depression (Pinder et al, 1977e).

2) In the absence of severe impairment of myocardial performance, depressed patients with pre-existing heart disease were treated effectively with IMIPRAMINE or DOXEPIN without an adverse effect on ventricular rhythm or hemodynamic function (Veith et al, 1982a). In a double-blind, randomized trial involving 24 depressed patients with heart disease treated with IMIPRAMINE or DOXEPIN 50 milligrams (mg) at bedtime or placebo. Doses were gradually increased every 3 days until side effects or a dose of 150 mg given at bedtime was achieved. No evidence of cardiovascular adverse effects were seen. As measured by radionuclide ventriculograms, tricyclic antidepressants had no effect on left ventricular ejection fraction at rest or during maximal exercise. The incidence of premature ventricular contractions was reduced in patients treated with IMIPRAMINE; however, no consistent change was observed in patients receiving DOXEPIN or placebo. IMIPRAMINE- and DOXEPIN-treated patients showed a significant improvement (p less than 0.001) in depression when compared with placebo-treated patients. Further evaluation of the tricyclics and their effect on cardiovascular function is required.

3) DOXEPIN has produced a more favorable response than AMITRIPTYLINE in patients with depression associated with anxiety or the MIXED DEPRESSION ANXIETY syndrome, and it is possible that DOXEPIN may have more prominent sedative effects than AMITRIPTYLINE (Pinder et al, 1977e).

4) Several studies have reported the benefits of doxepin in patients with mixed ANXIETY and depression (Goldberg et al, 1974; Goldstein et al, 1973).

5) Doxepin titrated in a conventional manor (beginning with 50 milligrams daily and titrating upwards to 250 mg daily over 1 week) was more effective than using pulse dosing (250 mg every 6 days) (Deuschle et al, 1997). Depressed patients were randomly assigned to receive either conventional dosing (n=10) or pulse dosing (n=9) over 39 days. In the pulse dosing group, scores on the Hamilton Depression Rating (HAM-D) scale differed from baseline after day 36 (p less than 0.03) while in the conventional dosing group, they differed after only 2 days (p less than 0.02). Starting on day 25, significantly lower HAM-D scores were seen in the conventional dosing group versus the pulse dosing group (p less than 0.05) and this continued through day 39 (p less than 0.01).

4.5.B.3 Anxiety - Depression - Psychoneurotic personality disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (12 years and older)
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:
Indicated for the treatment of psychoneurotic patients with depression and/or anxiety (Prod Info SINEQUAN(R) capsule, oral concentrate, 2005)

4.5.B.4 Cancer pain; Adjunct

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Case reports have described the use of doxepin in terminal cancer patients who are unresponsive to narcotic analgesics

c) Adult:
1) Four severely debilitated cancer patients with neuropathic pain were reported to be more comfortable following rectal administration of unmodified DOXEPIN capsules. Serum concentrations of N-desmethyldoxepin after two to five days of treatment with a constant dose of DOXEPIN were 573 micrograms/milliliter (mcg/mL) and 403 mcg/mL (with 50 milligrams (mg) three times/day), 204 mcg/mL (with 50 mg twice a day), and less than 25 mcg/mL (with 25 mg every day) (Storey & Trumble, 1992).
2) The combination of PIROXICAM (60 to 120 milligrams orally daily, given with SUCRALFATE 1 to 2 g daily) plus DOXEPIN (25 to 225 mg daily) was reported effective in the treatment of advanced cancer pain (Cohn et al, 1988). SUCRALFATE given concurrently with PIROXICAM was effective in preventing severe gastrointestinal (GI) toxicity. However, several patients did not administer sucralfate concurrently with PIROXICAM and developed GI symptoms (GI hemorrhage, gastric ulcer or perforation). It is recommended that PIROXICAM and DOXEPIN therapy (with adjunctive SUCRALFATE administration) be considered in patients with terminal cancer who are unresponsive to narcotic analgesics.

4.5.B.5 Chronic 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:
Patients with chronic pain have experienced some relief with doxepin therapy
A review of doxepin as adjunctive therapy for chronic pain has been published by the Boston Pain Center (Aronoff & Evans, 1982)

c) Adult:
1) DOXEPIN (up to 3 milligrams/kilogram/day (mg/kg)) for pain relief was better than placebo in 60 patients with chronic low back or cervical pain and depression (Hameroff et al, 1984). Relative to the percent of time the pain was felt, effect of pain on sleep, and muscle tension, DOXEPIN was slightly better than placebo at 1 week, and significantly better at 6 weeks. Benefit was most consistently derived when the daily dose was at least 2.5 mg/kg, and the combined DOXEPIN/desmethyldoxepin plasma level exceeded 70 ng/mL. The proposed mechanism, as demonstrated by the laboratory, was enhanced enkephalin activity.

4.5.B.6 Cocaine-induced anxiety disorder

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:
Not effective in the treatment of panic attacks associated with cocaine abuse

c) Adult:
1) The use of tricyclic antidepressant therapy in 10 patients with cocaine-induced panic attacks resulted in extreme anxiety and had to be discontinued (Louie et al, 1989). One patient improved after doxepin 50 milligrams/day (mg/day) but, at higher doses, became severely confused and panicky and had to be hospitalized. Another patient had a partial response to trazodone 150 mg/day and did not want to be switched to another agent. Other agents used in this patient population included amitriptyline, desipramine, and nortriptyline. Thus, heterocyclic antidepressants were not well tolerated except for trazodone and low doses of doxepin, two medications with relatively high serotonergic re-uptake

blockade.

4.5.B.7 Complex regional pain syndrome

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:

Topical doxepin reduced the symptoms of complex regional pain syndrome CRPS, including pain, discoloration, and thermal and mechanical allodynia

c) Adult:

1) A 32-year-old woman attained relief of symptoms of complex regional pain syndrome (CRPS) with topical application of doxepin 5% cream (Xepin(R)). After a fall on her left wrist, the woman developed the symptoms of CRPS, although the wrist was not broken. In addition to burning dermatomal pain, she showed blue discoloration, hyperhidrosis, and mechanical and thermal allodynia. A stellate ganglion block on the left side gave significant reduction in symptoms for 4 weeks. A second block provided similar relief. Topical application of doxepin cream twice daily reduced her symptoms significantly after 2 weeks. Each time she omitted using the cream for more than 5 days, her symptoms returned. In addition to reducing the pain, it decreased the thermal and mechanical allodynia and the discoloration (McCleane, 2002).

4.5.B.8 Cyclical vomiting syndrome

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:

Tricyclic antidepressant therapy, including DOXEPIN, may be beneficial in treating CYCLIC VOMITING SYNDROME

c) Adult:

1) In a retrospective case series (n=17), adults with CYCLIC VOMITING SYNDROME (CVS) were shown to derive benefit from treatment with low-dose tricyclic antidepressants (open-label), including DOXEPIN (median dose 50 milligrams (mg) daily; range 25 to 150 mg). However, a comparison group of 37 patients with usual functional nausea and vomiting had superior results from tricyclic-antidepressant therapy compared with those with CVS. Of the 17 patients with CVS, 3 (17.6%) achieved complete remission, and 10 (58.8%) attained partial response (decreased intensity of symptoms, decreased cycle frequency, or shortening of cycles). Of 7 patients who used doxepin, 6 experienced remission or improvement -- the same response as 7 patients given amitriptyline. No patient responded to desipramine (0 of 3) or imipramine (0 of 1), with 4 of 4 responding to nortriptyline. Of the patients with functional nausea and vomiting treated with tricyclic antidepressants, 19 of 37 (51.4%) achieved complete remission and 12 (32.4%) showed partial response. The authors suggest that the pathophysiology of CVS might be similar to that of migraine headache (Prakash & Clouse, 1999).

4.5.B.9 Depression - Opioid dependence

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:

DOXEPIN reduced the craving for HEROIN, nervousness, and the use of amphetamines

c) Adult:

1) Doxepin was superior in the treatment of depression when compared with placebo in a 5-week trial as adjunctive treatment in a methadone maintenance program. Only 46 of 76 patients completed the study. Relative to several depression parameters, doxepin was shown better than placebo. Doxepin did not significantly increase the incidence or severity of adverse effects to methadone (Titievsky et al, 1982)

2) DOXEPIN was efficacious in HEROIN addicts with associated anxiety and depression. Doses of 100 to 150 mg daily for periods of longer than 4 weeks significantly decreased symptoms of anxiety and depression as measured by the Hamilton depression rating scale (Woody et al, 1975).

4.5.B.10 Detrusor instability of bladder

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:
Effective in the treatment of detrusor overactivity in women

c) Adult:
1) DOXEPIN caused a significant decrease in the nighttime micturition frequency and the nighttime incontinence episodes. Cystometric parameters improved significantly during treatment with DOXEPIN. The authors concluded that DOXEPIN seems to offer a new alternative in the pharmacological treatment of detrusor overactivity and associated symptoms (Lose et al, 1989).
2) In this randomized, double-blind, placebo-controlled study of DOXEPIN, 19 females with detrusor overactivity and associated symptoms who had failed to respond to conventional pharmacotherapy, obtained relief ascribed to the ability of DOXEPIN to improve storage failure by decreasing bladder contractility and/or decreasing sensory input (Lose et al, 1989). DOXEPIN caused a significant decrease in the nighttime micturition frequency and the nighttime incontinence episodes (p less than 0.05). Cystometric parameters improved significantly during treatment with DOXEPIN. The authors concluded that DOXEPIN seems to offer a new alternative in the pharmacological treatment of detrusor overactivity and associated symptoms.

4.5.B.11 Disorder of gastrointestinal tract

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category A
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
An effective alternative in treating IRRITABLE BOWEL SYNDROME
Other types of epigastric distress have also reportedly responded to therapy

c) Adult:
1) A meta-analysis of controlled clinical trials related to the use of antidepressants for the treatment of functional gastrointestinal (GI) disorders concluded that this type of therapy (primarily tricyclic antidepressants) is efficacious in some patients. Included were 11 trials published between 1978 and 1998 focused on antidepressant therapy in irritable bowel syndrome (8) and dyspepsia (non-ulcer) (2); one study included patients with either disorder. Among the medications studied were amitriptyline (3), trimipramine (3), desipramine (2), DOXEPIN (1), mianserin (1), and either clomipramine or mianserin (1). All of the trials compared the treatment drug against placebo. In 8 studies using a dichotomous outcome measure, ie, response to treatment, the odds ratio for improvement with therapy was 4.2. In 7 studies using a continuous variable of pain scores, the standardized mean improvement in pain averaged 0.9 standard deviation (SD) (means for the treatment and control groups divided by the SD). Pooling of the risk difference indicated that 3.2 patients needed to be treated for 1 to experience symptom improvement. The authors were uncertain if the improvement in GI symptoms was an independent action of the drugs or if the improvement reflected the effects of the drugs on the psychological outlook of the recipients (Jackson et al, 2000).
2) A nondepressed patient obtained relief from irritable bowel syndrome, resistant to other therapies, while receiving DOXEPIN 150 milligrams/day (Gartrell & Mosbacher, 1982). Another similar case with similar results was reported (Pies, 1983).
3) Doxepin relieved 2 cases of epigastric distress (Shen et al, 1983). A 77-year-old man with an 8-year history of severe, unremitting epigastric distress experienced significant relief on DOXEPIN 100 milligrams/day. Similar results were observed in a 55-year-old man after initiation of DOXEPIN 125 milligrams/day.

4.5.B.12 Disorder of oral mucous membrane - 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:
Mucosal local doxepin rinse relieved mucosal pain caused by cancer or cancer treatment for more than 3 hours

c) Adult:
1) An oral rinse of doxepin solution gave relief of pain to patients with oral mucosal damage. In an single-dose, open trial, 41 patients with oral mucosal pain resulting from cancer or cancer treatment

rinsed their mouths for 1 minute with 5 milliliters (mL) of doxepin suspension 5 milligrams/mL. At 15 minutes post- rinsing, mean pain reduction was 60% (p less than 0.01), and at 3 hours, 25% (p less than 0.05). By 24 hours, pain had returned to pre-rinse levels. Thirty-five percent of patients reported absence of fatigue, 13% mild fatigue, 20% moderate, 16% moderate-to-severe, and 16% severe (Epstein et al, 2001).

4.5.B.13 Insomnia

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:

Used as a sedative-hypnotic, however, benzodiazepines are usually recommended for patients with sleep disturbances

c) Adult:

1) GENERAL INFORMATION

a) Doxepin has been promoted as a sedative-hypnotic for all patients, whether they have underlying symptoms of anxiety and depression or not. One manufacturer has indicated that doxepin is recommended for sleep disturbances that accompany anxiety neurosis and depression, but not for patients with INSOMNIA as the only disorder (Prod Info Sinequan(R), 1989). Doxepin does have marked sedative effects, similar to those of amitriptyline (Hollister, 1972; Ayd, 1969), and studies have shown that somnolence occurs in up to 19% of those on chronic treatment (Pitts, 1969a); (Belsasso, 1969; Gallant, 1969). These studies have most likely prompted the use of the drug as a sedative hypnotic. Indeed, some have recommended the drug be administered at bedtime because of its noticeable sedative and hypnotic properties, but this advice was referred to patients with emotional disorders or depression (Belasso et al, 1969). Doxepin also has been reported to produce insomnia, excitement, restlessness, agitation, euphoria, and anxiety which are certainly not the most desirable effects of a sedative (Pitts, 1969a).

2) In a randomized, double-blind, placebo-controlled trial, doxepin improved sleep and working ability in patients with chronic primary insomnia more than did placebo but was associated with more rebound insomnia upon discontinuation. Patients with DSM-IV primary insomnia (mean duration 11 years) were treated either with placebo (n=20) or doxepin 25 to 50 milligrams/night for 4 weeks. Polysomnographic measures showed improved sleep efficiency, increased total sleep time, and decreased time of wake-after- sleep-onset (WASO) with doxepin (relative to baseline and to values of placebo-treated patients, p less than 0.01 or better for all comparisons) at the first night of treatment. Improvements persisted at day 28 of treatment. Sleep efficiency with doxepin was 89% at day 1 and throughout treatment (compared to 78% at baseline). Average total sleep time with doxepin at day 28 was 7.1 hours (vs 6.3 hours at baseline). With discontinuation of treatment, the number of doxepin-treated patients experiencing rebound on 3 or more sleep parameters was significantly greater than the number of placebo-treated patients experiencing rebound (p less than 0.05) for the 3 nights of acute withdrawal. At night 42 (2 weeks without treatment), some sleep parameters in the doxepin group were better than at baseline (sleep efficiency, p less than 0.05; WASO, p less than 0.01), and none was worse. Frequency of adverse events did not differ significantly for the 2 groups. Dry mouth, dizziness, and somnolence tended to be more pronounced in the doxepin group, and diarrhea, dyspepsia, anorexia, sweating, and common colds more frequent in the placebo group. Sleep improvements with doxepin were rated slight or moderate by the authors (Hajak et al, 2001).

3) In June, 1971, three separate studies concerning the treatment of nondepressed insomniacs with doxepin were presented at the First International Congress, The Association for Psychophysiological Study of Sleep. Baseline sleep patterns, established while the patients received a placebo, were compared with sleep patterns recorded while receiving doxepin 25 or 50 milligrams at bedtime for 2 weeks. Each investigator reported a decrease in all the patient's REM sleep and awake time while receiving doxepin. During the placebo withdrawal administration, each patient experienced REM rebound. The authors did note a slight decrease of doxepin's effectiveness as the trials continued, however, they concluded that tolerance to drowsiness did not develop (Pers Comm, 1989). Because drug exposure lasted only 14 days, surmising that tolerance does not develop to doxepin therapy seems premature. No studies could be found indicating that tolerance occurs to the sedative effects. Tolerance to the drowsiness has been reported by Roerig, one manufacturer of doxepin, thus until proven otherwise tolerance to the sedative effects is assumed to occur (Prod Info Sinequan(R), 1999).

4) DOXEPIN had a positive effect on sleep disturbances in 9 patients with depression accompanied by disorders of sleep. DOXEPIN 75 and 150 milligrams/day improved sleep efficiency as evidenced by decreased sleep latency and increased total sleep time (Roth et al, 1982).

5) One study reported using doxepin 100 milligrams for treating insomnia in heroin addicts receiving clonidine to alleviate withdrawal symptoms. The investigators did not report the success rate for treating insomnia, however, doxepin seem to be beneficial for inhibiting the peripheral hypotensive actions of clonidine (Schanda et al, 1983).

6) Long-term side effects of doxepin were assessed in 1706 patients who received the drug for periods

of a few weeks to 22 months (mean 3.3 months) in doses ranging from 25 to 600 milligrams daily. The most common side effects (greater than 2%) consisted of: drowsiness (17.4%), anticholinergic effects, mostly dry mouth (22.9%), extrapyramidal symptoms, usually in high doses (6.3%), dizziness (5.9%), hypotension (2.8%), tachycardia (2.6%), gastrointestinal effects (3.7%), and insomnia (2.1%). No abnormalities in WBC, Hgb, Hct or evidence of BLOOD DYSCRASIAS were reported in the more than 800 patients for whom blood tests were done. AST, ALT, and ALKALINE PHOSPHATASE values were abnormal in only a few of the patients tested (less than 1%) (Pitts, 1969a).

4.5.B.14 Nicotine dependence

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:

Doxepin may be a useful adjunct in smoking cessation

c) Adult:

1) DOXEPIN was efficacious in the treatment of NICOTINE WITHDRAWAL (Edwards et al, 1990). DOXEPIN was given to 8 patients prior to smoking cessation with the following regimen: 25 milligrams at bedtime initially and titrated in increments of 25 milligrams every third day to reach a target dose of 150 milligrams. When 150 milligrams/day was maintained for 1 week, patients were instructed to terminate smoking. Twenty-one patients were instructed to begin smoking cessation after the initial visit. Dropouts were more frequent in the patients that did not receive DOXEPIN (72% compared with 50% in the DOXEPIN patients). DOXEPIN significantly suppressed symptom frequency during the first and second week as compared with the patients who did not receive DOXEPIN.

2) A 5-week pilot study revealed that DOXEPIN therapy was useful in nicotine withdrawal (Whelan & Davis, 1990). Of the original 8 subjects treated with DOXEPIN and 21 controls, only 4 of the DOXEPIN group and 6 controls finished the study. DOXEPIN reduced the severity of symptoms during the first 2 weeks but there was no significant difference in the last 3 weeks.

3) DOXEPIN was reported effective in achieving smoking cessation in a small double-blind study involving 19 adults (Murphy et al, 1990; Edwards et al, 1989). Prior to smoking cessation, the DOXEPIN (or placebo) was given in doses of 50 milligrams daily for 3 days, then 100 milligrams daily on days 4 through 6, followed by 150 milligrams daily from day 7 to 21. On day 22, subjects stopped smoking and DOXEPIN 150 milligrams daily or placebo was continued for an additional 4 weeks. The study medication was given at bedtime. Smoking cessation was achieved in all of the 9 subjects treated with DOXEPIN 7 days after stopping smoking and was maintained in 7 of the subjects at 9 weeks; only 1 of 10 placebo subjects reported cessation. A precessation DOXEPIN serum level higher than 10 ng/mL was associated with cessation of smoking in this study. In the 2 DOXEPIN subjects reporting relapse, DOXEPIN levels were less than 10 ng/mL. DOXEPIN appeared to reduce the intensity of cigarette craving (2.8 +/- 1.7 for DOXEPIN users versus 5.1 +/- 0.8 for placebo). Substantial weight gain was observed in subjects treated with DOXEPIN who were able to stop smoking (mean, 11.7 pounds). It is suggested that the weight gain attributable to cessation of smoking was most likely compounded by weight gain secondary to DOXEPIN use. This small study suggests that DOXEPIN may have a role in assisting smoking cessation.

4.5.B.15 Peptic ulcer disease

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:

Effective in the treatment of peptic ulcer disease due to its histamine blocking activity

c) Adult:

1) Tricyclic antidepressants have anti-histamine blocking properties, however, standard H2 antagonists are recommended for the treatment of peptic ulcer disease. For peptic ulcer disease, doxepin has been as effective as cimetidine (Shrivastava et al, 1985a; Ruud et al, 1982; Hoff et al, 1981) and doxepin was effective in patients who had failed cimetidine (Shrivastava et al, 1985a; Mangla & Pereira, 1982).

2) Doxepin was superior to placebo in a study of the effect of doxepin on gastric acid and salivary secretion in patients with asymptomatic, chronic duodenal ulcer disease. Seven patients received either 50 or 100 milligrams doxepin or placebo, and were evaluated at 3.5, 5.5, 7.5, and 9.5 hours after drug administration. Both gastric acid and salivary secretion were decreased significantly more by doxepin than placebo, but no statistically significant differences were seen between the 2 doses of doxepin (Brown-Cartwright et al, 1986).

4.5.B.16 Post-prandial hypoglycemia

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:
Has reduced symptoms of postprandial symptomatic hypoglycemic.

c) Adult:

1) DOXEPIN reduced symptoms of postprandial symptomatic hypoglycemic in 32 subjects (Lechin et al, 1991). There was a 4-week baseline period followed by an 8-week study with DOXEPIN 25 milligrams being substituted for placebo. During the placebo period, all patients showed hypoglycemia, hyperinsulinemia, and disorders of plasma neurotransmitters during the oral glucose tolerance test when compared with control subjects. The subjects were divided into 3 separate groups according to different blood levels of neurotransmitters. Groups I and II showed low basal noradrenalin/adrenalin ratios and low serotonin levels. Group III had a high noradrenalin/adrenalin ratio with a raised serotonin level and all subjects showed severe dysthymic depression. The symptoms of postprandial hypoglycemia did not correlate with a low glucose level but rather an imbalance in the neurotransmitter levels. Serotonin and noradrenalin stimulate hypothalamic activity which reduces pituitary-adrenocortical functioning. This in turn reduces the adrenaline level and causes hypoglycemia. All 32 subjects showed pituitary-adrenocortical hyperactivity before treatment. After treatment with DOXEPIN they were all asymptomatic.

4.5.B.17 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 C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Tricyclic antidepressant therapy including doxepin has been reported beneficial in the treatment of posttraumatic stress disorder in COMBAT VETERANS (Falcon et al, 1985)

c) Adult:

1) Posttraumatic stress disorder due to trauma, burns, rape, and other noncombat physical insults have been treated with antidepressants. A 36-year-old male suffered posttraumatic stress disorder several months after receiving second and third degree burns in a truck fire. The patient responded well to DOXEPIN (daily doses of 50 milligrams (mg) to start, increasing to 300 mg, then tapering to 50 mg) over a period of 1 year (Blake, 1986).

4.5.B.18 Pruritus (Moderate), Due to atopic dermatitis or lichen simplex chronicus

FDA Labeled Indication

a) Overview
FDA Approval: Adult, yes (5% cream); Pediatric, no
Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIa; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
DOXEPIN cream reduces the pruritus associated with atopic dermatitis and lichen simplex chronicus
Topical DOXEPIN combined with corticosteroids improves treatment results
Topical doxepin reduced erythema and itching in chronically pruritic burn wounds
Eliminated recalcitrant lichen simplex in a child (Thomson & Highet, 2001)

c) Adult:

1) GENERAL INFORMATION

a) Doxepin cream 5% is indicated for the short-term treatment (up to 8 days) of moderate pruritus in adult patients with atopic dermatitis or lichen simplex chronicus. The use of doxepin cream in children is not recommended (Prod Info Zonalon(R), 2004). In two multi-center, double-blind, placebo-controlled studies, atopic dermatitis, lichen simplex chronicus, and other eczemas were successfully treated with doxepin cream in 559 adults (Tech Info Zonalon(R), 1994).

2) MONOTHERAPY

a) Topical doxepin therapy effectively reduced erythema and itching in chronically pruritic burn wounds. In a prospective, randomized study, thirty-one patients reporting itch in healed burns 4 to 12 months of age (mean, 7 months) received either ongoing standard care with oral antihistamines (ie, diphenhydramine, hydroxyzine) or topical 5% doxepin cream applied 4 times daily to affected area(s) for 3 months. Both groups used a skin moisturizer two to three times daily during the study. Patients rated itch and erythema daily using a visual analog scale. Patients in the doxepin

treatment group had significantly greater reductions in itching and erythema at 1, 8, and 12 weeks as compared with the standard care group. Itching completely stopped in 75% of doxepin-treated patients compared to only 20% of standard care patients. Mild to moderate somnolence was reported in both groups (Demling & DeSanti, 2003).

b) Doxepin cream 5% was superior to placebo (ie, vehicle only) in 270 patients with moderate to severe atopic dermatitis with pruritus in a double-blind, randomized, vehicle-controlled trial lasting seven days. Eighty-five percent of patients receiving the active cream reported relief of pruritus, compared with 57% using the vehicle only. Localized stinging and burning requiring discontinuation in 37 doxepin and 3 placebo patients, were the only significant side effects (Drake et al, 1994).

c) In two multicenter, double-blind, placebo-controlled studies, atopic dermatitis, lichen simplex chronicus, and other eczemas, were successfully treated by DOXEPIN cream in 559 adults (Tech Info Zonalon(R), 1994).

d) Oral DOXEPIN has been effectively used to treat chronic urticaria in numerous clinical trials (Gupta et al, 1987; Goldsobel et al, 1986; Harto et al, 1985); (Greene et al, 1985)(Neittaanmaki et al, 1984a), however, few trials using topical preparations have been published. In one double-blind study, 40 subjects were injected with 8 different dilutions of histamine. Sixty-eight percent showed relief from itching with a 5% topical solution of DOXEPIN, compared to 53% with DIPHENHYDRAMINE and 25% with vehicle alone (Bernstein et al, 1981).

3) COMBINATION THERAPY

a) Patients with pruritic atopic dermatitis responded more promptly and their symptoms improved to a significantly greater extent when topical DOXEPIN was added to HYDROCORTISONE or TRIAMCINOLONE therapy compared with topical corticosteroid monotherapy. In a randomized, double-blind, multi-center trial, cream was applied 4 times daily for 8 days: hydrocortisone 2.5% (HC, n=83); triamcinolone 0.1% (TR, n=90); doxepin 5% plus HC 2.5% (n=86); and doxepin 5% plus TR 0.1% (n=90). Patient-rated visual analog scores for pruritus severity had declined by 8% and 10.7% for HC- and TR-treated patients at 12 hours after initiation of therapy. At the same time, mean reductions in the doxepin-HC and doxepin-TR groups were 31.6% and 22.4%, respectively (p less than 0.001; p=0.07). On day 2, pruritus relief was noted in 46.7%, 66.7%, 70.4%, and 79.1%, respectively, for groups receiving HC, TR, doxepin-HC, and doxepin-TR, according to physician ratings (p=0.01 doxepin-HC vs monotherapy; p=0.027, doxepin-TR vs monotherapy). Common side effects of the corticosteroids were local stinging or burning (not improved by doxepin). Mild and transient drowsiness occurred in 38% and 10% of patients using doxepin plus HC or TR, respectively; rates were 9% and 5% with single-agent corticosteroid therapy (Berberian et al, 1999).

d) Pediatric:

1) Recalcitrant lichen simplex in a 3-year-old boy was resolved by application of 5% doxepin cream. At age 1 year, the boy had intense pruritus of the lower left leg. With persistent scratching, the area developed lichen simplex, which was effectively treated with emollients. At 2 years of age, he had a recurrence, which did not respond to potent topical preparations and occlusive wraps, including mometasone ointment, hydrocolloid dressings, tar bandages, and clobetasol propionate, because the child would remove the dressings. At age 3 years, the boy was treated with 5% doxepin cream in an attempt to break the "itch- scratch cycle." Within 24 hours of doxepin application, scratching stopped, and at 14 days, there was complete resolution. No side effects were observed. In particular, there was no sedation (the principal side effect observed with topical doxepin) (Thomson & Highet, 2001).

4.5.B.19 Psychogenic headache

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:

Beneficial results of DOXEPIN have been reported in patients with PSYCHOGENIC HEADACHE

c) Adult:

1) Beneficial results of DOXEPIN were reported in patients with PSYCHOGENIC HEADACHE following anxiety/depressive illnesses (Okasha et al, 1973). Doses of 10 milligrams three times/day were administered and dosage increased when required by 2 mg daily after 2 weeks at weekly intervals. The study lasted 8 weeks, and by the fourth week the majority of patients noticed marked improvement. When compared with AMITRIPTYLINE and DIAZEPAM, DOXEPIN was the only drug with a highly significant effect on headache, anxiety, and depression. The investigators speculate that superiority of DOXEPIN may be attributed to its effect as an antianxiety agent, antidepressant, and central muscle relaxant.

4.5.B.20 Urticaria

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Effective in the treatment of urticaria

c) Adult:
1) Oral DOXEPIN 10 to 30 milligrams daily has been effective in the treatment of IDIOPATHIC COLD URTICARIA, effectively suppressing the wheal and itching responses and shortening the duration of the wheal response in the ice cube test (Neittaanmaki et al, 1984a).
2) Oral DOXEPIN 5 milligrams twice a day was effective in the treatment of chronic idiopathic URTICARIA in a controlled study. Oral MEQUITAZINE (a phenothiazine antihistamine) 5 mg twice a day was equally effective (Harto et al, 1985; Ledo et al, 1985).
3) Oral DOXEPIN 25 milligrams three times a day was effective in the treatment of CHRONIC IDIOPATHIC URTICARIA in a placebo-controlled trial involving 16 adult patients (Goldsobel et al, 1986). Patients were randomly assigned to receive either DOXEPIN or placebo for 4 weeks; each group was then crossed over for the next 4 weeks. DOXEPIN was associated with fewer waking hours with lesions, and less angioedema and swelling as compared to placebo-treated patients. Daily antihistamine use was less in patients treated with DOXEPIN. Lethargy was observed during DOXEPIN therapy but decreased with continued use of the drug; dry mouth and constipation were also reported.

4.6 Comparative Efficacy / Evaluation With Other Therapies

Amitriptyline

Amitriptylinoxide

Amoxapine

Bupropion

Capsaicin

Chlordiazepoxide

Cimetidine

Cinnarizine

Clomipramine

Clovoxamine

Desipramine

Diazepam

Diphenhydramine

Dothiepin

Fluoxetine

Imipramine

Loxapine

Maprotiline

Mianserin

Nomifensine

Opipramol

Paroxetine

Perphenazine/Amitriptyline Hydrochloride

Trazodone

Trimipramine

4.6.A Amitriptyline

4.6.A.1 Depression

a) Clinical studies have shown that doxepin and amitriptyline are of comparable efficacy in depression; side effects have occurred with greater frequency in patients receiving amitriptyline (Toru et al, 1972; Bianchi et al, 1971; Solis et al, 1970).

b) In one study, amitriptyline-perphenazine produced significantly greater improvement than doxepin on several measures of psychiatric tests. The combination also produced a greater incidence of sedation and anticholinergic side effects (Rickels et al, 1982a). Doxepin 100 to 150 milligrams/day was compared with a combination of amitriptyline 100 to 150 milligrams/day plus perphenazine 8 to 12 milligrams/day in 130 depressed, nonpsychotic outpatients over a period of 4 weeks.

c) Four antidepressants were used in a group of 116 private practice patients suffering from depression associated with chronic or recurrent pain. Dosage range was 150 to 300 milligrams/day, and the antidepressant was changed if necessary to get an adequate response. The response to the 4 antidepressants was not statistically significantly different: doxepin 17 of 22 (77%); imipramine 33 of 44 (75%); amitriptyline 21 of 25 (84%); and desipramine 34 of 44 (75%). A significant response was a 50% reduction in pain judged subjectively (Lindsay & Wyckoff, 1981).

d) Doxepin was compared with amitriptyline in acutely depressed patients using cortical evoked potentials as the measurement of success (Friedman et al, 1980). Many depressed patients have a magnified perception of intervisity to a stimulus; thus, often they complain of pain which to others might be described as discomfort. In 33 patients, baseline potentials were measured after 1 week of placebo therapy, then they received 150 milligrams/day of either doxepin or amitriptyline. Five visual and 5 auditory evoked potentials were recorded. Doxepin reduced the amplitudes of the evoked potentials significantly. Amitriptyline had a similar, but insignificant effect.

e) One author reported that doxepin showed faster pharmacologic activity and greater antidepressive and anxiolytic effects than amitriptyline (Solis et al, 1970).

4.6.B Amitriptylinoxide

4.6.B.1 Depression

a) Doxepin and amitriptylinoxide, in doses of 180 to 360 milligrams/day, had a similar efficacy in a four-week study involving 44 inpatients with severe depression. Efficacy was judged on several rating scales. The two drugs showed comparable efficacy and there were no significant differences in adverse effects (Konig et al, 1994).

4.6.C Amoxapine

4.6.C.1 Mixed anxiety and depressive disorder

a) Amoxapine 160 milligrams/day (maximum dose) was compared with doxepin 130 milligrams/day (maximum dose) in the treatment of mixed anxiety/depression in 142 patients. Twenty-four to 31 of amoxapine-treated subjects (n=71) and 16 to 24 of doxepin-treated subjects (n=71) receiving doxepin were identified as improved after 4 weeks. Amoxapine achieved a more rapid response. Side effects between the 2 treatments were comparable; however, doxepin caused more constipation (Hekimian et al, 1983).

4.6.D Bupropion

4.6.D.1 Depression

a) Bupropion 300 to 450 milligrams daily was reported similar in efficacy to doxepin 100 to 225 milligrams daily in the treatment of major depressive disorder in a double-blind study involving 147 outpatients (Feighner et al, 1986). Doxepin, however, improved sleep better than bupropion; anticholinergic side effects were more frequent with doxepin as compared with bupropion, as was increased appetite and weight gain.

4.6.E Capsaicin

4.6.E.1 Chronic pain - Neuropathic pain

a) Topical doxepin hydrochloride, topical capsaicin, or the combination of the 2 all provided analgesia in chronic human neuropathic pain (CNP), in contrast to placebo. In a randomized, double-blind, placebo-controlled trial, 200 patients with CNP were given placebo cream, 3.3% doxepin hydrochloride cream, 0.25% capsaicin cream, or a cream containing 3.3% doxepin and 0.25% capsaicin. Patients were to apply a volume of cream approximately equal in size to a grain of rice 3 times daily to the painful area for 4 weeks. Overall pain was unchanged in the placebo group. In the other 3 groups, overall pain decreased from approximately 7 to approximately 6 on a pain scale ranging from 0 to 10 (p less than 0.001 for all drug groups). Scores for burning pain were unchanged in the placebo group but increased in all 3 drug groups at week 1 and, though diminishing somewhat thereafter, remained significantly above that of the placebo group. Sensitivity was unchanged by placebo and doxepin but declined significantly, beginning in the first week, with both capsaicin (p less than 0.001) and doxepin/capsaicin (p less than 0.01) treatments. Shooting pain was reduced by the capsaicin treatments but not by doxepin or placebo. Ten percent of patients in the doxepin group and 5% in the doxepin/capsaicin group complained of drowsiness, suggesting the systemic absorption of doxepin. A burning sensation was reported by 81% of those in the capsaicin and by 61% of those in the doxepin/capsaicin group (McCleane, 2000).

4.6.F Chlordiazepoxide

4.6.F.1 Anxiety

a) Most clinical studies to date have indicated that doxepin has proven as useful as chlordiazepoxide in patients with anxiety neurosis (Simeon et al, 1970; Kingstone et al, 1970; Johnstone & Claghorn, 1968). At this point doxepin can not be recommended over chlordiazepoxide or other benzodiazepines in neurotic anxiety but is recommended as the drug of choice in patients with mixed anxiety-depression states (Pinder et al, 1977c).

4.6.G Cimetidine

4.6.G.1 Duodenal ulcer disease

a) In a double-blind randomized study of 21 patients, doxepin (50 milligrams at bedtime for 1 week, followed by 100 milligrams at bedtime) was comparable with cimetidine 300 milligrams four times a day for the treatment of duodenal ulcers (Shrivastava et al, 1985). After 6 weeks, the average ulcer size decreased by 97% in both groups. Interestingly, doxepin was significantly more effective in women than in men, while cimetidine was more effective in men than in women. Further large studies are needed to confirm whether there truly exists a sex-related difference in ulcer healing, especially with doxepin.

4.6.H Cinnarizine

4.6.H.1 Urticaria

a) A randomized, double-blind, crossover trial in 10 patients with primary acquired idiopathic cold urticaria compared the effects of cinnarizine 10 milligrams (mg) three times daily with doxepin 10 mg three times daily and placebo. Each arm of therapy lasted two weeks. Eight patients considered doxepin superior to cinnarizine. Cinnarizine provided some symptom relief in five patients, and was ineffective in four. One patient discontinued cinnarizine therapy due to excessive fatigue. Placebo produced no symptom relief (Neittaanmaki et al, 1984).

4.6.I Clomipramine

4.6.I.1 Dysthymia

a) Results were equivocal in a study that compared clomipramine and doxepin (75 milligrams/day of either) in a group of 66 patients with neurotic depression. Patient-rated measures did not show a superior agent. Clomipramine was rated better by physician-rated measures. There were no significant differences in side effects (Kornhaber & Horwitz, 1984).

b) Doxepin (25 milligrams three times a day) and clomipramine (25 milligrams three times a day), were more effective than L-tryptophan (500 mg three times a day) in 42 neurotically-depressed patients. The findings of the study were that doxepin and clomipramine resulted in more responses than L-tryptophan, therapeutic blood levels of clomipramine and doxepin were much smaller than those found in endogenously depressed patients, that responders had a significantly higher blood level of the two than non-responders at 21 days, and that the response to clomipramine, but not doxepin, parallelled its accumulation in the blood. (Linnoila et al, 1980).

4.6.J Clovoxamine

4.6.J.1 Depression

a) SUMMARY: Clovoxamine offered no clinical advantage over doxepin in the treatment of major depression in one small double-blind study.

b) In a small, double-blind study (n=34), clovoxamine 150 to 300 milligrams daily was generally comparable in efficacy with doxepin 75 to 150 milligrams daily in the treatment of major depression (Lodge & Freeman, 1986). However, doxepin was statistically superior to clovoxamine with regard to improvement of the anxiety/somatization component of Hamilton Rating Scale for Depression (HAM-D) during the first week of treatment. In addition, patient assessments of the response to treatment were highly in favor of doxepin; 97% of doxepin-treated patients indicated they had improved significantly compared to only 50% in the clovoxamine group. Adverse effects were similar in each group, although headache, sweating, and anticholinergic symptoms tended to occur more frequently with clovoxamine. Analysis of pretreatment data in this study indicated more severe depression in the clovoxamine group, which may have influenced results reported. However, several patients with severe psychotic depression were also treated effectively with clovoxamine, suggesting efficacy of the drug in this subgroup. A larger and placebo-controlled study comparing these agents is needed.

4.6.K Desipramine

Chronic pain

Endogenous depression

4.6.K.1 Chronic pain

a) Desipramine and doxepin had similar efficacy in treating depression and doxepin was more effective than desipramine in the treatment of pain severity in one study (Ward et al, 1984). Desipramine (mean dose 173 milligrams/day) was compared with doxepin (mean dose 188 milligrams/day) in 36 patients with depression and chronic back pain. Both drugs produced equal responses in depression ratings. Pain severity showed a better response to doxepin.

b) Four antidepressants had similar efficacy in a group of 116 private practice patients suffering from depression associated with chronic or recurrent pain. Dosage range was 150 to 300 milligrams/day, and the antidepressant was changed if necessary to get an adequate response. The response to the 4 antidepressants was not significantly different: doxepin 17 of 22 (77%); imipramine 33 of 44 (75%); amitriptyline 21 of 25 (84%); and desipramine 34 of 44 (75%). A significant response was a 50% reduction in pain subjectively judged (Lindsay & Wyckoff, 1981a).

4.6.K.2 Endogenous depression

a) Doxepin and desipramine were equally effective in a group of 38 patients with a diagnosis of primary affective disorder, endogenous depression. Both drugs had equal efficacy, but doxepin had a more rapid onset (Amsterdam et al, 1982).

4.6.K.3 Efficacy

a) A prospective study compared oral doses and corresponding plasma levels of doxepin with desipramine (as standard reference compound) for 31 patients (19 females, 12 males), mean age 76 (range, 66 to 86). The results in eight doxepin-treated patients (25 to 100 milligrams/day) showed zero levels of doxepin or its metabolite, desmethyldoxepin, in their plasma. The authors believed that doxepin's reputation for having fewer side effects may reflect the low plasma levels achieved at commonly prescribed doses and that at more appropriate doses, the side-effect profile may be more in line with standard tricyclics. The authors recommend routine monitoring of doxepin levels in the elderly and question poor bioavailability or absorption of this tricyclic antidepressant in some patients (Gosselin et al, 1989).

b) Desipramine suppressed wheal response for 2 days and flare for one day, whereas doxepin suppressed the wheal for 4 days and flare for 6 days in a double-blind, single dose, noncrossover study. Thirty-three healthy adult volunteers (32 males, 1 female) received a single, oral 25-milligram dose of desipramine or doxepin. The duration of H1-receptor blockade by these two tricyclic antidepressants were compared. Results showed significant differences in the suppression of the wheal-and-flare responses to histamine between the two drugs (Rao et al, 1988). These results suggest that doxepin should be withheld for at least 7 days before allergy skin testing.

4.6.L Diazepam

4.6.L.1 Anxiety

a) No significant difference has been observed in clinical trials in patients with anxiety (with or without depression) between doxepin and diazepam (d'Elia et al, 1974; Fielding et al, 1969; Kasich, 1969).

b) A double-blind, placebo-controlled study of 61 outpatients compared doxepin and diazepam in the treatment of anxious and anxious-depressive syndromes (Haskell et al, 1978). After the first week, an enhanced sense of well-being was associated with diazepam. By the end of 6 weeks, there was no significant difference for altering mood and symptomatology with either drug. Objective evaluation rated diazepam more effective than doxepin among anxious patients. Drowsiness was the most common side effect. Significant weight gain occurred with doxepin. Possible biases may have been induced by the sampling technique, population characteristics, and consequent drop-out rate.

4.6.M Diphenhydramine

4.6.M.1 Urticaria

a) Oral doxepin 10 milligrams three times a day was reported significantly superior to oral diphenhydramine 25 milligrams three times a day in the treatment chronic idiopathic urticaria in a controlled study involving 50 patients (Greene et al, 1985). Clearing of pruritus and urticarial lesions was observed in 5% and 43% of diphenhydramine and doxepin-treated patients, respectively; partial or total control pruritus and hives occurred in 10% and 74% of patients, respectively. Doxepin was also associated with significantly less sedation than diphenhydramine.

4.6.N Dothiepin

4.6.N.1 Depression

a) Dothiepin and doxepin were similarly effective when administered in single daily doses of 150 milligrams in a ten-week, placebo-controlled, double-blind study of 579 outpatients with major depressive disorder with psychotic features. Efficacy was judged by several rating scales. Only 341 patients completed the trial. Both drug groups were significantly superior to placebo and there were no significant differences between the two groups. Dothiepin was superior to doxepin relative to the incidence and severity of adverse events (Ferguson et al, 1994).

4.6.O Fluoxetine

4.6.O.1 Depression

a) Doxepin and fluoxetine had similar efficacy in a comparative study involving 80 depressed patients (61 outpatients, 19 inpatients) diagnosed as having major depressive disorder. The patients received either fluoxetine 20 to 60 milligrams/day (mean, 28.9 mg/day) or doxepin 100 to 200 milligrams/day (mean, 146.8 mg/day). Both treatment groups showed improvement over time, with no difference between fluoxetine and doxepin at study termination. The most common side effects of fluoxetine (headache, nausea, and insomnia) were in contrast to the pronounced anticholinergic side effects of doxepin (dry mouth, fatigue, constipation). Moreover, the significant weight gain associated with doxepin therapy was not seen with fluoxetine treatment (Remick et al, 1989).

b) Fluoxetine 20 to 80 milligrams daily (once daily or divided twice a day) and doxepin 50 to 200 milligrams daily (once daily or divided twice a day or three times a day) had comparable efficacy in the treatment of depression in geriatric patients (at least 64 years of age). Each drug was administered in increasing doses over the first two weeks of the study, with maintenance doses (up to 80 mg daily of fluoxetine and 200 mg daily of doxepin) being determined by the third week; this maintenance dose was given for three more weeks (total, six weeks). Both drugs were considered equally effective using the following parameters: Hamilton Psychiatric Rating Scale for Depression (HAM-D), Raskin Severity of Depression Scale, Covi Anxiety Scale, Clinical Global Impressions severity and improvement, Patient Global Improvement, and SCL-58 scales. Both drugs produced significant improvement compared to baseline scores. Fluoxetine was associated with a lower degree of drowsiness/sedation, dry mouth, constipation and vision disturbances. However, nervousness/anxiety, insomnia, sweating, dyspepsia, and nausea occurred to a greater degree with fluoxetine. Body weight decreased with fluoxetine and increased with doxepin (Feighner & Cohn, 1985).

c) In one study comparing fluoxetine and doxepin, both drugs were effective in major depressive disorder in geriatric patients, with a lower incidence of side effects being observed with fluoxetine (Feighner & Cohn, 1985). Weight loss occurred with fluoxetine, as compared to weight gain with doxepin, which was statistically significant. Heart rate was shown to increase in doxepin-treated patients as compared to decreases in fluoxetine-treated patients; this was also a statistically significant difference. Significant improvement in depressive symptoms was further demonstrated in a group (n=33) of geropsychiatric patients. Although this study only followed patients for a period of one month, significant side effects such as nausea, weight loss, and agitation were not noted. Doses of fluoxetine used were 20 mg every other day to 20 mg daily (Orengo et al, 1996).

4.6.P Imipramine

4.6.P.1 Depression

a) Imipramine may be slightly more effective than doxepin in the treatment of depression. Ninety-nine patients with neurotic depression received imipramine 100 to 200 milligrams/day or doxepin 100 to 200 milligrams/day for 4 weeks in a double-blind study. Imipramine was superior in 24 of 27 parameters. Imipramine was shown to be superior to doxepin in improving the symptoms of anxiety/depression; global evaluations showed improvement in 39 of 48 (81%) of imipramine patients and 34 and 49 (69%) of doxepin patients (Finnerty et al, 1978).

b) In a study involving 79 patients, a higher socioeconomic status and shorter duration of illness were indicative of a favorable response to imipramine, whereas a higher response rate to doxepin was found in male patients (Finnerty & Goldberg, 1981).

c) Amitriptyline was superior to imipramine and doxepin in relation to their effects on interpersonal learning in 50 depressed inpatients (Gillis, 1981). All subjects performed better, according to quantitative indices of

learning tasks, than patients who received antipsychotic or neuroleptic drugs but no antidepressants. Amitriptyline patients scored significantly higher than either imipramine or doxepin patients.
d) No significant differences in overall efficacy of the 2 drugs was reported in one study (Kimura, 1972), but doxepin 30 to 150 mg daily was superior to imipramine 150 mg daily in neurotic depression, whereas imipramine appeared to be superior to doxepin in endogenous depression (Pinder et al, 1977d).
e) Similar antidepressant effects of doxepin and imipramine were reported; however, imipramine had a more rapid onset of action. Doxepin appeared to have more sustained effects (Hasan & Akhtar, 1971).

4.6.P.2 Efficacy

a) In elderly patients doxepin produces less orthostatic effects than imipramine (10.5 mmHg vs 25.9 mmHg). The orthostatic effect observed with imipramine was weakly related to dose and did not correlate with pretreatment orthostatic hypotension or with duration of treatment (Neshkes et al, 1985).

4.6.Q Loxapine

4.6.Q.1 Anxiety

a) No significant differences were reported between doxepin and loxapine succinate in patients with anxiety neurosis (Charlalampous et al, 1974).

4.6.R Maprotiline

4.6.R.1 Depression

a) Single nightly doses of doxepin and maprotiline, 75 to 150 milligrams orally for 6 weeks produced moderate to marked improvement in depression in a majority of 47 depressed patients. Both drugs were rated equally effective in this double-blind study. Side effects were not significantly different (Anon, 1978).
b) Maprotiline and doxepin were equally effective in a double-blind, multicenter trial in 95 depressed (neurotic and psychotic) inpatients/outpatients who were randomized into 2 equal groups (Vaisanen et al, 1978). A dose of 75 milligrams daily of either maprotiline or doxepin was given initially; the dose was doubled if needed. Seventy-eight patients completed the three-to-four week trial. The dropout group included six due to unwanted effects (2 maprotiline, 4 doxepin), one from each group due to lack of efficacy and nine for other reasons (non-cooperation/noncompliance). Almost one-half of the patients in the study received additional psychoactive medication including sedatives, neuroleptics, and tranquilizers which were not thought to influence the trial. Overall assessment using a five point scale of target symptoms and a visual analogue scale showed no statistically significant difference between the two treatment groups. The most common side effects in both groups were dry mouth and fatigue. Fourteen patients continued treatment with maprotiline after the trial for a mean of 13 weeks (five received maprotiline for 30 weeks) with no pathological changes in laboratory values except for a slight rise in liver enzyme levels in two patients during initial therapy.

4.6.S Mianserin

4.6.S.1 Mixed anxiety and depressive disorder

a) Mianserin 60 milligrams/day and doxepin 150 milligrams/day had similar efficacy in 60 patients with mixed anxiety/depression. After 4 weeks of treatment, there was no consistent difference in efficacy, but a higher incidence of side effects occurred in the doxepin group (Khan et al, 1983).

4.6.T Nomifensine

4.6.T.1 Depression

a) Doxepin 186 mg daily was more effective than nomifensine 196 mg daily in treatment of endogenous and neurotic depression (Anderson, 1977). Fatigue and dizziness occurred more often with doxepin than nomifensine.

4.6.U Opipramol

4.6.U.1 Depression

a) In a randomized double-blind 5-week trial, doxepin was found to be more effective overall than opipramol. Patients were diagnosed with one of the following types of depression: neurotic depression, psychotic depression, involutional melancholia and senile depression. Eighteen patients were in the opipramol group and 22 in the doxepin group. The average dose of doxepin was between 10 and 20 milligrams (mg)/day and opipramol was between 50 and 100 mg/day. Effects of the drugs were viewed from three standpoints: nosologic classification, syndrome classification and individual symptoms. From the nosological standpoint, doxepin was significantly more effective; although opipramol was very effective in treating patients with involutional melancholia. From the syndrome classification standpoint, doxepin was once again better overall. From the individual symptoms standpoint, doxepin was more effective in relieving depressive mood, fear, suicidal thoughts, feeling of insufficiency, guilt, insomnia, vegetative symptoms and psychomotor disturbances than was opipramol. Drowsiness was the only adverse effect reported with either drug (Terzani, 1972).

4.6.V Paroxetine

4.6.V.1 Depression

a) Paroxetine was at least as effective as doxepin in the treatment of major depression in 272 geriatric patients in a double-blind, randomized trial. After a washout-period of 4 to 14 days, patients over 60 years of age received either paroxetine 10 to 40 milligrams (mg) (mean 23.4 mg) as a single daily dose or doxepin (up to 200 milligrams (mg), mean 105.2 mg/day) divided in two doses. Therapy continued for 42 days. Paroxetine was as effective as doxepin by several measures and more effective by others. Doxepin caused more sedation, confusion, and anticholinergic effects, and less nausea and headache compared with paroxetine (Dunner et al, 1992).

4.6.W Perphenazine/Amitriptyline Hydrochloride

4.6.W.1 Depression

a) Doxepin (100 to 150 milligrams/day) was not as effective as amitriptyline/perphenazine (100/8 to 150/12 milligrams/day) in 130 nonpsychotic depressed outpatients over 4 weeks. Amitriptyline/perphenazine produced greater improvement based on several rating scales. The combination also showed a greater incidence of anticholinergic and sedative side effects (Rickels et al, 1982).

4.6.X Trazodone

4.6.X.1 Depression

a) No significant difference in safety or efficacy was seen in a comparison of trazodone (mean daily dose during weeks 1, 3, and 6 was 125 milligrams (mg), 221 mg, and 246 mg) with doxepin (mean daily dose during weeks 1, 3, and 6 was 58 mg, 105 mg, and 127 mg) in 30 outpatients with major depressive disorder in a 6-week, double-blind, parallel study (Himmelhoch, 1986).

b) No significant difference was reported in a double-blind study of 101 patients, on the efficacy of trazodone and doxepin in the treatment of depression (Murphy & Ankier, 1980).

4.6.Y Trimipramine

4.6.Y.1 Depression

a) The therapeutic efficacy and cardiac safety of trimipramine and doxepin were comparable in 37 patients with major depressive disorder. Patients received one week of placebo followed by five weeks of either trimipramine or doxepin in doses up to 200 milligrams/day. Based on ECG and psychiatric and cognitive function tests, the drugs were concluded to be equally safe and efficacious in this group of patients (Nair et al, 1993).

b) Trimipramine was superior to doxepin in safety and efficacy in a 4-week study. Trimipramine and doxepin (150 milligrams/day of each) were compared in 25 depressed hospitalized patients. Comparisons of efficacy favored trimipramine over doxepin. Doxepin had a higher incidence of side effects (Assalian et al, 1985).

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DRUGDEX® Evaluations

ATOMOXETINE

0.0 Overview

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

2) Dosing Information
- **a)** Atomoxetine Hydrochloride
  - **1)** Adult
    - **a)** Attention deficit hyperactivity disorder
      - **1)** 40 mg/day ORALLY; increase after a minimum of 3 days to a target dose of approximately 80 mg/day; MAX dosage of 100 mg/day may be considered after 2 to 4 additional weeks in patients who have not achieved adequate response on lower doses (Prod Info STRATTERA(R) oral capsules, 2008)
  - **2)** Pediatric
    - **a)** safety and effectiveness not established in children less than 6 years of age (Prod Info STRATTERA(R) oral capsules, 2008)
      - **1)** Attention deficit hyperactivity disorder
        - **a)** acute treatment: (weight of 70 kg or less) 0.5 mg/kg/day ORALLY; increase after a minimum of 3 days to a target dose of 1.2 mg/kg/day; MAX dosage is 1.4 mg/kg/day or 100 mg/day (whichever is less) (Prod Info STRATTERA(R) oral capsules, 2008)
        - **b)** acute treatment: (weight greater than 70 kg) 40 mg/day ORALLY; increase after a minimum of 3 days to a target dose of approximately 80 mg/day; MAX dosage of 100 mg/day may be considered after 2 to 4 additional weeks in patients who have not achieved adequate response on lower doses (Prod Info STRATTERA(R) oral capsules, 2008)
        - **c)** maintenance: 1.2 to 1.8 mg/kg/day ORALLY has been studied in 1 clinical trial; MAX dosage is 1.4 mg/kg/day or 100 mg/day, whichever is less (weight of 70 kg or less) OR 100 mg/day (weight greater than 70 kg) (Prod Info STRATTERA(R) oral capsules, 2008)

3) Contraindications
- **a)** Atomoxetine Hydrochloride
  - **1)** hypersensitivity to atomoxetine or to other components of the product (Prod Info STRATTERA(R) oral capsules, 2009)
  - **2)** MAO inhibitor use; do not administer atomoxetine during therapy with or within 2 weeks of discontinuing an MAO inhibitor (Prod Info STRATTERA(R) oral capsules, 2009)
  - **3)** narrow angle glaucoma; increased risk of mydriasis (Prod Info STRATTERA(R) oral capsules, 2009)

4) Serious Adverse Effects
- **a)** Atomoxetine Hydrochloride
  - **1)** Angioedema
  - **2)** Cerebrovascular accident
  - **3)** Dyskinesia
  - **4)** Injury of liver (Severe)
  - **5)** Mania
  - **6)** Myocardial infarction
  - **7)** Priapism
  - **8)** Prolonged QT interval
  - **9)** Psychotic disorder
  - **10)** Seizure
  - **11)** Sudden cardiac death
  - **12)** Suicidal thoughts

5) Clinical Applications
- **a)** Atomoxetine Hydrochloride
  - **1)** FDA Approved Indications
    - **a)** Attention deficit hyperactivity disorder

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
Atomoxetine
Atomoxetine HCl
Atomoxetine Hydrochloride
Tomoxetine

C) Physicochemical Properties
1) Molecular Weight
a) 291.82 (Prod Info Strattera(R), 2004)
2) Solubility
a) 27.8 mg/mL in water (Prod Info Strattera(R), 2004)

1.2 Storage and Stability

A) Atomoxetine Hydrochloride
1) Preparation
a) Oral route
1) Atomoxetine hydrochloride (HCl) may be taken with or without food. Swallow capsules whole, and do not open (Prod Info STRATTERA(R) oral capsules, 2008).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Other Disease States

1.3.1 Normal Dosage

1.3.1.A Atomoxetine Hydrochloride

1.3.1.A.1 Oral route

1.3.1.A.1.a Attention deficit hyperactivity disorder

1) The recommended starting dose of atomoxetine hydrochloride (HCl) in adult patients with attention-deficit hyperactivity disorder is 40 milligrams (mg)/day orally. The dose may be increased after a minimum of 3 days to a target dose of approximately 80 mg/day, given as a single daily dose (in the morning) or as 2 divided doses (in the morning and late afternoon/early evening). The maximum dose of atomoxetine 100 mg/day may be given after 2 to 4 additional weeks in patients who have not achieved an adequate response on lower doses. Tapering of the dose is not required upon therapy discontinuation (Prod Info STRATTERA(R) oral capsules, 2008).

2) Concomitant CYP2D6 Inhibitors
a) Atomoxetine hydrochloride should be initiated at 40 milligrams (mg)/day in adult patients receiving concomitant strong CYP2D6 inhibitors, such as paroxetine, fluoxetine, or quinidine. Patients should only be titrated to the maximum dose of 80 mg/day after 4 weeks if they have tolerated the initial dose but did not achieve an adequate response on lower doses (Prod Info STRATTERA(R) oral capsules, 2008).

1.3.2 Dosage in Renal Failure

A) Atomoxetine Hydrochloride
1) No dose adjustment of atomoxetine hydrochloride is necessary in patients with renal insufficiency (Prod Info STRATTERA(R) oral capsules, 2008).

1.3.3 Dosage in Hepatic Insufficiency

A) Atomoxetine Hydrochloride
1) Atomoxetine hydrochloride (HCl) is metabolized in the liver, and dose adjustments are necessary in patients with hepatic impairment. Starting and target doses of atomoxetine HCl should be reduced by 50%

of the normal dose in patients with moderate hepatic insufficiency (Child-Pugh Class B) and reduced to 25% of the normal dose in patients with severe hepatic insufficiency (Child-Pugh Class C) (Prod Info STRATTERA(R) oral capsules, 2008).

1.3.6 Dosage in Other Disease States

A) Atomoxetine Hydrochloride

1) CYP2D6 Poor Metabolizers

a) In patients who are known poor metabolizers of CYP2D6, atomoxetine hydrochloride should be initiated at 40 milligrams/day (mg/day). Patients should only be titrated to the target dose of 80 mg/day after 4 weeks if they have tolerated the initial dose but did not achieve an adequate response on lower doses (Prod Info STRATTERA(R) oral capsules, 2008).

1.4 Pediatric Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Other Disease States

1.4.1 Normal Dosage

1.4.1.A Atomoxetine Hydrochloride

1.4.1.A.1 Oral route

1.4.1.A.1.a Attention deficit hyperactivity disorder

1) Acute Therapy

a) Patients Weighing 70 Kilograms or Less

1) The recommended starting dose of atomoxetine hydrochloride (HCl) in children and adolescent patients with attention-deficit hyperactivity disorder who weigh 70 kilograms (kg) or less is approximately 0.5 milligrams (mg)/kg/day orally. The dose may be increased after a minimum of 3 days to a target dose of approximately 1.2 mg/kg/day, given as a single daily dose (in the morning) or as 2 divided doses (in the morning and late afternoon/early evening). Although no additional benefits were observed in clinical studies with doses higher than 1.2 mg/kg/day, the maximum dose in children and adolescents is atomoxetine 1.4 mg/kg/day or 100 mg/day, whichever is less. Tapering of the dose is not required upon therapy discontinuation (Prod Info STRATTERA(R) oral capsules, 2008).

2) Concomitant CYP2D6 Inhibitors

a) Atomoxetine hydrochloride should be initiated at 0.5 milligrams/kilogram/day (mg/kg/day) in patients receiving concomitant strong CYP2D6 inhibitors, such as paroxetine, fluoxetine, or quinidine. Patients should only be titrated to the maximum dose of 1.2 mg/kg/day after 4 weeks if they have tolerated the initial dose but did not achieve an adequate response on lower doses (Prod Info STRATTERA(R) oral capsules, 2008).

b) Patients Weighing Greater than 70 Kilograms

1) The recommended starting dose of atomoxetine hydrochloride (HCl) in children and adolescent patients with attention-deficit hyperactivity disorder who weigh greater than 70 kilograms is 40 milligrams (mg)/day orally. The dose may be increased after a minimum of 3 days to a target dose of approximately 80 mg/day, given as a single daily dose (in the morning) or as 2 divided doses (in the morning and late afternoon/early evening). The maximum dose of atomoxetine 100 mg/day may be given after 2 to 4 additional weeks in patients who have not achieved an adequate response on lower doses. Tapering of the dose is not required upon therapy discontinuation (Prod Info STRATTERA(R) oral capsules, 2008).

2) Concomitant CYP2D6 Inhibitors

a) Atomoxetine hydrochloride should be initiated at 40 milligrams (mg)/day in patients receiving concomitant strong CYP2D6 inhibitors, such as paroxetine, fluoxetine, or quinidine. Patients should only be titrated to the maximum dose of 80 mg/day after 4 weeks if they have tolerated the initial dose but did not achieve an adequate response on lower doses (Prod Info STRATTERA(R) oral capsules, 2008).

c) The safety of single doses exceeding 120 mg or total daily doses exceeding 150 mg has not been evaluated (Prod Info STRATTERA(R) oral capsules, 2008).

2) Maintenance Therapy

a) In one study, pediatric patients (ages 6 to 15 years) with attention-deficit hyperactivity disorder continued on atomoxetine hydrochloride (HCl) 1.2 to 1.8 milligrams (mg)/kilogram (kg)/day after achieving a continuous response during an initial 10-week, open-label treatment phase. The maximum recommended total daily dose is 1.4 mg/kg/day or 100 mg/day (whichever is less) in patients weighing 70 kg or less, and 100 milligrams/day in patients weighing over 70 kg. Tapering of the dose is not required upon therapy discontinuation. Patients who receive atomoxetine HCl for extended time periods should be periodically reassessed to verify drug effectiveness (Prod Info STRATTERA(R) oral capsules, 2008).

b) The safety of single doses exceeding 120 mg or total daily doses exceeding 150 mg has not been evaluated (Prod Info STRATTERA(R) oral capsules, 2008).

2) The safety and effectiveness of atomoxetine hydrochloride have not been evaluated in pediatric patients less than 6 years of age (Prod Info STRATTERA(R) oral capsules, 2008).

1.4.2 Dosage in Renal Failure

A) Atomoxetine Hydrochloride

1) No dose adjustment of atomoxetine hydrochloride is necessary in patients with renal insufficiency (Prod Info STRATTERA(R) oral capsules, 2008).

1.4.3 Dosage in Hepatic Insufficiency

A) Atomoxetine Hydrochloride

1) Atomoxetine hydrochloride (HCl) is metabolized in the liver, and dose adjustments are necessary in patients with hepatic impairment. Starting and target doses of atomoxetine HCl should be reduced by 50% of the normal dose in patients with moderate hepatic insufficiency (Child-Pugh Class B) and reduced to 25% of the normal dose in patients with severe hepatic insufficiency (Child-Pugh Class C) (Prod Info STRATTERA(R) oral capsules, 2008).

1.4.5 Dosage in Other Disease States

A) Atomoxetine Hydrochloride

1) CYP2D6 Poor Metabolizers

a) In patients who are known poor metabolizers of CYP2D6, atomoxetine hydrochloride should be initiated at 0.5 milligrams/kilogram/day (mg/kg/day). Patients should only be titrated to the target dose of 1.2 mg/kg/day after 4 weeks if they have tolerated the initial dose but did not achieve an adequate response on lower doses (Prod Info STRATTERA(R) oral capsules, 2008).

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset

1) Initial Response

a) ATTENTION-DEFICIT/HYPERACTIVITY DISORDER, ORAL: 1 week (Spencer et al, 2001).

1) Based on data from children with ADHD in an open study (twice-daily dosing).

2) In adults with ADHD, a significant reduction in symptoms versus placebo was seen after 2 weeks of treatment (Spencer et al, 1998).

b) MAJOR DEPRESSION, ORAL: within one week (Chouinard et al, 1985).

1) Based on limited patient data from an open study.

2.2 Drug Concentration Levels

A) Therapeutic Drug Concentration

1) Not established in any indication.

B) Time to Peak Concentration

1) ORAL: 1 to 2 hours (Farid et al, 1985); (Prod Info Strattera(R), 2002).

a) In children ages 7 to 14 years with attention deficit hyperactivity disorder and classified as extensive metabolizers, maximal concentration was achieved in 2 hours after either a single dose of atomoxetine 10 milligrams (mg) or steady-state dosing (20 to 45 mg twice daily) (Witcher et al, 2003).

b) Following single 90-mg oral doses in healthy subjects (extensive metabolizers), peak plasma levels of atomoxetine varied considerably, ranging from 315 to 1231 ng/mL. Plasma levels fell to undetectable levels

at 36 hours postdosing. In poor metabolizers, peak levels tended to be higher, and occurred later (based on two subjects) (Farid et al, 1985).

c) With administration of 20 and 40 mg twice daily for 7 days in extensive metabolizers (healthy subjects), peak levels on day 1 were approximately 100 and 250 ng/mL, respectively; there was no significant accumulation on days 2 through 7. Plasma concentrations of the metabolite, noratomoxetine, were low in these subjects (less than 10 ng/mL). In subjects who were poor metabolizers in this study (n=2), significant accumulation of both atomoxetine and noratomoxetine was observed during repeat dosing (Farid et al, 1985).

C) Area Under the Curve

1) mean 2766 ng x hr/mL after 90-mg single dose (extensive metabolizers) (Farid et al, 1985).

a) In children ages 7 to 14 years with attention deficit disorder and classified as extensive metabolizers, plasma concentrations of the active metabolite 4-hydroxyatomoxetine were 26 to 35 times less than those for atomoxetine (Witcher et al, 2003).

b) During repeat dosing in extensive metabolizers (healthy subjects), AUC data indicated no significant accumulation of atomoxetine; in subjects receiving 20 mg and 40 mg twice daily for one week, AUC(0-24) values at steady-state (last dose) were 975 to 1126 ng x hr/mL and 2460 to 3710 ng x hr/mL, respectively. In poor metabolizers receiving these doses, accumulation was significant, with corresponding values of 10,490 ng x hr/mL and 29,330 ng x hr/mL (based on data from two subjects) (Farid et al, 1985).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption

A) Bioavailability

1) ORAL: 63% in extensive metabolizers; 94% in poor metabolizers (Prod Info Strattera(TM), 2002t).

B) Effects of Food

1) extent of absorption unaffected (Prod Info Strattera(TM), 2002t).

a) The rate of absorption is reduced when given with food in adults (by 37%) and time to peak levels prolonged (by about 3 hours); however, AUC is unaffected (Prod Info Strattera(TM), 2002t).

2.3.2 Distribution

A) Distribution Sites

1) Protein Binding

a) 98% (albumin) (Prod Info Strattera(TM), 2002t).

B) Distribution Kinetics

1) Volume of Distribution

a) Approximately 74 to 250 liters (extensive metabolizers) (Witcher et al, 2003; Farid et al, 1985).

1) Volume of distribution was similar (74 to 328 liters) between single oral doses (10 to 90 milligrams (mg)), and repeat dosing (20 to 45 mg twice daily) in extensive metabolizers (healthy subjects). In poor metabolizers (data limited), a slightly lower volume of distribution was reported (about 90 L) (Witcher et al, 2003; Farid et al, 1985).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics

1) LIVER, extensive (Michelson et al, 2001; Farid et al, 1985).

a) Cytochrome P450 (CYP)-2D6 is involved in the metabolism of atomoxetine (Michelson et al, 2001). An active metabolite, 4-hydroxyatomoxetine, undergoes significant glucuronidation and renal excretion (Michelson et al, 2001).

b) Some patients are poor metabolizers of atomoxetine and will have significantly higher AUC values (10-fold) and plasma levels compared to extensive metabolizers; lab tests are available to identify poor metabolizers (Prod Info Strattera(TM), 2002t).

B) Metabolites

1) 4-Hydroxyatomoxetine (active) (Michelson et al, 2001; Farid et al, 1985).

a) Equipotent to the parent compound as a norepinephrine transporter inhibitor; however, it is present in low concentrations in plasma relative to the parent compound (about 1%) (Prod Info Strattera(TM),

2002t). Its contribution to clinical effects is unknown.
2) Noratomoxetine (inactive) (Farid et al, 1985).
3) N-desmethylatomoxetine (inactive) (Witcher et al, 2003).

2.3.4 Excretion
A) Kidney
1) Renal Excretion (%)
a) less than 3% unchanged (Prod Info Strattera(TM), 2002t).
1) Most of an oral dose of atomoxetine is excreted in the urine as 4-hydroxyatomoxetine-O-glucuronide (80%) (Prod Info Strattera(TM), 2002t; Michelson et al, 2001).
B) Total Body Clearance
1) 0.3 to 0.5 L/hr/kg (extensive metabolizers) (Farid et al, 1985; Prod Info Strattera(TM), 2002t).
a) Clearance is about 10-fold lower in poor metabolizers (0.03 to 0.04 L/hr/kg) (Farid et al, 1985; Prod Info Strattera(TM), 2002t).
b) Plasma clearance was similar (17 to 62 liters/hour; average, 36 to 40 liters/ hour) between single oral doses (10 to 90 mg) and repeat dosing (20 to 45 mg twice daily) in extensive metabolizers (healthy subjects); there was no evidence of dose-dependency. In poor metabolizers receiving repeat doses, a substantially lower clearance was observed (about 3 L/hr) (Witcher et al, 2003; Farid et al, 1985).
C) Other
1) OTHER EXCRETION
a) FECES
1) Less than 17% of a dose is excreted in feces as 4-hydroxyatomoxetine-O-glucuronide (Prod Info Strattera(TM), 2002t).

2.3.5 Elimination Half-life
A) Parent Compound
1) ELIMINATION HALF-LIFE
a) 4 to 5 hours (in extensive metabolizers; 22 hours in poor metabolizers (Farid et al, 1985; Michelson et al, 2001; Prod Info Strattera(TM), 2002).
1) Half-life was similar (3 to 6 hours) between single oral doses (10 to 90 milligrams (mg)), and repeat dosing (20 to 45 mg twice daily) in extensive metabolizers (healthy subjects); there was no evidence of dose-dependency. In poor metabolizers receiving the same repeat doses, a substantially longer half-life was observed (17 to 21 hours) (Witcher et al, 2003; Farid et al, 1985).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING
1) Atomoxetine Hydrochloride
a) Oral (Capsule)
Suicidal Ideation in Children and Adolescents:
Atomoxetine increased the risk of suicidal ideation in short-term studies in children or adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD). Anyone considering the use of atomoxetine in a child or adolescent must balance this risk with the clinical need. Co-morbidities occurring with ADHD may be associated with an increase in the risk of suicidal ideation and/or behavior. Patients who are started on therapy should be monitored closely for suicidality (suicidal thinking and behavior), clinical worsening, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Atomoxetine is approved for ADHD in pediatric and adult patients. Atomoxetine is not approved for major depressive disorder.
Pooled analyses of short-term (6 to 18 weeks) placebo-controlled trials of atomoxetine in children and adolescents (a total of 12 trials involving over 2200 patients, including 11 trials in ADHD and 1 trial in enuresis) have revealed a greater risk of suicidal ideation early during treatment in those receiving atomoxetine compared to placebo. The average risk of suicidal ideation in patients receiving atomoxetine was 0.4% (5/1357 patients), compared to none in placebo-treated patients (851 patients). No suicides occurred in these trials (Prod Info STRATTERA(R) oral capsules, 2009).

3.1 Contraindications

A) Atomoxetine Hydrochloride

1) hypersensitivity to atomoxetine or to other components of the product (Prod Info STRATTERA(R) oral capsules, 2009)

2) MAO inhibitor use; do not administer atomoxetine during therapy with or within 2 weeks of discontinuing an MAO inhibitor (Prod Info STRATTERA(R) oral capsules, 2009)

3) narrow angle glaucoma; increased risk of mydriasis (Prod Info STRATTERA(R) oral capsules, 2009)

3.2 Precautions

A) Atomoxetine Hydrochloride

1) suicidal ideation has occurred; increased risk in children and adolescents during the first few months of therapy or following a dosage adjustment; monitoring for signs of suicidality, clinical worsening, and unusual changes in behavior (eg, agitation, irritability) recommended; discontinuation may be necessary (Prod Info STRATTERA(R) oral capsules, 2009; US Food and Drug Administration, 2005)

2) bipolar disorder; mixed/manic episode may be induced; screening recommended prior to therapy for patients with comorbid depressive symptoms (Prod Info STRATTERA(R) oral capsules, 2009)

3) cardiovascular disease, cerebrovascular disease, hypertension, tachycardia; risk of increased blood pressure and heart rate; monitoring recommended (Prod Info STRATTERA(R) oral capsules, 2009)

4) liver injury has been reported rarely; if signs of liver injury occur (eg, elevated liver enzymes, jaundice, pruritus, dark urine, right upper quadrant tenderness), discontinue use and do not restart (Prod Info STRATTERA (R) oral capsules, 2009)

5) orthostatic hypotension and syncope have been reported; use cautiously in conditions predisposing to hypotension or associated with abrupt heart rate or blood pressure changes (Prod Info STRATTERA(R) oral capsules, 2009)

6) priapism has been reported rarely in children and adults; seek prompt medical attention (Prod Info STRATTERA(R) oral capsules, 2009)

7) psychotic or manic symptoms, hallucinations, delusional thinking or mania may occur in children and adolescents without a prior history of psychotic illness or mania at usual doses; discontinuation may be necessary (Prod Info STRATTERA(R) oral capsules, 2009)

8) structural cardiac abnormalities; risk of sudden death at usual doses; should not be used in adult or pediatric patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious heart problems (Prod Info STRATTERA(R) oral capsules, 2009)

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hepatic Effects

Immunologic Effects

Neurologic Effects

Psychiatric Effects

Renal Effects

Reproductive Effects

Other

3.3.1 Cardiovascular Effects

3.3.1.A Atomoxetine Hydrochloride

Increased diastolic arterial pressure

Increased systolic arterial pressure

Myocardial infarction

Orthostatic hypotension

Palpitations

Prolonged QT interval

Raynaud's phenomenon

Sudden cardiac death

Syncope

Tachycardia

3.3.1.A.1 Increased diastolic arterial pressure

a) Incidence: pediatrics, 3.5% to 4% (Prod Info STRATTERA(R) oral capsules, 2008)

b) In clinical studies, increased diastolic blood pressure (mean increase of 1 and 2.4 mmHg in adults and pediatric patients, respectively, compared to placebo) has been reported in atomoxetine-treated patients with attention-deficit hyperactivity disorder (ADHD). Use caution in patients receiving atomoxetine who have preexisting hypertension, tachycardia, or cardiovascular or cerebrovascular disease due to the risk of heart rate and blood pressure elevation in these patients. Pulse and blood pressure monitoring is recommended at baseline, following dose increases, and periodically during therapy (Prod Info STRATTERA(R) oral capsules, 2008). In addition, greater increases in heart rate and systolic pressure have been reported among cytochrome P450 2D6 poor metabolizers (Michelson et al, 2001a; Chouinard et al, 1985a).

c) In placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), diastolic blood pressures of 105 mm Hg or greater were reported in 0% of patients who received atomoxetine (n=0 of 510) compared to 0.3% of patients who received placebo (n=1 of 393). No patients had a high diastolic blood pressure documented on more than one occasion (Prod Info STRATTERA(R) oral capsules, 2008).

d) In pediatric placebo-controlled trials, high diastolic blood pressures were reported in 4% of atomoxetine-treated patients (n=50 of 1262) compared to 1.1% of placebo-treated patients (n=8 of 759) at the final study visit. Additionally, high systolic blood pressures were reported on 2 or more occasions in 3.5% (n=44 of 1262) of pediatric patients treated with atomoxetine and 0.5% (n=4 of 759) treated with placebo during the study (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.1.A.2 Increased systolic arterial pressure

a) Incidence: pediatrics, 4.4% to 4.8% (Prod Info STRATTERA(R) oral capsules, 2008)

b) In clinical studies, increased systolic blood pressure (mean increase of 2 and 1.6 mmHg in adults and pediatric patients, respectively, compared to placebo) has been reported in atomoxetine-treated patients with attention-deficit hyperactivity disorder (ADHD). Use caution in patients receiving atomoxetine who have preexisting hypertension, tachycardia, or cardiovascular or cerebrovascular disease due to the risk of heart rate and blood pressure elevation in these patients. Pulse and blood pressure monitoring is recommended at baseline, following dose increases, and periodically during therapy (Prod Info STRATTERA(R) oral capsules, 2008). In addition, greater increases in heart rate and systolic pressure have been reported among cytochrome P450 2D6 poor metabolizers (Michelson et al, 2001a; Chouinard et al, 1985a).

c) In placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), systolic blood pressures of 180 mm Hg or greater were not reported in patients taking atomoxetine (n=510) or placebo (n=393). No patients had a high systolic blood pressure documented on more than one occasion (Prod Info STRATTERA(R) oral capsules, 2008).

d) In pediatric placebo-controlled trials, high systolic blood pressures were reported in 4.8% of atomoxetine-treated patients (n=59 of 1226) compared to 3.5% of placebo-treated patients (n=26 of 748) at the final study visit. Additionally, high systolic blood pressures were reported on 2 or more occasions in 4.4% (n=54 of 1226) of pediatric patients treated with atomoxetine and 1.9% (n=14 of 748) treated with placebo during the study (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.1.A.3 Myocardial infarction

a) Myocardial infarction has occurred in adult patients receiving atomoxetine at usual doses. Consider not using atomoxetine in adult patients with clinically significant cardiac abnormalities (eg, coronary artery disease, serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, other serious cardiac problems) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.1.A.4 Orthostatic hypotension

a) Incidence: pediatric, up to 1.8% (Prod Info STRATTERA(R) oral capsules, 2008)

b) Orthostatic hypotension has been reported in 0.2% of atomoxetine-treated child and adolescent patients (n=12 of 5596). Additionally, in child and adolescent patients with attention-deficit hyperactivity disorder (ADHD), orthostatic hypotension occurred in 1.8% of patients who received atomoxetine (n=6 of 340) compared to 0.5% of patients who received placebo (n=1 of 207) in short-term, placebo-controlled studies. Patients with any condition that may predispose them to hypotension should use atomoxetine with caution (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.1.A.5 Palpitations

a) Incidence: adults, 3% (Prod Info STRATTERA(R) oral capsules, 2008)

b) In acute (up to 25 weeks), placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), palpitations were reported in 3% of patients who received atomoxetine (n=540) compared to 1% of patients who received placebo (n=402) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.1.A.6 Prolonged QT interval

a) There have been spontaneous postmarketing reports of QT prolongation with atomoxetine use (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.1.A.7 Raynaud's phenomenon

a) New onset and exacerbation of preexisting Raynaud's phenomenon have been reported in spontaneous postmarketing accounts (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.1.A.8 Sudden cardiac death

a) Sudden death has occurred in adult patients receiving atomoxetine at usual doses and in children and adolescent patients with structural cardiac abnormalities or other serious heart problems who were receiving atomoxetine at usual doses. Therefore, consider not using atomoxetine in adult patients with clinically significant cardiac abnormalities (eg, coronary artery disease, serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, other serious cardiac problems). Additionally, use of atomoxetine is not recommended in pediatric patients with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems. Patients should be assessed prior to starting atomoxetine therapy for a family history of sudden death or ventricular arrhythmia and should receive a physical exam to look for signs of cardiac disease. Furthermore, a prompt cardiac evaluation should be performed in patients who develop symptoms suggesting cardiac disease (eg, exertional chest pain, unexplained syncope) during atomoxetine therapy (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.1.A.9 Syncope

a) Incidence: pediatric, 0.8% (Prod Info STRATTERA(R) oral capsules, 2008)

b) Syncope has been reported in 0.8% of atomoxetine-treated child and adolescent patients (n=46 of 5596) and there have been spontaneous postmarketing reports of syncope; however, syncope has not been reported with atomoxetine use in child and adolescent patients with attention-deficit hyperactivity disorder (ADHD) during short-term, placebo-controlled studies. Patients with any condition that may predispose them to hypotension should use atomoxetine with caution (Prod Info STRATTERA(R) oral capsules, 2008).

c) Reports of syncope were significantly higher in patients classified as poor metabolizers of CYP2D6 drugs than those classified as extensive metabolizers (3% and 1%, respectively) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.1.A.10 Tachycardia

a) Incidence: adults, 1.5%; pediatrics, 0.3% (Prod Info STRATTERA(R) oral capsules, 2008)

b) In clinical studies, tachycardia has been reported in atomoxetine-treated patients with attention-deficit hyperactivity disorder (ADHD). Use caution in patients receiving atomoxetine who have preexisting hypertension, tachycardia, or cardiovascular or cerebrovascular disease due to the risk of heart rate and blood pressure elevation in these patients. Pulse and blood pressure monitoring is recommended at baseline, following dose increases, and periodically during therapy (Prod Info STRATTERA(R) oral capsules, 2008). In addition, greater increases in heart rate and systolic pressure have been reported among cytochrome P450 2D6 poor metabolizers (Michelson et al, 2001a; Chouinard et al, 1985a).

c) In placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD),

tachycardia was reported more frequently in patients taking atomoxetine (1.5%; n=8 of 540) than placebo (0.5%; n=2 of 402). Compared to placebo, mean increases in heart rate of 5 beats/minute were reported for atomoxetine-treated patients (Prod Info STRATTERA(R) oral capsules, 2008).
d) In pediatric placebo-controlled trials, tachycardia was reported in 0.3% of atomoxetine-treated patients (n=5 of 1597) compared to 0% of placebo-treated patients (n=0 of 934). At the final study visit, heart rates greater than or equal to 110 beats/minute with increases of at least 25 beats/minute were reported for 2.5% of patients taking atomoxetine (n=36 of 1434) compared to 0.2% receiving placebo (n=2 of 850). Heart rates of at least 110 beats/minute with increases of at least 25 beats/minute were reported on more than one occasion in 1.1% (n=15 of 1417) of pediatric patients treated with atomoxetine during the study. Additionally, patients identified as extensive metabolizers had reported increases in mean heart rate of 5 beats/minute while poor metabolizers had increases of 9.4 beats/minute (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.2 Dermatologic Effects

3.3.2.A Atomoxetine Hydrochloride

Rash

Urticaria

3.3.2.A.1 Rash
a) Incidence: adults, 2%; pediatrics, 2% (Prod Info STRATTERA(R) oral capsules, 2008)
b) Allergic reactions, including rash, have been reported with atomoxetine use (Prod Info STRATTERA (R) oral capsules, 2008).
c) In acute (up to 25 weeks), placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), rash was reported in 2% of patients who received atomoxetine (n=540) compared to 1% of patients who received placebo (n=402) (Prod Info STRATTERA(R) oral capsules, 2008).
d) In acute (up to 18 weeks), placebo-controlled trials in pediatric patients with attention-deficit hyperactivity disorder (ADHD), rash was reported in 2% of atomoxetine-treated patients (n=1597) compared to 1% of placebo-treated patients (n=934) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.2.A.2 Urticaria
a) Allergic reactions, including urticaria, have been reported with atomoxetine use (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.3 Endocrine/Metabolic Effects

3.3.3.A Atomoxetine Hydrochloride

Abnormal height in relation to growth / age standard

Hyponatremia

Weight loss

3.3.3.A.1 Abnormal height in relation to growth / age standard
a) The weight and height gains in atomoxetine-treated pediatric patients lags behind the normative population for the first 9 to 12 months of therapy and rebounds at about 3 years of treatment regardless of pubertal status at the time of treatment initiation. After approximately 12 months of atomoxetine therapy, gain in height stabilizes and at 3 years pediatric patients gain 19.4 cm on average, which is 0.4 cm less than predicted by baseline data. Poor metabolizers of CYP2D6 treated for at least 2 years gained an average of 1.1 cm less than predicted and extensive metabolizers of CYP2D6 gained an average of 0.4 cm less than predicted. In short-term controlled 9 week studies atomoxetine-treated patients gained an average of 0.9 cm compared to 1.1 cm in placebo (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.3.A.2 Hyponatremia
a) A 32-year-old man receiving atomoxetine hydrochloride (HCl) for attention deficit hyperactivity disorder (ADHD) experienced hyponatremia which resolved upon drug withdrawal. After taking atomoxetine 60 milligrams daily for 2 months with good results, the patient presented to his outpatient psychiatrist with a few week history of nausea and fatigue. He reported no psychiatric symptoms or

other medical problems and was not taking any other medications. A laboratory workup revealed a low serum sodium level of 122 millimole/liter (mmol/L), which was decreased from a sodium level of 141 mmol/L obtained 1-year previously. All other laboratory results were reported as normal. Hyponatremia due to medication-induced syndrome of inappropriate antidiuretic hormone (SIADH) was suspected by the patient's primary care physician who did not find any other cause for the low sodium level; therefore, atomoxetine HCl was discontinued. Sodium levels obtained 1 and 2 weeks later were 130 mmol/L and 140 mmol/L, respectively. Two weeks after discontinuing atomoxetine HCl, the patient initiated amphetamine/dextroamphetamine (Adderall XR(R)) for the treatment of his ADHD. Consider monitoring serum sodium and other signs and symptoms of hyponatremia and SIADH in patients receiving atomoxetine HCl (Singh, 2007).

3.3.3.A.3 Weight loss

a) Incidence: pediatrics, 7.1% to 29.1% (Prod Info STRATTERA(R) oral capsules, 2008)
b) The weight and height gains in atomoxetine-treated pediatric patients lags behind the normative population for the first 9 to 12 months of therapy and rebounds at about 3 years (17.9 kg on average, 0.5 kg more than predicted from baseline data) of treatment regardless of pubertal status at the time of treatment initiation. In short-term controlled 9 week studies atomoxetine-treated patients lost an average of 0.4 kg compared to a gain of 1.5 kg in the placebo group. Poor metabolizers of CYP2D6 treated for at least 2 years gained an average 2.4 kg less than predicted and extensive metabolizers of CYP2D6 gained an average of 0.2 kg less than predicted. Additionally, in a fixed-dose controlled trial patients lost at least 3.5% of their body weight in the atomoxetine-treated patients in 7.1% (0.5 mg/kg day dose), 19.3% (1.2 mg/kg day dose), and 29.1% (1.8 mg/kg day dose) of patients compared with 1.3% in the placebo group (Prod Info STRATTERA(R) oral capsules, 2008).
c) Weight loss and anorexia have been reported more often with atomoxetine than placebo in limited controlled studies (Michelson et al, 2001a; Zerbe et al, 1985a; Spencer et al, 1998a). Both effects are dose-related, and were also observed in open studies. The magnitude of weight loss was similar to that observed during methylphenidate therapy in ADHD patients in an unpublished study (Michelson et al, 2001a).

3.3.4 Gastrointestinal Effects

3.3.4.A Atomoxetine Hydrochloride

Abdominal pain

Constipation

Decrease in appetite

Indigestion

Loss of appetite

Nausea

Sialolithiasis

Vomiting

Xerostomia

3.3.4.A.1 Abdominal pain

a) Incidence: adults, 7%; pediatrics, 17% to 18% (Prod Info STRATTERA(R) oral capsules, 2008)
b) In acute (up to 25 weeks), placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), abdominal pain was reported in 7% of patients who received atomoxetine (n=540) compared to 5% of patients who received placebo (n=402) (Prod Info STRATTERA(R) oral capsules, 2008).
c) In acute (up to 18 weeks), placebo-controlled trials in pediatric patients with attention-deficit hyperactivity disorder (ADHD), abdominal pain was reported in 18% of atomoxetine-treated patients (n=1597) compared to 10% of placebo-treated patients (n=934) (Prod Info STRATTERA(R) oral capsules, 2008).
d) In acute (up to 18 weeks), placebo-controlled trials in pediatric patients with attention-deficit

hyperactivity disorder (ADHD), abdominal pain was reported in 18% and 17% of patients treated with atomoxetine once (n=882) and twice (n=715) daily, respectively, compared to 7% and 13% of patients treated with placebo once (n=500) and twice (n=434) daily, respectively (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.4.A.2 Constipation

a) Incidence: adults, 9%; pediatric, 1% to 2%(Prod Info STRATTERA(R) oral capsules, 2008)
b) In acute (up to 25 weeks), placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), constipation was reported in 9% of patients who received atomoxetine (n=540) compared to 3% of patients who received placebo (n=402) (Prod Info STRATTERA(R) oral capsules, 2008).
c) In acute (up to 18 weeks), placebo-controlled trials in pediatric patients with attention-deficit hyperactivity disorder (ADHD), constipation was reported in 1% and 2% of patients treated with atomoxetine once (n=882) and twice (n=715) daily, respectively, compared to 0% and 1% of patients treated with placebo once (n=500) and twice (n=434) daily, respectively. Reports of constipation were significantly higher in patients classified as poor metabolizers of CYP2D6 drugs than those classified as extensive metabolizers (7% and 4%, respectively) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.4.A.3 Decrease in appetite

a) Incidence: adult, 11%; pediatrics, 16% (Prod Info STRATTERA(R) oral capsules, 2008),
b) In acute (up to 25 weeks), placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), decreased appetite was reported in 11% of patients who received atomoxetine (n=540) compared to 2% of patients who received placebo (n=402) (Prod Info STRATTERA(R) oral capsules, 2008).
c) In acute (up to 18 weeks), placebo-controlled trials in pediatric patients with attention-deficit hyperactivity disorder (ADHD), anorexia was reported in 16% of atomoxetine-treated patients (n=1597) compared to 4% of placebo-treated patients (n=934) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.4.A.4 Indigestion

a) Incidence: adults, 4% (Prod Info STRATTERA(R) oral capsules, 2008)
b) In acute (up to 25 weeks), placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), dyspepsia was reported in 4% of patients who received atomoxetine (n=540) compared to 2% of patients who received placebo (n=402) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.4.A.5 Loss of appetite

a) Incidence: pediatrics, 3% (Prod Info STRATTERA(R) oral capsules, 2008),
b) In acute (up to 18 weeks), placebo-controlled trials in pediatric patients with attention-deficit hyperactivity disorder (ADHD), anorexia was reported in 3% of atomoxetine-treated patients (n=1597) compared to 1% of placebo-treated patients (n=934) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.4.A.6 Nausea

a) Incidence: adults, 21%; pediatrics, 7% to 13% (Prod Info STRATTERA(R) oral capsules, 2008)
b) In acute (up to 25 weeks), placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), nausea was reported in 21% of patients who received atomoxetine (n=540) compared to 5% of patients who received placebo (n=402) (Prod Info STRATTERA(R) oral capsules, 2008).
c) In acute (up to 18 weeks), placebo-controlled trials in pediatric patients with attention-deficit hyperactivity disorder (ADHD), nausea was reported in 10% of atomoxetine-treated patients (n=1597) compared to 5% of placebo-treated patients (n=934) (Prod Info STRATTERA(R) oral capsules, 2008).
d) In acute (up to 18 weeks), placebo-controlled trials in pediatric patients with attention-deficit hyperactivity disorder (ADHD), nausea was reported in 13% and 7% of patients treated with atomoxetine once (n=882) and twice (n=715) daily, respectively, compared to 4% and 6% of patients treated with placebo once (n=500) and twice (n=434) daily, respectively (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.4.A.7 Sialolithiasis

a) Sialolithiasis developed and then recurred each time atomoxetine was restarted in a 36-year-old male. Initially, he was on dextroamphetamine spansules 20 mg/day for 16 weeks for attention deficit hyperactivity disorder prior to adding atomoxetine 18 mg/day. An extruded, left submandibular sialolith in the salivary gland developed within 10 days of starting atomoxetine, with a second recurrence 10 days later. Subsequently, atomoxetine was discontinued and the stone passed. Within 4 to 5 days of restarting atomoxetine 2 weeks later, the sialolithiasis recurred with 3 subsequent episodes each time atomoxetine was discontinued and restarted. The time to onset was quicker for each recurrence. The stone was passed by massaging the gland. Pain and swelling of the gland was evident and at no time did he experience dry mouth. At a 6-month follow-up after permanently discontinuing atomoxetine, no further stones developed. Significant medical history included 3 events of sialolithiasis, all occurring within a few months of each other and 18 months prior to starting atomoxetine. The first of these 3

episodes was identified by computed tomography scan, and each time the stone was passed by massaging the gland (Jerome et al, 2007).

3.3.4.A.8 Vomiting

a) Incidence: adults, 3%; pediatrics, 11%(Prod Info STRATTERA(R) oral capsules, 2008)
b) In acute (up to 25 weeks), placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), vomiting was reported in 3% of patients who received atomoxetine (n=540) compared to 2% of patients who received placebo (n=402) (Prod Info STRATTERA(R) oral capsules, 2008).
c) In acute (up to 18 weeks), placebo-controlled trials in pediatric patients with attention-deficit hyperactivity disorder (ADHD), vomiting was reported in 11% of atomoxetine-treated patients (n=1597) compared to 6% of placebo-treated patients (n=934) (Prod Info STRATTERA(R) oral capsules, 2008).
d) In acute (up to 18 weeks), placebo-controlled trials in pediatric patients with attention-deficit hyperactivity disorder (ADHD), vomiting was reported in 11% of patients treated with either atomoxetine once (n=882) or twice (n=715) daily compared to 4% and 8% of patients treated with placebo once (n=500) and twice (n=434) daily, respectively (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.4.A.9 Xerostomia

a) Incidence: adults, 21% (Prod Info STRATTERA(R) oral capsules, 2008)
b) In acute (up to 25 weeks), placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), dry mouth was reported in 21% of patients who received atomoxetine (n=540) compared to 7% of patients who received placebo (n=402) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.6 Hepatic Effects

3.3.6.A Atomoxetine Hydrochloride

3.3.6.A.1 Injury of liver (Severe)

a) Incidence: rare (Prod Info STRATTERA(R) oral capsules, 2008)
b) During postmarketing surveillance severe liver injury has occurred in rare instances including hepatic enzymes elevated by up to 40 times the upper limit of normal (ULN) and jaundice with a bilirubin up to 12 times ULN recurring upon rechallenge and recovering upon discontinuation of atomoxetine. Severe liver injury may occur several months after therapy initiation and may worsen for several weeks upon discontinuation with the potential to progress to acute liver failure and death or the need for a liver transplant. In patients with laboratory evidence of liver injury or jaundice, atomoxetine should be discontinued and not reinstituted. Additionally, at the first sign or symptom of liver dysfunction (eg, pruritus, dark urine, jaundice, right upper quadrant tenderness, unexplained flu-like symptoms), liver enzyme levels should be obtained (Prod Info STRATTERA(R) oral capsules, 2008).
c) Liver injury has been reported in clinical trials and postmarketing reports in patients with attention-deficit hyperactivity disorder (ADHD) treated with atomoxetine. Of 7961 pediatric or adult patients with ADHD who received treatment with atomoxetine in 45 clinical trials, 41 cases of liver injury were possibly related to atomoxetine therapy and included mild to moderate increases in total bilirubin consistent with Gilbert's syndrome (n=18) and elevated ALT, AST, alkaline phosphatase (ALP) and CPK levels. When laboratory data from 14 pediatric and 2 adult placebo-controlled trials were reviewed, no significant differences in treatment-related elevations in AST, ALT, ALP, CPK, or total bilirubin levels were found between patients who received atomoxetine and placebo. Additionally, out of 351 postmarketing case reports (calculated reported liver injury rate of less than 0.01%), 133 and 3 cases, respectively, were possibly and probably related to atomoxetine therapy. All 3 probable cases were reversible: (Bangs et al, 2008).

1) A male adolescent patient developed lethargy and abdominal pain after receiving atomoxetine 40 mg twice daily for 3 to 4 months. Atomoxetine and sertraline were discontinued and liver enzyme elevations were noted the following day (ALT, 33 x ULN; AST, 15 x ULN; total bilirubin, 1.5 x ULN). Liver enzymes returned to normal within 2 months; however, upon rechallenge with atomoxetine 40 mg/day, liver enzymes and bilirubin were elevated within approximately 5 weeks of therapy and a liver biopsy revealed hepatitis with focal hepatocellular necrosis. A subsequent liver biopsy 2 months later revealed hepatitis with cholestasis, primarily lymphocytic inflammatory infiltrate. Liver enzymes returned to normal within 4.5 months (Bangs et al, 2008).
2) The second patient was a female adolescent who was hospitalized with jaundice, abdominal pain, diarrhea, vomiting, conjunctival icterus, and right upper quadrant tenderness after receiving atomoxetine 40 mg/day for almost one year. On admission, liver enzyme elevations were present (ALT, 65 x ULN; AST, 67 x ULN; total bilirubin, 9.1 x ULN). Liver biopsy showed moderate, mixed portal inflammatory infiltrate (mainly lymphoid with some eosinophils) and normal interlobular ducts and central veins. After discontinuing atomoxetine, liver enzymes returned to normal and symptoms resolved over the next 4 weeks (Bangs et al, 2008).
3) The third patient was a female child who was receiving atomoxetine 25 mg/day (1.03 mg/kg/day) presented with a 2-day history of emesis after 37 days of therapy, and was admitted to the hospital. The patient had elevated liver enzymes (ALT, 80 x ULN; AST, 115 x ULN; total

bilirubin, 10.8 x ULN; alkaline phosphatase, 3.5 x ULN), and symptoms of jaundice and hepatomegaly. A liver biopsy demonstrated mixed portal inflammation with lymphocytes, neutrophils and eosinophils in the lobule with moderate piecemeal necrosis. Improvement of signs and symptoms was observed and the patient was discharged from the hospital after 13 days (Bangs et al, 2008).

3.3.7 Immunologic Effects

3.3.7.A Atomoxetine Hydrochloride

3.3.7.A.1 Immune hypersensitivity reaction

a) Allergic reactions, including angioneurotic edema, urticaria, and rash, have been reported with atomoxetine use (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.9 Neurologic Effects

3.3.9.A Atomoxetine Hydrochloride

Akathisia

Cerebrovascular accident

Dizziness

Dyskinesia

Headache

Insomnia

Seizure

Sinus headache

Somnolence

Tic

3.3.9.A.1 Akathisia

a) Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania have been reported with atomoxetine use and may be precursors to emerging suicidality. It is recommended that pediatric patients receiving atomoxetine be monitored for clinical worsening, suicidal ideation, suicidal behavior, irritability, agitation, or unusual changes in behavior, particularly during the first few months of therapy or following a dosage adjustment. Monitoring should be daily by family members or caregivers and by healthcare providers weekly for the first 4 weeks, then every other week for 4 weeks, then every 12 weeks and as clinically indicated thereafter. Consider changing the therapeutic regimen and possibly discontinuing atomoxetine therapy if patients experience suicidality or precursors to emerging suicidality, particularly if symptoms are severe or present with an abrupt onset and were not part of original presenting symptoms (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.9.A.2 Cerebrovascular accident

a) Stroke has occurred in adult patients receiving atomoxetine at usual doses. Consider not using atomoxetine in adult patients with clinically significant cardiac abnormalities (eg, coronary artery disease, serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, other serious cardiac problems) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.9.A.3 Dizziness

a) Incidence: adult, 6%; pediatric, 5% (Prod Info STRATTERA(R) oral capsules, 2008)
b) In acute (up to 25 weeks), placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), dizziness was reported in 6% of patients who received atomoxetine (n=540) compared to 4% of patients who received placebo (n=402) (Prod Info STRATTERA(R) oral

capsules, 2008).
c) In acute (up to 18 weeks), placebo-controlled trials in pediatric patients with attention-deficit hyperactivity disorder (ADHD), dizziness was reported in 5% of atomoxetine-treated patients (n=1597) compared to 2% of placebo-treated patients (n=934) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.9.A.4 Dyskinesia
a) Dyskinesias with other neurological abnormalities developed in 2 pediatric patients with attention deficit hyperactivity disorder after starting atomoxetine. Both patients required hospitalization due to severity of tremors and psychiatric disturbances. The events resolved after discontinuation of atomoxetine in 1 patient and atomoxetine and venlafaxine in the other patient (Bond et al, 2007).
1) A 9-year-old boy on amphetamine/dextroamphetamine extended-release and clonidine for attention deficit hyperactivity disorder developed insomnia and involuntary hand and mouth movements within 14 days of starting atomoxetine 25 mg every day. He initially developed anorexia a few days after starting atomoxetine with subsequent signs of disturbed sleep, compulsive lip licking, seeing things ("bugs") that caused fear. All signs progressively worsened. Vital signs were a temperature of 36.9 degrees Celsius, heart rate of 89 beats per minute, respiration rate of 24 breaths/minute, and blood pressure of 145/93 mmHg, which was slightly above his baseline diastolic blood pressure. He was alert and oriented to person and place. Neurologic examination revealed involuntary, continuous twitching movements of his perioral area and writhing fingers and restless legs, which moved continuously as he lay on the bed. Intravenous diphenhydramine 50 mg failed to provide any improvement in symptoms. He was admitted for observation. Amphetamine/dextroamphetamine and atomoxetine were discontinued. Although he did not sleep that night, the abnormal movements resolved the next day. At a 5-month follow-up visit, there was no evidence of movement disorder while on amphetamine/dextroamphetamine, clonidine, and sertraline (Bond et al, 2007).
2) An 18-year-old female with attention deficit hyperactivity disorder and generalized anxiety disorder with panic attacks on venlafaxine developed severe tremors and abnormal facial movements after starting atomoxetine. Approximately 2 months prior to the event she started paroxetine, which was subsequently replaced with venlafaxine 37.5 mg daily. Atomoxetine 18 mg every day was started about 3 weeks prior to the event. The dose of venlafaxine and atomoxetine were gradually increased. Approximately 5 days after attaining maximum doses of venlafaxine 225 mg every day and atomoxetine 40 mg every day, she developed fine hand tremors present only at rest. The dose of venlafaxine was reduced to 150 mg every day and atomoxetine was discontinued. Within 3 days the following evolved: the tremors worsened in her upper extremities and progressed to her lower extremities (intentional movements did not improve the tremors); she developed abnormal facial movements with muscular twitching and uncontrollable movements of her lips and tongue, which rendered her unable to vocalize; and the tremors progressively worsened rendering her unable to ambulate. Vital signs were a temperature of 36.5 degrees Celsius, heart rate of 110 beats per minute, respiration rate of 18 breaths/minute, and blood pressure of 108/67 mmHg. Neurologic examination revealed intact cranial nerves II-XII, no nystagmus, intact sensations, and slightly increased deep tendon reflexes (DTR) of the lower and normal DTR of the upper extremities. She was admitted and administered diphenhydramine 50 mg intramuscularly and intravenous (IV) normal saline. The tremors improved slightly. An additional diphenhydramine 12.5 mg IV was of no benefit. She was discharged 24 hours later with moderate improvement in tremors. Complete resolution of the event was reported at follow-up day 7, while off venlafaxine and atomoxetine (Bond et al, 2007).

3.3.9.A.5 Headache
a) Incidence: pediatrics, 19% (Prod Info STRATTERA(R) oral capsules, 2008)
b) In acute (up to 18 weeks), placebo-controlled trials in pediatric patients with attention-deficit hyperactivity disorder (ADHD), headache was reported in 19% of atomoxetine-treated patients (n=1597) compared to 15% of placebo-treated patients (n=934) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.9.A.6 Insomnia
a) Incidence: adults, 16%; pediatrics, at least 2%; (Prod Info STRATTERA(R) oral capsules, 2008)
b) Insomnia has been commonly reported in adult patients with attention-deficit hyperactivity disorder (ADHD) who were receiving atomoxetine in clinical trials. However, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania may be precursors to emerging suicidality. It is recommended that pediatric patients receiving atomoxetine be monitored for clinical worsening, suicidal ideation, suicidal behavior, irritability, agitation, or unusual changes in behavior, especially during the first few months of therapy or following a dosage adjustment. Monitoring should be daily by family members or caregivers and by healthcare providers weekly for the first 4 weeks, then every other week for 4 weeks, then every 12 weeks and as clinically indicated thereafter. Consider changing the therapeutic regimen and possibly discontinuing atomoxetine therapy if patients experience suicidality or precursors to emerging suicidality, particularly if symptoms are severe or with an abrupt onset and were not part of original presenting symptoms (Prod Info STRATTERA(R) oral capsules, 2008).
c) In acute (up to 25 weeks), placebo-controlled trials in adult patients with attention-deficit

hyperactivity disorder (ADHD), insomnia was reported in 15% of patients who received atomoxetine (n=540) compared to 7% of patients who received placebo (n=402) (Prod Info STRATTERA(R) oral capsules, 2008).
d) In acute (up to 18 weeks), placebo-controlled trials in pediatric patients with attention-deficit hyperactivity disorder (ADHD), insomnia was reported in at least 2% of atomoxetine-treated patients (n=1597) compared to 2% or less of placebo-treated patients (n=934). Reports of insomnia were significantly higher in patients classified as poor metabolizers of CYP2D6 drugs than those classified as extensive metabolizers (15% and 10%, respectively) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.9.A.7 Seizure
a) Incidence: adults, 0.1%; pediatrics, 0.2% (Prod Info STRATTERA(R) oral capsules, 2008)
b) Clinical studies did not systematically evaluate adult or pediatric patients with seizure disorders. However, in clinical development program, seizures were reported in children (average age 10 years, range 6 to 16 years) with an incidence of 0.2% (12/5073). In clinical trials among poor metabolizers of CYP2D6 the incidence of seizure in pediatrics was 0.3% (1/293) and was 0.2% (11/4741) for extensive metabolizers of CYP2D6 (Prod Info STRATTERA(R) oral capsules, 2008).
c) In adults, the incidence of seizures was 0.1% (1/748) and was 0.1% (1/705) of adult extensive metabolizers of CYP2D6. There have also been postmarketing reports of seizures, which have included patients both with and without a history of seizure disorders or identified risk factors for developing seizures (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.9.A.8 Sinus headache
a) Incidence: adults, 3% (Prod Info STRATTERA(R) oral capsules, 2008)
b) In acute (up to 25 weeks), placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), sinus headache was reported in 3% of patients who received atomoxetine (n=540) compared to 1% of patients who received placebo (n=402) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.9.A.9 Somnolence
a) Incidence: adult, 4%; pediatrics, 11% (Prod Info STRATTERA(R) oral capsules, 2008)
b) In acute (up to 25 weeks), placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), somnolence was reported in 4% of patients who received atomoxetine (n=540) compared to 3% of patients who received placebo (n=402) (Prod Info STRATTERA(R) oral capsules, 2008).
c) In acute (up to 18 weeks), placebo-controlled trials in pediatric patients with attention-deficit hyperactivity disorder (ADHD), somnolence was reported in 11% of atomoxetine-treated patients (n=1597) compared to 4% of placebo-treated patients (n=934) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.9.A.10 Tic
a) Tics reoccurred or were exacerbated in 4 pediatric patients within approximately 5 to 30 days of starting atomoxetine for attention deficit hyperactivity disorder (ADHD). Three of the 4 patients had experienced tics on stimulants such as amphetamine/dextroamphetamine and 1 patient had a comorbid condition of Tourette's syndrome. Significant improvement or resolution resulted when atomoxetine was discontinued. Two of the patients subsequently tolerated guanfacine for ADHD (Lee et al, 2004).
1) A 9-year-old boy with combined type attention deficit hyperactivity disorder developed motor tics with the stimulants methylphenidate, amphetamine/dextroamphetamine, and dextroamphetamine. The tics resolved after discontinuation of the stimulants. After a 6-month washout, atomoxetine was started at 10 mg every day for 7 days then 20 mg every day. Within a few days of starting 20 mg, he developed motor tics described as rapid, severe eye blinking. This event was similar to the event with previous stimulants. Vocal tics were absent. Within 1 to 2 days of stopping atomoxetine, the tics resolved. There was no recurrence of tics after 1 year on guanfacine (Lee et al, 2004).
2) A 14-year-old boy with attention deficit hyperactivity disorder developed eye-blinking motor tic on methylphenidate. Methylphenidate was discontinued and atomoxetine 20 mg every day was started. The eye blinking worsened, and he subsequently developed a vocal tic of severe episodes of throat clearing. The vocal tics stopped and the eye-blinking improved following discontinuation of atomoxetine. Mild eye blinking persisted with no other signs of tics while on guanfacine (Lee et al, 2004).
3) A 9-year-old boy with attention deficit hyperactivity disorder and chronic tic disorders experienced tic exacerbations on stimulants. Prior to starting atomoxetine, facial tics were the sole symptoms. He started atomoxetine 18 mg every day and within 30 days developed dramatic vocal tics and increased motor tics. Associated adverse effects were irritability, anxiety, dysphoria, compulsive finger picking, and obsessional ruminations. The event improved after discontinuation of atomoxetine (Lee et al, 2004).
4) A 15-year-old boy with attention deficit hyperactivity disorder and Tourette's syndrome experienced tic exacerbations on stimulants. Significant increase in tics, impulsivity, and fatigue occurred within 5 days of starting atomoxetine 10 mg every day. The event improved after discontinuation of atomoxetine(Lee et al, 2004).

3.3.12 Psychiatric Effects

3.3.12.A Atomoxetine Hydrochloride

Aggressive behavior

Agitation

Anxiety

Hostile behavior

Hypomania

Impulsive character

Irritability

Mania

Panic attack

Psychotic disorder

Suicidal thoughts

3.3.12.A.1 Aggressive behavior

a) Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania have been reported with atomoxetine use and may be precursors to emerging suicidality. It is recommended that pediatric patients receiving atomoxetine be monitored for clinical worsening, suicidal ideation, suicidal behavior, irritability, agitation, or unusual changes in behavior, particularly during the first few months of therapy or following a dosage adjustment. Monitoring should be daily by family members or caregivers and by healthcare providers weekly for the first 4 weeks, then every other week for 4 weeks, then every 12 weeks and as clinically indicated thereafter. Consider changing the therapeutic regimen and possibly discontinuing atomoxetine therapy if patients experience suicidality or precursors to emerging suicidality, particularly if symptoms are severe or present with an abrupt onset and were not part of original presenting symptoms (Prod Info STRATTERA(R) oral capsules, 2008).

b) Although not statistically significant, short-term placebo-controlled clinical trials of children and adolescents with attention-deficit hyperactivity disorder reported observations of aggressive behavior or hostility more frequently in atomoxetine-treated patients (1.6%; n=21 of 1308) than placebo-treated patients (1.1%; n=9 of 806) (overall risk ratio of 1.33; 95% confidence interval, 0.67-2.64; p=nonsignificant). Monitor patients for the appearance or worsening of aggressive behavior or hostility (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.12.A.2 Agitation

a) An 11-year-old boy on atomoxetine for attention deficit hyperactivity disorder developed acute agitation and suicidal ideation within 17 days of starting atomoxetine. He also had anxiety, obsessive compulsive disorder and oppositional defiant behaviors. Atomoxetine 25 mg was administered every day for 14 days, with the medication scheduled to increase to 60 mg every day thereafter. He initially showed a marked reduction in anxiety and obsessive symptoms; however, the family noted increased emotional liability, cycling of his mood and agitation, and that his handwriting had changed from neat script to messy and 'tiny.' After the dose increase as planned on day 14, the boy developed increased agitation, greater mood swings with more rapid cycling, increased crying, and he threatened suicide. The family discontinued the medication, and the patient’s agitation calmed after a few days and he was described as back to his normal self (Paxton & Cranswick, 2008).

b) Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania have been reported with atomoxetine use and may be precursors to emerging suicidality. It is recommended that pediatric patients receiving atomoxetine be monitored for clinical worsening, suicidal ideation, suicidal behavior, irritability, agitation, or unusual changes in behavior, particularly during the first few months of therapy or following a dosage adjustment. Monitoring should

be daily by family members or caregivers and by healthcare providers weekly for the first 4 weeks, then every other week for 4 weeks, then every 12 weeks and as clinically indicated thereafter. Consider changing the therapeutic regimen and possibly discontinuing atomoxetine therapy if patients experience suicidality or precursors to emerging suicidality, particularly if symptoms are severe or present with an abrupt onset and were not part of original presenting symptoms (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.12.A.3 Anxiety

a) Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania have been reported with atomoxetine use and may be precursors to emerging suicidality. It is recommended that pediatric patients receiving atomoxetine be monitored for clinical worsening, suicidal ideation, suicidal behavior, irritability, agitation, or unusual changes in behavior, particularly during the first few months of therapy or following a dosage adjustment. Monitoring should be daily by family members or caregivers and by healthcare providers weekly for the first 4 weeks, then every other week for 4 weeks, then every 12 weeks and as clinically indicated thereafter. Consider changing the therapeutic regimen and possibly discontinuing atomoxetine therapy if patients experience suicidality or precursors to emerging suicidality, particularly if symptoms are severe or present with an abrupt onset and were not part of original presenting symptoms (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.12.A.4 Hostile behavior

a) Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania have been reported with atomoxetine use and may be precursors to emerging suicidality. It is recommended that pediatric patients receiving atomoxetine be monitored for clinical worsening, suicidal ideation, suicidal behavior, irritability, agitation, or unusual changes in behavior, particularly during the first few months of therapy or following a dosage adjustment. Monitoring should be daily by family members or caregivers and by healthcare providers weekly for the first 4 weeks, then every other week for 4 weeks, then every 12 weeks and as clinically indicated thereafter. Consider changing the therapeutic regimen and possibly discontinuing atomoxetine therapy if patients experience suicidality or precursors to emerging suicidality, particularly if symptoms are severe or present with an abrupt onset and were not part of original presenting symptoms (Prod Info STRATTERA(R) oral capsules, 2008).

b) Although not statistically significant, short-term placebo-controlled clinical trials of children and adolescents with attention-deficit hyperactivity disorder reported observations of aggressive behavior or hostility more frequently in atomoxetine-treated patients (1.6%; n=21 of 1308) than placebo-treated patients (1.1%; n=9 of 806) (overall risk ratio of 1.33; 95% confidence interval, 0.67-2.64; p=nonsignificant). Monitor patients for the appearance or worsening of aggressive behavior or hostility (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.12.A.5 Hypomania

a) Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania have been reported with atomoxetine use and may be precursors to emerging suicidality. It is recommended that pediatric patients receiving atomoxetine be monitored for clinical worsening, suicidal ideation, suicidal behavior, irritability, agitation, or unusual changes in behavior, particularly during the first few months of therapy or following a dosage adjustment. Monitoring should be daily by family members or caregivers and by healthcare providers weekly for the first 4 weeks, then every other week for 4 weeks, then every 12 weeks and as clinically indicated thereafter. Consider changing the therapeutic regimen and possibly discontinuing atomoxetine therapy if patients experience suicidality or precursors to emerging suicidality, particularly if symptoms are severe or present with an abrupt onset and were not part of original presenting symptoms (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.12.A.6 Impulsive character

a) Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania have been reported with atomoxetine use and may be precursors to emerging suicidality. It is recommended that pediatric patients receiving atomoxetine be monitored for clinical worsening, suicidal ideation, suicidal behavior, irritability, agitation, or unusual changes in behavior, particularly during the first few months of therapy or following a dosage adjustment. Monitoring should be daily by family members or caregivers and by healthcare providers weekly for the first 4 weeks, then every other week for 4 weeks, then every 12 weeks and as clinically indicated thereafter. Consider changing the therapeutic regimen and possibly discontinuing atomoxetine therapy if patients experience suicidality or precursors to emerging suicidality, particularly if symptoms are severe or present with an abrupt onset and were not part of original presenting symptoms (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.12.A.7 Irritability

a) Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania have been reported with atomoxetine use and may be precursors to emerging

suicidality. It is recommended that pediatric patients receiving atomoxetine be monitored for clinical worsening, suicidal ideation, suicidal behavior, irritability, agitation, or unusual changes in behavior, particularly during the first few months of therapy or following a dosage adjustment. Monitoring should be daily by family members or caregivers and by healthcare providers weekly for the first 4 weeks, then every other week for 4 weeks, then every 12 weeks and as clinically indicated thereafter. Consider changing the therapeutic regimen and possibly discontinuing atomoxetine therapy if patients experience suicidality or precursors to emerging suicidality, particularly if symptoms are severe or present with an abrupt onset and were not part of original presenting symptoms (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.12.A.8 Mania

a) In a review of 49 randomized, controlled pediatric ADHD clinical trials involving pscyhostimulant medications (atomoxetine hydrochloride, methylphenidate hydrochloride, modafinil and dextromethylphenidate hydrochloride), the rate of psychosis/mania events in pediatric subjects receiving active drug was 1.48 (95% CI, 0.74 to 2.65) per 100 person-years, with no comparable adverse events recorded in the placebo group. A request from the US Food and Drug Administration to manufacturers of marketed ADHD drugs for submission of postmarketing case reports of psychosis or mania events between 2000 and 2005, yielded a total of 865 reports (pediatrics and adults) in which signs and/or symptoms of psychoses or mania were reported. The majority of reports involved pediatric subjects, with almost half of the reports in children 10 years-old or younger, and approximately 90% of cases involving no prior history of similar psychiatric conditions. Visual and/or tactile sensations of insects, snakes, or worms were commonly reported. Positive rechallenge was reported for each of the psychostimulant medications (methylphenidate hydrochloride, atomoxetine hydrochloride, and mixed salts of a single entity amphetamine product) included in the analysis; and in many cases a strong temporal association was identified. The onset of psychiatric symptoms ranged from days to weeks, but in some cases it was months or years from the start of ADHD treatment and symptom onset (Mosholder et al, 2009).

b) Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania have been reported with atomoxetine use and may be precursors to emerging suicidality. It is recommended that pediatric patients receiving atomoxetine be monitored for clinical worsening, suicidal ideation, suicidal behavior, irritability, agitation, or unusual changes in behavior, particularly during the first few months of therapy or following a dosage adjustment. Monitoring should be daily by family members or caregivers and by healthcare providers weekly for the first 4 weeks, then every other week for 4 weeks, then every 12 weeks and as clinically indicated thereafter. Consider changing the therapeutic regimen and possibly discontinuing atomoxetine therapy if patients experience suicidality or precursors to emerging suicidality, particularly if symptoms are severe or present with an abrupt onset and were not part of original presenting symptoms (Prod Info STRATTERA(R) oral capsules, 2008).

c) A pooled analysis of multiple short-term, placebo-controlled studies in children and adolescents without a prior history of psychotic illness or mania demonstrated that about 0.2% of atomoxetine-treated patients (n=4 of 1939) exhibited treatment emergent psychotic or manic symptoms (eg, hallucinations, mania, delusional thinking) compared to 0% of placebo-treated patients (n=0 of 1056). Discontinuation of treatment should be considered if such symptoms develop during atomoxetine therapy (Prod Info STRATTERA(R) oral capsules, 2008).

d) Mania was described in one patient with major depression after more than a year of atomoxetine therapy (up to 80 mg daily). However, a causal relationship to the drug was not established; numerous other factors may have contributed to the manic episode (Steinberg & Chouinard, 1985).

3.3.12.A.9 Panic attack

a) Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania have been reported with atomoxetine use and may be precursors to emerging suicidality. It is recommended that pediatric patients receiving atomoxetine be monitored for clinical worsening, suicidal ideation, suicidal behavior, irritability, agitation, or unusual changes in behavior, particularly during the first few months of therapy or following a dosage adjustment. Monitoring should be daily by family members or caregivers and by healthcare providers weekly for the first 4 weeks, then every other week for 4 weeks, then every 12 weeks and as clinically indicated thereafter. Consider changing the therapeutic regimen and possibly discontinuing atomoxetine therapy if patients experience suicidality or precursors to emerging suicidality, particularly if symptoms are severe or present with an abrupt onset and were not part of original presenting symptoms (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.12.A.10 Psychotic disorder

a) In a review of 49 randomized, controlled pediatric ADHD clinical trials involving pscyhostimulant medications (atomoxetine hydrochloride, methylphenidate hydrochloride, modafinil and dextromethylphenidate hydrochloride), the rate of psychosis/mania events in pediatric subjects receiving active drug was 1.48 (95% CI, 0.74 to 2.65) per 100 person-years, with no comparable adverse events recorded in the placebo group. A request from the US Food and Drug Administration to manufacturers of marketed ADHD drugs for submission of postmarketing case reports of psychosis or

mania events between 2000 and 2005, yielded a total of 865 reports (pediatrics and adults) in which signs and/or symptoms of psychoses or mania were reported. The majority of reports involved pediatric subjects, with almost half of the reports in children 10 years-old or younger, and approximately 90% of cases involving no prior history of similar psychiatric conditions. Visual and/or tactile sensations of insects, snakes, or worms were commonly reported. Positive rechallenge was reported for each of the psychostimulant medications (methylphenidate hydrochloride, atomoxetine hydrochloride, and mixed salts of a single entity amphetamine product) included in the analysis; and in many cases a strong temporal association was identified. The onset of psychiatric symptoms ranged from days to weeks, but in some cases it was months or years from the start of ADHD treatment and symptom onset (Mosholder et al, 2009).

3.3.12.A.11 Suicidal thoughts

a) Incidence: pediatrics, 0.4% (Prod Info STRATTERA(R) oral capsules, 2008)

b) An 11-year-old boy on atomoxetine for attention deficit hyperactivity disorder developed acute agitation and suicidal ideation within 17 days of starting atomoxetine. He also had anxiety, obsessive compulsive disorder and oppositional defiant behaviors. Atomoxetine 25 mg was administered every day for 14 days, with the medication scheduled to increase to 60 mg every day thereafter. He initially showed a marked reduction in anxiety and obsessive symptoms; however, the family noted increased emotional liability, cycling of his mood and agitation, and that his handwriting had changed from neat script to messy and 'tiny.' After the dose increase as planned on day 14, the boy developed increased agitation, greater mood swings with more rapid cycling, increased crying, and he threatened suicide. The family discontinued the medication, and the patient's agitation calmed after a few days and he was described as back to his normal self (Paxton & Cranswick, 2008).

c) An association has been reported between the use of atomoxetine and the development of suicidal ideation in children and adolescents. A pooled analysis of 12 short-term (6 to 18 weeks) clinical trials conducted in pediatric patients with attention-deficit hyperactivity disorder (11 trials) or enuresis (1 trial) demonstrated that 0.4% of patients (n=5 of 1357) who received atomoxetine therapy experienced suicidal ideation compared to no patients who received placebo (n=0 of 851). Although no suicides were reported in these trials (one suicide attempt), it is recommended that pediatric patients receiving atomoxetine be monitored for clinical worsening, suicidal ideation, suicidal behavior, irritability, agitation, or unusual changes in behavior, particularly during the first few months of therapy or following a dosage adjustment. Monitoring should be daily by family members or caregivers and by healthcare providers weekly for the first 4 weeks, then every other week for 4 weeks, then every 12 weeks and as clinically indicated thereafter. Consider changing the therapeutic regimen and possibly discontinuing atomoxetine therapy if patients experience suicidality or possible precursors to emerging suicidality (eg, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, mania) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.13 Renal Effects

3.3.13.A Atomoxetine Hydrochloride

Delay when starting to pass urine

Urinary retention

3.3.13.A.1 Delay when starting to pass urine

a) Incidence: adults, 5.6% (Prod Info STRATTERA(R) oral capsules, 2008)

b) In controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), urinary hesitation has been reported in 5.6% of atomoxetine-treated patients (n=30 of 540) compared to 0.5% of placebo-treated patients (n=4 of 402). Additionally, urinary hesitation and/or urinary retention were reported in 7% of patients who received atomoxetine compared to 1% of patients who received placebo (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.13.A.2 Urinary retention

a) Incidence: adults, 1.7% (Prod Info STRATTERA(R) oral capsules, 2008)

b) In controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), urinary retention has been reported in 1.7% of atomoxetine-treated patients (n=9 of 540) compared to 0% of placebo-treated patients (n=0 of 402). Additionally, urinary hesitation and/or urinary retention were reported in 7% of patients who received atomoxetine compared to 1% of patients who received placebo (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.14 Reproductive Effects

3.3.14.A Atomoxetine Hydrochloride

Disorder of ejaculation

Dysmenorrhea

Erectile dysfunction

Priapism

Sexual dysfunction

3.3.14.A.1 Disorder of ejaculation

a) In acute (up to 25 weeks), placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), ejaculation delayed and/or ejaculation disorder were reported in 3% of patients who received atomoxetine (n=326) compared to 1% of patients who received placebo (n=260) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.14.A.2 Dysmenorrhea

a) Incidence: adults, 6% (Prod Info STRATTERA(R) oral capsules, 2008)

b) In acute (up to 25 weeks), placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), dysmenorrhea was reported in 6% of patients who received atomoxetine (n=214) compared to 2% of patients who received placebo (n=142) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.14.A.3 Erectile dysfunction

a) Incidence: adults, 9% (Prod Info STRATTERA(R) oral capsules, 2008)

b) In acute (up to 25 weeks), placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), erectile dysfunction was reported in 9% of patients who received atomoxetine (n=326) compared to 1% of patients who received placebo (n=260) (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.14.A.4 Priapism

a) Incidence: rare (Prod Info STRATTERA(R) oral capsules, 2008)

b) There have been rare postmarketing reports of priapism lasting more than 4 hours in pediatric and adult patients receiving atomoxetine. If priapism occurs during atomoxetine therapy, patients should seek prompt medical attention (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.14.A.5 Sexual dysfunction

a) While changes in sexual desire, sexual performance, and sexual satisfaction have not been assessed in clinical trials, atomoxetine appears to impair sexual function in some male and female patients. Patients receiving atomoxetine should be routinely asked about sexual side effects (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.16 Other

3.3.16.A Atomoxetine Hydrochloride

Angioedema

Fatigue

Menopausal flushing

3.3.16.A.1 Angioedema

a) Allergic reactions, including angioneurotic edema, have been reported with atomoxetine use (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.16.A.2 Fatigue

a) Incidence: adults, 9%; pediatrics, 6% to 9% (Prod Info STRATTERA(R) oral capsules, 2008)

b) In acute (up to 25 weeks), placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), fatigue was reported in 9% of patients who received atomoxetine (n=540) compared to 4% of patients who received placebo (n=402) (Prod Info STRATTERA(R) oral capsules, 2008).

c) In acute (up to 18 weeks), placebo-controlled trials in pediatric patients with attention-deficit hyperactivity disorder (ADHD), fatigue was reported in 8% of atomoxetine-treated patients (n=1597) compared to 3% of placebo-treated patients (n=934) (Prod Info STRATTERA(R) oral capsules, 2008).
d) In acute (up to 18 weeks), placebo-controlled trials in pediatric patients with attention-deficit hyperactivity disorder (ADHD), fatigue was reported in 9% and 6% of patients treated with atomoxetine once (n=882) and twice (n=715) daily, respectively, compared to 2% and 4% of patients treated with placebo once (n=500) and twice (n=434) daily, respectively (Prod Info STRATTERA(R) oral capsules, 2008).

3.3.16.A.3 Menopausal flushing

a) Incidence: adults, 8% (Prod Info STRATTERA(R) oral capsules, 2008)
b) In acute (up to 25 weeks), placebo-controlled trials in adult patients with attention-deficit hyperactivity disorder (ADHD), hot flushes were reported in 8% of patients who received atomoxetine (n=214) compared to 1% of patients who received placebo (n=142) (Prod Info STRATTERA(R) oral capsules, 2008).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy
1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info Strattera(TM), 2002s) (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.
See Drug Consult reference: PREGNANCY RISK CATEGORIES
2) Crosses Placenta: Unknown
3) Clinical Management
a) There is insufficient clinical experience with the use of atomoxetine in pregnancy to confirm its safety in that patient population. Until additional data are available, caution should be exercised with the use of atomoxetine in pregnant women.
4) Literature Reports
a) Adverse fetal effects and some evidence of teratogenicity was reported with relatively high doses of atomoxetine in animal studies (Prod Info Strattera(TM), 2002s).
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) It is not known whether atomoxetine is excreted into human breast milk and the potential for adverse effects in the nursing infant from exposure to the drug are unknown. It is not known if atomoxetine affects the quantity or composition of breastmilk. According to the manufacturer, atomoxetine and/or its metabolites were excreted into the milk of lactating rats (Prod Info STRATTERA(TM) Oral Capsule, 2002).
3) Literature Reports
a) No reports describing the use of atomoxetine during human lactation or measuring the amount, if any, of the drug excreted into milk have been located.

3.5 Drug Interactions

3.5.1 Drug-Drug Combinations

Albuterol

Amitriptyline

Amoxapine

Brofaromine

Clomipramine

Clorgyline

Desipramine

Dibenzepin

Dothiepin

Doxepin

Fluoxetine

Furazolidone

Imipramine

Iproniazid

Isocarboxazid

Lazabemide

Linezolid

Lofepramine

Moclobemide

Nialamide

Nortriptyline

Opipramol

Pargyline

Paroxetine

Phenelzine

Procarbazine

Protriptyline

Quinidine

Rasagiline

Selegiline

Tianeptine

Toloxatone

Tranylcypromine

Trimipramine

3.5.1.A Albuterol

1) Interaction Effect: an increase in heart rate and blood pressure
2) Summary: Albuterol (600 mcg intravenously over 2 hours) induced increases in heart rate and blood pressure. The effects were potentiated by atomoxetine (60 mg BID for 5 days) and were most marked after the initial coadministration of albuterol and atomoxetine (Prod Info Strattera(TM), 2002h).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Close monitoring of blood pressure and heart rate is indicated during combined therapy with atomoxetine and albuterol or other beta-2 agonists, particularly in patients with cardiovascular disease.
7) Probable Mechanism: unknown

3.5.1.B Amitriptyline
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as amitriptyline. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with amitriptyline, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002n).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with amitriptyline.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by amitriptyline

3.5.1.C Amoxapine
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as amoxapine. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with amoxapine, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002j).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with amoxapine.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by amoxapine

3.5.1.D Brofaromine
1) Interaction Effect: an increased risk of serotonin syndrome (hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delerium and coma)
2) Summary: The combination of atomoxetine and a monoamine oxidase inhibitor (MAOI) may increase the risk of serotonin syndrome. There have been reports of serious, sometimes fatal, reactions (including 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) when atomoxetine is coadministered with an MAOI. Some case presented with signs and symptoms similar to neuroleptic malignant syndrome (Prod Info Strattera(TM), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Atomoxetine should not be taken with a monoamine oxidase inhibitor (MAOI), or within 2 weeks after discontinuing an MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing atomoxetine. Observe the patient closely for signs and symptoms of serotonin syndrome or neuroleptic malignant syndrome.
7) Probable Mechanism: additive serotonergic effect

3.5.1.E Clomipramine
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are

increased with selective inhibitors of CYP2D6, such as clomipramine. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with clomipramine, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002m).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with clomipramine.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by clomipramine

3.5.1.F Clorgyline
1) Interaction Effect: an increased risk of serotonin syndrome (hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delerium and coma)
2) Summary: The combination of atomoxetine and a monoamine oxidase inhibitor (MAOI) may increase the risk of serotonin syndrome. There have been reports of serious, sometimes fatal, reactions (including 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) when atomoxetine is coadministered with an MAOI. Some case presented with signs and symptoms similar to neuroleptic malignant syndrome (Prod Info Strattera(TM), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Atomoxetine should not be taken with a monoamine oxidase inhibitor (MAOI), or within 2 weeks after discontinuing an MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing atomoxetine. Observe the patient closely for signs and symptoms of serotonin syndrome or neuroleptic malignant syndrome.
7) Probable Mechanism: additive serotonergic effect

3.5.1.G Desipramine
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as desipramine. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with desipramine, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002r).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with desipramine.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by desipramine

3.5.1.H Dibenzepin
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as dibenzepin. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with dibenzepin, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002e).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with dibenzepin.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by dibenzepin

3.5.1.I Dothiepin
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-

hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as dothiepin. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with dothiepin, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002d).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with dothiepin.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by dothiepin

3.5.1.J Doxepin
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as doxepin. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with doxepin, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002g).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with doxepin.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by doxepin

3.5.1.K Fluoxetine
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as fluoxetine. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with fluoxetine, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002c).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with fluoxetine.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by fluoxetine

3.5.1.L Furazolidone
1) Interaction Effect: an increased risk of serotonin syndrome (hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delerium and coma)
2) Summary: The combination of atomoxetine and a monoamine oxidase inhibitor (MAOI) may increase the risk of serotonin syndrome. There have been reports of serious, sometimes fatal, reactions (including 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) when atomoxetine is coadministered with an MAOI. Some case presented with signs and symptoms similar to neuroleptic malignant syndrome (Prod Info Strattera(TM), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Atomoxetine should not be taken with a monoamine oxidase inhibitor (MAOI), or within 2 weeks after discontinuing an MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing atomoxetine. Observe the patient closely for signs and symptoms of serotonin syndrome or neuroleptic malignant syndrome.
7) Probable Mechanism: additive serotonergic effect

3.5.1.M Imipramine
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are

increased with selective inhibitors of CYP2D6, such as imipramine. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with imipramine, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002a).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with imipramine.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by imipramine

3.5.1.N Iproniazid
1) Interaction Effect: an increased risk of serotonin syndrome (hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delerium and coma)
2) Summary: The combination of atomoxetine and a monoamine oxidase inhibitor (MAOI) may increase the risk of serotonin syndrome. There have been reports of serious, sometimes fatal, reactions (including 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) when atomoxetine is coadministered with an MAOI. Some case presented with signs and symptoms similar to neuroleptic malignant syndrome (Prod Info Strattera(TM), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Atomoxetine should not be taken with a monoamine oxidase inhibitor (MAOI), or within 2 weeks after discontinuing an MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing atomoxetine. Observe the patient closely for signs and symptoms of serotonin syndrome or neuroleptic malignant syndrome.
7) Probable Mechanism: additive serotonergic effect

3.5.1.O Isocarboxazid
1) Interaction Effect: an increased risk of serotonin syndrome (hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delerium and coma)
2) Summary: The combination of atomoxetine and a monoamine oxidase inhibitor (MAOI) may increase the risk of serotonin syndrome. There have been reports of serious, sometimes fatal, reactions (including 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) when atomoxetine is coadministered with an MAOI. Some case presented with signs and symptoms similar to neuroleptic malignant syndrome (Prod Info Strattera(TM), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Atomoxetine should not be taken with a monoamine oxidase inhibitor (MAOI), or within 2 weeks after discontinuing an MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing atomoxetine. Observe the patient closely for signs and symptoms of serotonin syndrome or neuroleptic malignant syndrome.
7) Probable Mechanism: additive serotonergic effect

3.5.1.P Lazabemide
1) Interaction Effect: an increased risk of serotonin syndrome (hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delerium and coma)
2) Summary: The combination of atomoxetine and a monoamine oxidase inhibitor (MAOI) may increase the risk of serotonin syndrome. There have been reports of serious, sometimes fatal, reactions (including 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) when atomoxetine is coadministered with an MAOI. Some case presented with signs and symptoms similar to neuroleptic malignant syndrome (Prod Info Strattera(TM), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Atomoxetine should not be taken with a monoamine oxidase inhibitor (MAOI), or within 2 weeks after discontinuing an MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing atomoxetine. Observe the patient closely for signs and symptoms of serotonin syndrome or neuroleptic malignant syndrome.
7) Probable Mechanism: additive serotonergic effect

3.5.1.Q Linezolid

1) Interaction Effect: an increased risk of serotonin syndrome (hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delerium and coma)
2) Summary: The combination of atomoxetine and a monoamine oxidase inhibitor (MAOI) may increase the risk of serotonin syndrome. There have been reports of serious, sometimes fatal, reactions (including 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) when atomoxetine is coadministered with an MAOI. Some case presented with signs and symptoms similar to neuroleptic malignant syndrome (Prod Info Strattera(TM), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Atomoxetine should not be taken with a monoamine oxidase inhibitor (MAOI), or within 2 weeks after discontinuing an MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing atomoxetine. Observe the patient closely for signs and symptoms of serotonin syndrome or neuroleptic malignant syndrome.
7) Probable Mechanism: additive serotonergic effect

3.5.1.R Lofepramine

1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as lofepramine. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with lofepramine, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002o).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with lofepramine.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by lofepramine

3.5.1.S Moclobemide

1) Interaction Effect: an increased risk of serotonin syndrome (hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delerium and coma)
2) Summary: The combination of atomoxetine and a monoamine oxidase inhibitor (MAOI) may increase the risk of serotonin syndrome. There have been reports of serious, sometimes fatal, reactions (including 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) when atomoxetine is coadministered with an MAOI. Some case presented with signs and symptoms similar to neuroleptic malignant syndrome (Prod Info Strattera(TM), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Atomoxetine should not be taken with a monoamine oxidase inhibitor (MAOI), or within 2 weeks after discontinuing an MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing atomoxetine. Observe the patient closely for signs and symptoms of serotonin syndrome or neuroleptic malignant syndrome.
7) Probable Mechanism: additive serotonergic effect

3.5.1.T Nialamide

1) Interaction Effect: an increased risk of serotonin syndrome (hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delerium and coma)
2) Summary: The combination of atomoxetine and a monoamine oxidase inhibitor (MAOI) may increase the risk of serotonin syndrome. There have been reports of serious, sometimes fatal, reactions (including 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) when atomoxetine is coadministered with an MAOI. Some case presented with signs and symptoms similar to neuroleptic malignant syndrome (Prod Info Strattera(TM), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical

6) Clinical Management: Atomoxetine should not be taken with a monoamine oxidase inhibitor (MAOI), or within 2 weeks after discontinuing an MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing atomoxetine. Observe the patient closely for signs and symptoms of serotonin syndrome or neuroleptic malignant syndrome.
7) Probable Mechanism: additive serotonergic effect

3.5.1.U Nortriptyline
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as nortriptyline. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with nortriptyline, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002l).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with nortriptyline.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by nortriptyline

3.5.1.V Opipramol
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as opipramol. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with opipramol, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002f).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with opipramol.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by opipramol

3.5.1.W Pargyline
1) Interaction Effect: an increased risk of serotonin syndrome (hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delerium and coma)
2) Summary: The combination of atomoxetine and a monoamine oxidase inhibitor (MAOI) may increase the risk of serotonin syndrome. There have been reports of serious, sometimes fatal, reactions (including 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) when atomoxetine is coadministered with an MAOI. Some case presented with signs and symptoms similar to neuroleptic malignant syndrome (Prod Info Strattera(TM), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Atomoxetine should not be taken with a monoamine oxidase inhibitor (MAOI), or within 2 weeks after discontinuing an MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing atomoxetine. Observe the patient closely for signs and symptoms of serotonin syndrome or neuroleptic malignant syndrome.
7) Probable Mechanism: additive serotonergic effect

3.5.1.X Paroxetine
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as paroxetine. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with paroxetine, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002i).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical

6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with paroxetine.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by paroxetine

3.5.1.Y Phenelzine
1) Interaction Effect: an increased risk of serotonin syndrome (hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delerium and coma)
2) Summary: The combination of atomoxetine and a monoamine oxidase inhibitor (MAOI) may increase the risk of serotonin syndrome. There have been reports of serious, sometimes fatal, reactions (including 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) when atomoxetine is coadministered with an MAOI. Some case presented with signs and symptoms similar to neuroleptic malignant syndrome (Prod Info Strattera(TM), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Atomoxetine should not be taken with a monoamine oxidase inhibitor (MAOI), or within 2 weeks after discontinuing an MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing atomoxetine. Observe the patient closely for signs and symptoms of serotonin syndrome or neuroleptic malignant syndrome.
7) Probable Mechanism: additive serotonergic effect

3.5.1.Z Procarbazine
1) Interaction Effect: an increased risk of serotonin syndrome (hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delerium and coma)
2) Summary: The combination of atomoxetine and a monoamine oxidase inhibitor (MAOI) may increase the risk of serotonin syndrome. There have been reports of serious, sometimes fatal, reactions (including 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) when atomoxetine is coadministered with an MAOI. Some case presented with signs and symptoms similar to neuroleptic malignant syndrome (Prod Info Strattera(TM), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Atomoxetine should not be taken with a monoamine oxidase inhibitor (MAOI), or within 2 weeks after discontinuing an MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing atomoxetine. Observe the patient closely for signs and symptoms of serotonin syndrome or neuroleptic malignant syndrome.
7) Probable Mechanism: additive serotonergic effect

3.5.1.AA Protriptyline
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as protriptyline. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with protriptyline, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002q).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with protriptyline.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine

3.5.1.AB Quinidine
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as quinidine. The exposure is similar to that observed in poor metabolizers (Prod Info Strattera(TM), 2002p).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with

quinidine.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by quinidine

3.5.1.AC Rasagiline
1) Interaction Effect: an increased risk of serotonin syndrome (hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delerium and coma)
2) Summary: The combination of atomoxetine and a monoamine oxidase inhibitor (MAOI) may increase the risk of serotonin syndrome. There have been reports of serious, sometimes fatal, reactions (including 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) when atomoxetine is coadministered with an MAOI. Some case presented with signs and symptoms similar to neuroleptic malignant syndrome (Prod Info Strattera(TM), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Atomoxetine should not be taken with a monoamine oxidase inhibitor (MAOI), or within 2 weeks after discontinuing an MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing atomoxetine. Observe the patient closely for signs and symptoms of serotonin syndrome or neuroleptic malignant syndrome.
7) Probable Mechanism: additive serotonergic effect

3.5.1.AD Selegiline
1) Interaction Effect: an increased risk of serotonin syndrome (hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delerium and coma)
2) Summary: The combination of atomoxetine and a monoamine oxidase inhibitor (MAOI) may increase the risk of serotonin syndrome. There have been reports of serious, sometimes fatal, reactions (including 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) when atomoxetine is coadministered with an MAOI. Some case presented with signs and symptoms similar to neuroleptic malignant syndrome (Prod Info Strattera(TM), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Atomoxetine should not be taken with a monoamine oxidase inhibitor (MAOI), or within 2 weeks after discontinuing an MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing atomoxetine. Observe the patient closely for signs and symptoms of serotonin syndrome or neuroleptic malignant syndrome.
7) Probable Mechanism: additive serotonergic effect

3.5.1.AE Tianeptine
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as tianeptine. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with tianeptine, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002k).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with tianeptine.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by tianeptine

3.5.1.AF Toloxatone
1) Interaction Effect: an increased risk of serotonin syndrome (hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delerium and coma)
2) Summary: The combination of atomoxetine and a monoamine oxidase inhibitor (MAOI) may increase the risk of serotonin syndrome. There have been reports of serious, sometimes fatal, reactions (including 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) when atomoxetine is coadministered with an MAOI. Some case presented with signs and symptoms similar to neuroleptic malignant syndrome (Prod Info Strattera(TM), 2002).

3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Atomoxetine should not be taken with a monoamine oxidase inhibitor (MAOI), or within 2 weeks after discontinuing an MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing atomoxetine. Observe the patient closely for signs and symptoms of serotonin syndrome or neuroleptic malignant syndrome.
7) Probable Mechanism: additive serotonergic effect

3.5.1.AG Tranylcypromine

1) Interaction Effect: an increased risk of serotonin syndrome (hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delerium and coma)
2) Summary: The combination of atomoxetine and a monoamine oxidase inhibitor (MAOI) may increase the risk of serotonin syndrome. There have been reports of serious, sometimes fatal, reactions (including 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) when atomoxetine is coadministered with an MAOI. Some case presented with signs and symptoms similar to neuroleptic malignant syndrome (Prod Info Strattera(TM), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Atomoxetine should not be taken with a monoamine oxidase inhibitor (MAOI), or within 2 weeks after discontinuing an MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing atomoxetine. Observe the patient closely for signs and symptoms of serotonin syndrome or neuroleptic malignant syndrome.
7) Probable Mechanism: additive serotonergic effect

3.5.1.AH Trimipramine

1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as trimipramine. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with trimipramine, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002b).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with trimipramine.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by trimipramine

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

4.1 Monitoring Parameters

A) Atomoxetine Hydrochloride
1) Therapeutic
a) Physical Findings
1) Improvement in mental and behavioral symptoms of ADHD, including inappropriate inattention, impulsivity, hyperactivity, and cognitive performance.
2) Toxic

a) Laboratory Parameters

1) Monitor hepatic function tests if signs of liver dysfunction are present including pruritus, dark urine, jaundice, right upper quadrant tenderness, or unexplained flu-like symptoms (Prod Info STRATTERA(R) oral capsules, 2009).

b) Physical Findings

1) The American Academy of Pediatrics (AAP) does not recommend the routine use of electrocardiograms (ECGS) or routine subspecialty cardiology evaluations (which were previously recommended by the American Heart Association (AHA) scientific statement to detect cardiac conditions that might place the child at risk for sudden cardiac death) before initiating stimulant therapy to treat attention-deficit/hyperactivity disorder ADHD in most children. The APA cited specific reasons for changing the recommendation including: lack of evidence establishing a relationship between stimulant drugs used to treat ADHD and sudden cardiac death (SCD), the frequency of sudden unexpected deaths among patients taking stimulant drugs is not higher than that in the general population of children, and lack of cost-effective analysis to support ECG screening or special evaluation by pediatric cardiologist (Perrin et al, 2008).

2) Based on the American Academy of Pediatrics (AAP) and the American Heart Association (AHA) consensus statements, the following cardiac monitoring recommendations have been established to assist clinicians in the evaluation of children treated with stimulant drugs, including atomoxetine, for ADHD (Perrin et al, 2008; Vetter et al, 2008):

- Conduct a thorough examination prior to initiating atomoxetine therapy for a diagnosis of ADHD. Special attention should be given to symptoms indicative of a cardiac condition, including palpitations, near syncope, or syncope. Palpitations have been reported with atomoxetine use in adults.
- Obtain a complete family and patient history for conditions associated with SCD, and determine current use of any other prescription or over-the-counter medications.
- Conduct a complete physical evaluation of the patient for hypertension, cardiac murmurs, physical findings associated with Marfan syndrome, and signs of irregular cardiac rhythms.
- Perform further evaluation if family history, patient history or physical exam is suggestive of cardiac disease during initial visit or at follow up visits, and if indicated, consult pediatric cardiologist .
- Continue to assess the patient for cardiac symptoms and any changes in family history at follow up visits.
- Blood pressure and heart rate should be evaluated at baseline, during routine follow-up within 1 to 3 months, and at follow up visits every 6 to 12 months. Increases in blood pressure and heart rate have been reported with the use of certain ADHD drugs.

3) Monitor children and adolescents receiving atomoxetine for signs of clinical worsening, suicidal thinking or behaviors, and unusual changes in behavior at the start of therapy and during the first few months of therapy or when the dose is increased or decreased. Symptoms of clinical worsening may include anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania (Prod Info STRATTERA(R) oral capsules, 2009; US Food and Drug Administration, 2005).

4) Monitor for signs of liver dysfunction including pruritus, dark urine, jaundice, right upper quadrant tenderness, or unexplained flu-like symptoms (Prod Info STRATTERA(R) oral capsules, 2009).

5) Monitor growth in pediatric patients (Prod Info STRATTERA(R) oral capsules, 2006).

6) Monitor for signs of hypersensitivity including angioneurotic edema, urticaria, and rash.

4.2 Patient Instructions

A) Atomoxetine (By mouth)

Atomoxetine

Treats attention-deficit/hyperactivity disorder (ADHD).

When This Medicine Should Not Be Used:
You should not use this medicine if you or your child have had an allergic reaction to atomoxetine, if you or your child have narrow angle glaucoma, or have used an MAO inhibitor such as Eldepryl®, Marplan®, Nardil®, or Parnate® in the past 14 days. After you or your child stop using atomoxetine, do not use an MAO inhibitor for at least 14 days.

How to Use This Medicine:
Capsule

Your doctor will tell you how much of this medicine to use and how often. Do not use more medicine or use it more often than your doctor tells you to.
This medicine should come with a Medication Guide. Read and follow these instructions carefully. Ask your doctor 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.
For children or teenagers, the dose may need to be changed several times in order to find out what works best for them. Pay close attention to any changes in behavior that might happen.
Swallow the capsule whole. Do not crush, break, chew, or open it.

You may take this medicine with or without food.

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 leftover medicine after you have finished your treatment. You will also need to throw away old medicine after the expiration date has passed.
Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.
Make sure your doctor knows if you are using dopamine (Intropin®), dobutamine (Dobutrex®), an asthma medicine (such as albuterol), or a heart rhythm medicine (such as disopyramide, procainamide, quinidine, Norpace®, or Procanbid®). Tell your doctor if you are also using a medicine for depression, such as fluoxetine, paroxetine, Luvox®, Paxil®, Prozac®, or Sarafem®.

Warnings While Using This Medicine:
Make sure your doctor knows if you or your child are pregnant or breastfeeding, or if you or your child have high or low blood pressure, liver disease, heart disease, heart rhythm problems, blood vessel disease, or problems with urination.
This medicine may make you or your child dizzy or drowsy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert.
This medicine may cause slow growth. If your child is using this medicine, the doctor will need to keep track of your child's height and weight to make sure that your child is growing properly.
For some children and teenagers, this medicine can increase thoughts of suicide. All of the warnings in this leaflet are true for a child or teenager who is using this medicine.Tell your doctor right away if you start to feel more depressed. Also tell your doctor right away if you have thoughts about hurting yourself. Report any unusual thoughts or behaviors that trouble you, especially if they are new or get worse quickly.Make sure your caregiver knows if you have trouble sleeping, get upset easily, have a big increase in energy, or start to act reckless. Also tell your doctor if you have sudden or strong feelings, such as feeling nervous, angry, restless, violent, or scared.Let your doctor know if you or anyone in your family has bipolar disorder (manic-depressive) or has tried to commit suicide.
Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to keep all appointments.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing.
Change in how much or how often you urinate.
Chest pain or shortness of breath.
Dark-colored urine or pale stools.
Fast, pounding, or irregular heartbeat.
Flu-like symptoms.
Headache, lightheadedness, dizziness, or fainting.
Mood changes, aggressiveness, irritability, or depression.
Nausea, vomiting, loss of appetite, constipation, upset stomach, or pain in your upper stomach.
Painful, prolonged erection of the penis.
Seeing, hearing, or feeling things that are not there.
Seizures or tremors.
Yellowing of your skin or the whites of your eyes.

If you notice these less serious side effects, talk with your doctor:
Changes in your menstrual cycle (periods), or menstrual cramps.
Dry mouth.
Loss of interest in sex, or trouble having sex.
Tiredness.
Trouble sleeping.
Warmth or redness in your face, neck, arms, or upper chest.

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

4.3 Place In Therapy

A) ADHD

1) Atomoxetine is promoted as an equally efficacious form of ADHD therapy as conventional agents (eg, methylphenidate, dextroamphetamine, pemoline, bupropion, tricyclic antidepressants). Controlled studies, essential for evaluation of this agent, have shown evidence of efficacy; direct comparisons are lacking. Unpublished data suggest that the frequency and severity of some adverse effects are similar to those of methylphenidate (eg, cardiovascular effects, weight loss).

2) At the very least, prospective comparisons with short- and long-acting forms of methylphenidate (usual agent of choice) are indicated before the place in therapy of atomoxetine can be addressed.

3) Until additional data for atomoxetine are made available, it should not be considered over conventional therapy.

B) DEPRESSION

1) Clinical data for atomoxetine in major depression are limited to small, uncontrolled studies. Placebo-controlled studies are required to confirm efficacy; comparisons with selective serotonin reuptake inhibitors (SSRIs)/other antidepressants are needed to assess its role in therapy.

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) Atomoxetine is a methylphenoxy-benzene propanamine derivative with antidepressant activity (Zerbe et al, 1985; Chouinard et al, 1985); its structure is unlike that of other antidepressants. The drug is under investigation as a "nonstimulant" treatment of attention-deficit/hyperactivity disorder (ADHD) in both adults and children, and for treatment of adult depression.

2) Atomoxetine purportedly enhances noradrenergic function via selective inhibition of the presynaptic norepinephrine transporter (Ki of 4.5 nanomols (nM)) (Michelson et al, 2001; Kratochvil et al, 2001). It has minimal-to-no affinity for other neuronal transporters or neurotransmitter receptor sites (eg, muscarinic, histaminic, dopaminergic, serotonergic, alpha-adrenergic) (Zerbe et al, 1985; Cusack et al, 1994; Spencer et al, 1998a; Chouinard et al, 1985; Spencer et al, 1998).

3) Animal and human studies suggest a low propensity for anticholinergic and adverse cardiovascular effects with atomoxetine (Zerbe et al, 1985; Kratochvil et al, 2001; Spencer et al, 2001). No significant hypertensive effects were seen in healthy subjects given single doses of 20 or 40 mg twice daily for one week in one study (Zerbe et al, 1985).

B) REVIEW ARTICLES

1) Drug treatment of attention-deficit/hyperactivity disorder (ADHD) (Popper, 2000).

2) Diagnostic dilemmas in ADHD and treatment modalities (Spencer et al, 1998a).

3) Use of nonstimulant agents in ADHD (Biederman & Spencer, 2000).

4.5 Therapeutic Uses

4.5.A Atomoxetine Hydrochloride

Attention deficit hyperactivity disorder

Attention deficit hyperactivity disorder - Social phobia

Nocturnal enuresis

4.5.A.1 Attention deficit hyperactivity disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (6 years and older)
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:

Atomoxetine hydrochloride (HCl) is indicated for the acute treatment of attention-deficit hyperactivity disorder (ADHD) in pediatric (ages 6 years and older) and adult patients and as maintenance/extended therapy in pediatric patients (aged 6 to 15 years) (Prod Info STRATTERA (R) oral capsules, 2008).

Atomoxetine is used as an integral part of a total treatment program for (ADHD) that may include other psychological, educational, and/or social measures (Prod Info STRATTERA(R) oral capsules, 2008).

In two 10-week, randomized, placebo-controlled studies (n=536), atomoxetine hydrochloride produced significant improvement in symptoms in adult patients with attention-deficit/hyperactivity disorder (Prod Info STRATTERA(R) oral capsules, 2008).

Oral atomoxetine has shown short-term efficacy for treating attention-deficit hyperactivity disorder (ADHD) in over 600 children/adolescents (6 to 18 years of age) in open and placebo-controlled trials (Spencer et al, 2002; Kratochvil et al, 2001a; Michelson et al, 2001b; Spencer et al, 2001a). Pediatric patients (ages 6 to 15 years) with attention-deficit hyperactivity disorder who received maintenance treatment with atomoxetine hydrochloride had significantly longer times to relapse compared to patients who received placebo (Prod Info STRATTERA(R) oral capsules, 2008).

c) Adult:

1) In two 10-week, randomized, placebo-controlled studies in adult patients with attention-deficit hyperactivity disorder (n=536), atomoxetine hydrochloride (HCl) produced significant improvement in symptoms as assessed on the ADHD symptom score from the Conners Adult ADHD Rating Scale Screening Version (CAARS). Atomoxetine HCl was titrated to 60 to 120 mg/day given in 2 daily divided doses (mean daily dose, 95 mg). Efficacy was similar regardless of gender and age (older or younger than 42 years) (Prod Info STRATTERA(R) oral capsules, 2008).

2) Oral atomoxetine 40 to 80 milligrams (mg) daily for three weeks was effective in adult attention-deficit/hyperactivity disorder (ADHD). In a small placebo-controlled crossover study (n=21), improvements in the ADHD Rating Scale significantly favored atomoxetine after the second week of treatment; the average dose at week three was 76 mg daily. A 30% or greater decrease in ADHD symptoms was observed in 52% of patients during treatment (10% response with placebo) (Spencer et al, 1998b). However, several aspects of the study design were not included, and this response rate is less than that observed with methylphenidate or desipramine in some other studies.

d) Pediatric:

1) Acute Treatment

a) Oral atomoxetine has shown short-term efficacy for treating Attention- Deficit/Hyperactivity Disorder (ADHD) in over 600 children/adolescents (6 to 18 years of age) in open and placebo-controlled trials. The primary efficacy measure was ADHD Rating Scale-IV-Parent Version (ADHD RS), which has demonstrated validity in prior studies. Compared to placebo, oral atomoxetine in doses ranging from 1.2 to 1.8 milligrams/kilogram/day resulted in a significantly greater mean reduction in ADHD RS total score (p less than 0.05 for all studies); smaller doses failed to show consistent efficacy. Therapeutic doses of atomoxetine also generally but less consistently produced significant improvements on select subscales of the ADHD RS, namely scores of inattentiveness and hyperactivity/impulsivity. Other secondary measures showing improvements with atomoxetine included the Clinical Global Impressions-ADHD- Severity (CGI-ADHD-S) score (p less than 0.05 for all studies) and the Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S) (p less than or equal to 0.05 for all studies). Similar efficacy was reported in a subset analysis in school- age girls. Furthermore, no differences were reported between patients with and without previous psychostimulant treatment or among age groups (Biderman et al, 2002)(Spencer et al, 2002; Kratochvil et al, 2001a; Michelson et al, 2001b; Spencer et al, 2001a).

2) Maintenance Treatment

a) Pediatric patients with attention-deficit hyperactivity disorder (ADHD) who received maintenance treatment with atomoxetine hydrochloride (HCl) had significantly longer times to relapse compared to patients who received placebo. Patients (aged 6 to 15 years) who had a continuous response (defined as a Clinical Global Impressions of Severity of ADHD (CGI-ADHD-S) score of 2 or less and 25% or greater decrease from baseline in the ADHD rating scale-IV Parent Version with the hyperactivity/impulsive and inattentive subscales (ADHDRS-IV-Parent:Inv) total score) for approximately 4 weeks during an initial 10-week, open-label treatment phase were randomized to either their current atomoxetine HCl dose (n=292) of 1.2 to 1.8 milligrams/kilogram/day or placebo (n=124). Patients who experienced a continuous response for approximately 8 months with atomoxetine HCl therapy were randomized again to either their current atomoxetine HCl dose (n=81) or placebo (n=82). In both randomized, double-blind maintenance treatment phases, time to relapse (defined as the time to a CGI-ADHD-S score increase of 2 or more and a ADHDRS-IV-Parent:Inv total score of 90% or greater from baseline for 2 consecutive visits) was significantly longer in patients who received atomoxetine HCl compared to placebo (Prod Info STRATTERA(R) oral capsules, 2008).

b) Maintenance treatment with low-dose atomoxetine did not lead to a statistically significant difference in relapse rates compared to the higher, acute treatment dose in a randomized, double-blind, dose-response study in patients with Attention-Deficit/Hyperactivity Disorder (ADHD). Patients aged 6 to 16 years (n=229), who had a robust response to initial 7- to 9-week treatment with oral atomoxetine for ADHD, were randomized to either continue atomoxetine at the same dose (mean dose, 1.43 +/- 0.28 milligrams/kilogram (mg/kg) per day; n=116) or at a low dose of 0.5 mg/kg per day (n=113) for up to 8 months. Symptom severity was low and similar in both groups at randomization. The primary efficacy measure was relapse, which was determined using the investigator-administered and investigator-scored version of the ADHD Rating Scale (ADHD-RS) and was defined as a total ADHD-RS score of 90% of more of the original baseline value (prior to acute treatment) for 2 consecutive visits. At study conclusion, relapse rates did not differ significantly between the 2 groups (p=0.924), and were 2.6% (3/116) and 2.7% (3/113) for the continued same-dose and the low-dose groups, respectively. The mean change in the ADHD-RS total scores was similar for both groups (p=0.237), with a mean change of 1.1 +/- 10.8 (p=0.751) for the continued same-dose group and 3.1 +/- 10.4 (p=0.017) for the low-dose group. Among

secondary measures, there were no statistically significant differences between the 2 groups in mean changes in the Clinical Global Impressions-ADHD-Severity scores (p=0.078) and in the Child Health Questionnaire psychosocial summary scores (p=0.205). However, scores on the role emotion/behavior subscale were significantly lower (worsening) for patients in the low-dose group (-1.13 +/- 33.9) compared to patients in the continued same-dose group (5.75 +/- 29.9) (p=0.017). Among treatment-emergent adverse events, reports of affective lability were higher in the low-dose group (5/112 versus 0/116; p=0.027) while increases in heart rate (HR) were higher in the continued same-dose group (mean change in HR, 9 +/- 12.5 versus 5.2 +/- 13.9; p=0.013) (Newcorn et al, 2006).

4.5.A.2 Attention deficit hyperactivity disorder - Social phobia

a) Overview

FDA Approval: Adult, no; Pediatric, no
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:

Atomoxetine was superior to placebo for the treatment of attention deficit hyperactivity disorder (ADHD) in adults with comorbid social anxiety disorder in a randomized, double-blind, placebo-controlled trial demonstrated (n=442) (Adler et al, 2009).
Atomoxetine was superior to placebo for the treatment of attention deficit hyperactivity disorder (ADHD) in pediatric and adolescent patients with comorbid generalized anxiety disorder (GAD) in a randomized, double-blind, placebo-controlled trial (n=176) (Geller et al, 2007).

c) Adult:

1) A multicenter, randomized, double-blind, placebo-controlled, parallel-group study demonstrated that atomoxetine was superior to placebo for the treatment of attention deficit hyperactivity disorder (ADHD) in adults with comorbid social anxiety disorder (SAD) (n=442). Adult patients, aged 18 to 65 years, with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnosis for ADHD and SAD were enrolled. Patients were randomized to receive either placebo (n=218) or atomoxetine (n=224) 40 milligrams (mg) daily in 2 divided doses for a minimum of 7 days, then 80 mg total daily dose (target dose) for a minimum of 7 days. After randomization, all patients entered a 2-week placebo lead-in period. At week 10, atomoxetine may be increased to 100 mg/day if significant residual symptoms remained. The study duration was 16 weeks. The primary outcome was the mean change from baseline to endpoint in the Conners' Adult ADHD Rating Scale: Investigator-Rates: Screening Version (CAARS:Inv:SV) Total ADHD symptoms score. The statistical analysis for the primary outcome was performed on the per protocol population of qualified patients (n=342). Qualified patients included those who had 25% or less improvement in social anxiety symptoms during the placebo lead-in phase. At baseline, the mean CAARS:Inv:SV total ADHD score was 29.6 +/- 10.4 and 31.2 +/- 9.4 in the atomoxetine and placebo group, respectively. The per protocol analysis revealed that atomoxetine was significantly superior to placebo in the mean CAARS:Inv:SV total ADHD score improvement from baseline (-8.7 +/- 10 vs -5.6 +/- 10.2; p less than 0.001). Similarly, the mean change in Liebowitz Social Anxiety Scale total score (LSAS) from baseline to endpoint was -22.9 +/- 25.3 and -14.4 +/-20.3 (p less than 0.001) in the atomoxetine and placebo groups, respectively. Common adverse effects included insomnia (17% vs 9%), nausea (16% vs 7.6%), dry mouth (15.6% vs 4.3%) and dizziness (7.5% vs 2.4%) in the atomoxetine vs placebo groups, respectively (Adler et al, 2009).

d) Pediatric:

1) Atomoxetine was superior to placebo for the treatment of attention deficit hyperactivity disorder (ADHD) in pediatric and adolescent patients with comorbid generalized anxiety disorder (GAD) in a multicenter, randomized, double-blind, parallel-design, placebo-controlled trial, with an optional, open-label extension period (n=176). Patients aged 8 to 17 years (yr), who met the DSM-IV criteria for ADHD and at least 1 of the following anxiety disorders (separation anxiety, generalized anxiety or social phobia) were enrolled. Study period I included a medication washout period for approximately 2 weeks. Study period II included a 2-week, placebo lead-in period to identify high placebo responders. After the placebo lead-in period, patients were randomized to receive atomoxetine (n=87; mean age 12.2 +/- 2.8 yr; 62.1% male) or placebo (n=89; age 11.8 +/- 2.5 yr; 67.4% male) twice daily for 12 weeks. The atomoxetine group received an initial dose of 0.8 milligrams/kilogram (mg/kg) daily, in 2 divided doses for 3 days, then a target dose of 1.2 mg/kg/day. At visit 6, atomoxetine could be increased to a maximum dose of 1.8 mg/kg/day for significant residual ADHD symptoms. The primary outcome was reduction of ADHD and GAD symptoms assessed by the mean change from baseline to endpoint in the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored (ADHDRS-IV-PI) and the Pediatric Anxiety Rating Scale (PARS) total scores. Statistical analysis for the primary outcome was performed on the per protocol population of eligible patients (n=133) who had a baseline and at least 1 post baseline measurement and 25% or less reduction on the PARS total score during the blinded placebo lead-in period. The per protocol analysis revealed that atomoxetine was significantly superior to placebo for improvement of both the ADHDRS-IV-PI and PARS total scores. The mean change from baseline in the ADHDRS-IV-PI scale improvement was -10.5 vs -1.4 (95% CI for difference, -12.56 to -5.58; p less than 0.001) in the atomoxetine group compared with the

placebo group. The corresponding mean change in the PARS score was -5.5 and -3.2, respectively (95% CI for difference, -4.01 to -0.52; p less than 0.012). Subjects in the atomoxetine group had a higher response rate compared with cohorts in the placebo group (61.8% vs 12.1%; p less than 0.001). Atomoxetine was associated with higher incidence of decreased appetite (14.3% vs 3.8%), headache (14.3% vs 8.8%), upper abdominal pain (11.7% vs 5%) and vomiting (10.4% vs 5%) relative to placebo (Geller et al, 2007).

4.5.A.3 Nocturnal enuresis

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:

Efficacy is limited to case report; a controlled trial is needed

c) Pediatric:

1) Atomoxetine shows efficacy in treatment of nocturnal enuresis. In a multicenter, randomized, double-blind, placebo-controlled, intent-to-treat (ITT) trial in which 87 patients (aged 6 to 18 years) received atomoxetine (n=44) or placebo (n=43) for 12 weeks. Atomoxetine was dosed at 0.5 milligrams/kilogram (mg/kg) daily for 3 days, followed by 1 mg/kg/day for the next 3 days and then increased to 1.5 mg/kg/day for the rest of the study. Doses were given twice daily, in the morning and late afternoon. The primary outcome measure was change from baseline in the number of dry nights as recorded on the Day Night Log-Parent Report. At baseline, the mean number of dry nights was 1.51 for the atomoxetine group and 1.01 for the placebo group (statistical difference not provided). Results were reported for 42 atomoxetine-treated and 41 placebo- treated patients. Patients treated with atomoxetine had an average increase of 1.47 dry nights per week compared with 0.60 for the placebo-treated patients (p=0.02). Headache was the most common adverse event occurring in 9 atomoxetine-treated patients and 4 placebo-treated patients (Sumner et al, 2003; Sumner et al, 2003a); (Anon, 2003; Anon, 2003a).

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