DRUGDEX® Evaluations

IMIPRAMINE

0.0 Overview

1) Class

a) This drug is a member of the following class(es):
Antidepressant
Antidepressant, Tricyclic
Urinary Enuresis Agent

2) Dosing Information

a) Imipramine Hydrochloride

1) Adult

a) Depression

1) (hospitalized patients) 100 mg ORALLY per day in divided doses; may increase up to a MAX of 300 r TOFRANIL(R) tablets, 2005)

2) (outpatients) 75 mg ORALLY per day; may increase up to a MAX of 200 mg/day; usual maintenance mg/day (Prod Info TOFRANIL(R) tablets, 2005).

b) Panic disorder

1) 100-200 mg ORALLY in divided doses (1-3 doses per day), higher doses may be required if agoraph

c) Urinary incontinence

1) 25 mg ORALLY at bedtime, may increase in 25 mg increments to max dose of 150mg at bedtime

2) Pediatric

a) safety and effectiveness in children with nocturnal enuresis below the age of 6 years have not been estab effectiveness in pediatric patients for any other condition has not been established (Prod Info TOFRANIL(R) t

1) Nocturnal enuresis

a) (children 6 to 12 y) initial, 25 mg ORALLY 1 h before bedtime, may increase in 25 mg increments 50 mg/d or 2.5 mg/kg/d (Prod Info TOFRANIL(R) tablets, 2005)

b) (children over 12 y) initial, 25 mg ORALLY 1 h before bedtime, may increase in 25 mg increment 75 mg/d or 2.5 mg/kg/d (Prod Info TOFRANIL(R) tablets, 2005)

b) Imipramine Pamoate

1) Adult

a) Depression

1) (hospitalized patients) initial, 100 to 150 mg ORALLY once daily at bedtime; may increase up to MAX usual maintenance dose, 75 to 150 mg ORALLY once daily at bedtime (Prod Info TOFRANIL-PM(R) cap

2) (outpatients) 75 mg ORALLY once daily at bedtime; may increase up to a max of 200 mg/day; usual 75 to 150 mg ORALLY once daily at bedtime (Prod Info TOFRANIL-PM(R) capsules, 2005)

b) Panic disorder

1) 100-200 mg/day ORALLY in divided doses (1-3 doses per day), higher doses may be required if agor

2) Pediatric

a) safety and effectiveness have not been established in children (Prod Info TOFRANIL-PM(R) capsules, 20

3) Contraindications

a) Imipramine Hydrochloride

1) coadministration with a MAOI or use within 14 days of discontinuing a MAOI; may cause serious reactions (eg crisis, convulsive seizures, death) (Prod Info imipramine hcl oral tablets, 2007)

2) hypersensitivity to dibenzazepines; risk of cross-sensitivity reactions (Prod Info imipramine hcl oral tablets, 20

3) hypersensitivity to imipramine hydrochloride (Prod Info imipramine hcl oral tablets, 2007)

4) myocardial infarction, during the acute recovery period (Prod Info imipramine hcl oral tablets, 2007)

b) Imipramine Pamoate

1) coadministration with an MAOI or use within 14 days of discontinuing an MAOI; may cause serious reactions (crisis, severe convulsive seizures, death) (Prod Info TOFRANIL-PM(R) oral capsules, 2007)

2) hypersensitivity to dibenzazepines; risk of cross-sensitivity reactions (Prod Info TOFRANIL-PM(R) oral capsule

3) hypersensitivity to imipramine pamoate (Prod Info TOFRANIL-PM(R) oral capsules, 2007)

4) myocardial infarction, during the acute recovery period (Prod Info TOFRANIL-PM(R) oral capsules, 2007)

4) Serious Adverse Effects

a) Imipramine Hydrochloride

1) Agranulocytosis
2) Atrioventricular conduction pattern - finding
3) Cardiac dysrhythmia
4) Cerebrovascular accident
5) Decreased liver function
6) Depression, worsening
7) Heart block
8) Hypertension
9) Jaundice

10) Myocardial infarction
11) Orthostatic hypotension
12) Palpitations
13) Psychotic disorder
14) Seizure
15) Suicidal thoughts
16) Suicide
17) Syncope

b) Imipramine Pamoate
1) Agranulocytosis
2) Atrioventricular conduction pattern - finding
3) Cardiac dysrhythmia
4) Cardiac dysrhythmia
5) Cerebrovascular accident
6) Decreased liver function
7) Depression, worsening
8) Hypertension
9) Jaundice
10) Myocardial infarction
11) Orthostatic hypotension
12) Seizure
13) Suicidal thoughts
14) Suicide
15) Syncope

5) Clinical Applications
a) Imipramine Hydrochloride
1) FDA Approved Indications
a) Depression
b) Nocturnal enuresis
2) Non-FDA Approved Indications
a) Panic disorder
b) Urinary incontinence

b) Imipramine Pamoate
1) FDA Approved Indications
a) Depression
2) Non-FDA Approved Indications
a) Panic 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 In

B) Synonyms
Imipramine
Imipramine HCl
Imipramine Hydrochloride
Imipramine Pamoate

1.2 Storage and Stability

A) Oral route
1) Store between 59 and 86 degrees F (15 to 30 degrees C) (Prod Info Tofranil(R), 1995).

B) Parenteral route
1) Store between 59 to 86 degrees F (15 to 30 degrees C). Upon storing, minute crystals may form; this has no ir drug's therapeutic efficacy. Crystals will dissolve when the ampul is immersed in hot water (Prod Info Tofranil(R), al, 1994; Trissel, 1994).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Geriatric Patients

Dosage Adjustment During Dialysis

Dosage in Other Disease States

1.3.1 Normal Dosage

Imipramine

Imipramine Hydrochloride

Imipramine Pamoate

1.3.1.A Imipramine

1.3.1.A.1 Cataplexy - Narcolepsy

See Drug Consult reference: NARCOLEPSY AND CATAPLEXY - DRUG THERAPY

1.3.1.B Imipramine Hydrochloride

Intramuscular route

Oral route

1.3.1.B.1 Intramuscular route

1.3.1.B.1.a Depression

1) Initial intramuscular dose of up to 100 milligrams/day in divided doses. Lower dosages are recom
adolescents and for outpatients (Prod Info Tofranil(R), 1995b; Anon, 1983a; Trissel, 1994).

1.3.1.B.2 Oral route

Agoraphobia

Bulimia nervosa

Depression

Diabetic neuropathy

Panic disorder

Urinary incontinence

1.3.1.B.2.a Agoraphobia

1) Efficacy is dose related and may require doses of 150 milligrams/day or greater (Cohen et al, 19
(Mavissaakalian & Perel, 1985a)(Mavissakalian & Perel, 1994; Mavissakalian & Michelson, 1986).

1.3.1.B.2.b Bulimia nervosa

1) The doses used in the treatment of bulimia have ranged from the doses commonly used in the tr depression (75 to 275 milligrams/day) (Pope et al, 1983a; Pope et al, 1983; Rothschild et al, 1994).

1.3.1.B.2.c Depression

1) HOSPITALIZED PATIENTS

a) The recommended initial dose for hospitalized patients is 100 milligrams (mg) orally per day and gradually increased to 200 mg/day as required. If no response is seen after 2 weeks, then t increased up to 250 to 300 mg ORALLY per day in divided doses (Prod Info TOFRANIL(R) tabl as high as 750 milligrams/day maintenance in divided doses have been reported (Schuckit & Fe are not recommended.

2) OUTPATIENTS

a) The recommended initial dose for outpatients is 75 milligrams (mg) orally per day, increased day. Usual maintenance dose ranges from 50 to 150 mg daily. The recommended maximum do (Prod Info TOFRANIL(R) tablets, 2005).

b) Maintenance doses greater than 150 milligrams/day have been well tolerated and may be re patients to prevent relapses, but are associated with a higher incidence of persistent side effect headache, nausea, and vomiting) (Kupfer et al, 1989). The best method, other than experience, the optimal maintenance dose for a particular individual has not been established.

c) Patients with chronic depression that respond to imipramine may benefit from long-term mai (Kocsis et al, 1991).

1.3.1.B.2.d Diabetic neuropathy

1) Standard doses of 100 milligrams/day of imipramine may not be high enough to produce therape some patients with diabetic neuropathy. In one study, the therapeutic dose range was 125 milligram milligrams/day. The maximum therapeutic effect in neuropathy is reached within a week. Dosage titr started with a dose corresponding to a plasma level of 100 to 200 nmol/L for imipramine plus desipra should then be increased in a stepwise fashion (Sindrup et al, 1990a).

1.3.1.B.2.e Panic disorder

1) Based upon a dose-response study in patients with panic disorder with agoraphobia, IMIPRAMIN doses of 1.5 milligrams/kilogram/day (approximately 100 milligrams daily) may be effective in the tre some patients, whereas higher doses (3 milligrams/kilogram/day, approximately 200 milligrams daily for the agoraphobic dimension of this disorder (Mavissakalian & Perel, 1989); (Mavissakalian & Pera 1989a).

2) The suggested target dose is 2.25 milligrams/kilogram/day or a total (imipramine and N-desmeth plasma concentration of 110 to 140 nanograms/milliliter in the acute treatment of patients with panic agoraphobia. Higher doses were associated with good clinical response but a greater dropout rate s effects (Mavissakalian & Peral, 1995).

1.3.1.B.2.f Urinary incontinence

1) The dose used in the treatment of urinary incontinence is 75 to 150 milligrams/day. The dose car milligrams per day and titrated to clinical effect. Some patients may require the dose to be administe doses throughout the day instead of single dose administration (Rabey et al, 1979; Gilja et al, 1984) 1981)(Jarvis, 1981).

2) Imipramine 25 milligrams three times daily has been used in the treatment of females with urinar to detrusor instability (Jarvis, 1981).

1.3.1.C Imipramine Pamoate

1.3.1.C.1 Oral route

Agoraphobia

Bulimia nervosa

Depression

Diabetic neuropathy

Panic disorder

1.3.1.C.1.a Agoraphobia

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(Mavissaakalian & Perel, 1985a)(Mavissakalian & Perel, 1994; Mavissakalian & Michelson, 1986).

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1.3.1.C.1.c Depression

1) HOSPITALIZED PATIENTS

a) The initial oral dose for hospitalized patients is usually 100 to 150 milligrams (mg) once daily may be increased to 200 mg/day as required. If no response is seen after 2 weeks, then the dos increased up to 250 to 300 mg/day. Doses greater than 150 mg daily may be administered once optimum dosage and tolerance have been determined. The usual maintenance dose ranges fro once daily at bedtime (Prod Info TOFRANIL-PM(R) capsules, 2005). Doses as high as 750 milli maintenance in divided doses have been reported (Schuckit & Feighner, 1972) but are not reco

2) OUTPATIENTS

a) The usual initial oral dose for outpatients is 75 milligrams (mg) once daily at bedtime and ma to 200 mg/day. Doses greater than 75 mg daily may be administered once a day after the optim tolerance have been determined. The usual maintenance dose ranges from 75 to 150 mg once (Prod Info TOFRANIL-PM(R) capsules, 2005).

b) Maintenance doses greater than 150 milligrams/day have been well tolerated and may be re patients to prevent relapses, but are associated with a higher incidence of persistent side effect headache, nausea, and vomiting) (Kupfer et al, 1989). The best method, other than experience the optimal maintenance dose for a particular individual has not been established.

c) Patients with chronic depression that respond to imipramine may benefit from long-term mai (Kocsis et al, 1991).

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1.3.1.C.1.e Panic disorder

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2) The suggested target dose is 2.25 milligrams/kilogram/day or a total (imipramine and N-desmeth plasma concentration of 110 to 140 nanograms/milliliter in the acute treatment of patients with panic agoraphobia. Higher doses were associated with good clinical response but a greater dropout rate s effects (Mavissakalian & Peral, 1995).

1.3.2 Dosage in Renal Failure

A) Imipramine Hydrochloride

1) No specific dosage adjustment is necessary (Bennett et al, 1994).

B) Imipramine Pamoate

1) No specific dosage adjustment is necessary (Bennett et al, 1994).

1.3.4 Dosage in Geriatric Patients

A) Imipramine Hydrochloride

1) GENERAL INFORMATION

a) Dosage reduction is recommended in elderly patients since this patient population is reported to have incidence of confusional-type reactions and other central nervous system symptoms while on tricyclic an therapy (Davies et al, 1971). A one-third to one-half reduction in tricyclic antidepressant dosage is sugge An increase in age is correlated with elevated steady-state serum levels of imipramine, desipramine and (Hicks et al, 1981a; Benetello et al, 1990).

2) DEPRESSION

a) The initial recommended dose for depression in geriatric patients is 30 to 40 milligrams orally daily; it necessary to exceed 100 milligrams/day (Prod Info TOFRANIL(R) tablets, 2005).

3) URINARY INCONTINENCE

a) In elderly patients with urinary incontinence associated with spontaneous unstable detrusor contractio imipramine is started at 25 milligrams at bedtime and increased by 25 milligrams, until the patient is cont side effects, or reaches 150 milligrams/day (Castleden et al, 1981).

b) A review for utilizing antidepressants in the treatment of depression in geriatric patients has been pub 1985).

B) Imipramine Pamoate

1) GENERAL INFORMATION

a) Dosage reduction is recommended in elderly patients since this patient population is reported to have incidence of confusional-type reactions and other central nervous system symptoms while on tricyclic an therapy (Davies et al, 1971). A one-third to one-half reduction in tricyclic antidepressant dosage is sugge An increase in age is correlated with elevated steady-state serum levels of imipramine, desipramine and (Hicks et al, 1981a; Benetello et al, 1990).

b) It is recommended that therapy in geriatric patients is initiated with imipramine hydrochloride tablets (orally per day (Prod Info TOFRANIL(R) tablets, 2005)) since lower dosages should be used. Imipramine may be used once a total daily dosage of 75 mg or higher is established (Prod Info TOFRANIL-PM(R) ca

1.3.5 Dosage Adjustment During Dialysis

A) Imipramine Hydrochloride

1) HEMODIALYSIS

a) No dosage supplementation is required following hemodialysis or peritoneal dialysis (Bennett et al, 19

2) PERITONEAL DIALYSIS

a) No dosage supplementation is required following hemodialysis or peritoneal dialysis (Bennett et al, 19

B) Imipramine Pamoate

1) HEMODIALYSIS

a) No dosage supplementation is required following hemodialysis or peritoneal dialysis (Bennett et al, 19

2) PERITONEAL DIALYSIS

a) No dosage supplementation is required following hemodialysis or peritoneal dialysis (Bennett et al, 19

1.3.6 Dosage in Other Disease States

A) Imipramine Hydrochloride

1) DIABETES

a) Studies in mice have shown that imipramine stimulates insulin secretion in the presence of low glucos whereas it inhibits insulin secretion in the presence of high glucose levels. Imipramine should be adminis to type II diabetic patients (El-Dakhakhny et al, 1996).

B) Imipramine Pamoate

1) DIABETES

a) Studies in mice have shown that imipramine stimulates insulin secretion in the presence of low glucos whereas it inhibits insulin secretion in the presence of high glucose levels. Imipramine should be adminis to type II diabetic patients (El-Dakhakhny et al, 1996).

1.4 Pediatric Dosage

Normal Dosage

Dosage in Renal Failure

Dosage Adjustment During Dialysis

1.4.1 Normal Dosage

Imipramine

Imipramine Hydrochloride

Imipramine Pamoate

1.4.1.A Imipramine

1.4.1.A.1 Anorexia nervosa

See Drug Consult reference: ANOREXIA NERVOSA - DRUG THERAPY

1.4.1.B Imipramine Hydrochloride

1.4.1.B.1 Oral route

Attention deficit hyperactivity disorder, predominantly inattentive type

Depression

Nocturnal enuresis

1.4.1.B.1.a Attention deficit hyperactivity disorder, predominantly inattentive type

1) The dose used ranges from 25 to 100 milligrams/day and tends to be lower than those needed to Children tend to respond within 24 hours after initiating therapy. The monitoring of serum imipramine levels may be useful. The serum levels associated with reported responses have been 10 to 54 nan imipramine and 10 to 65 nanograms/milliliter of desipramine (Hussey & Wright, 1970)(Linnoila et al, 1985; Winsberg et al, 1980).

1.4.1.B.1.b Depression

1) For the treatment of depression in children the initial starting dose of imipramine is 1.5 milligrams given in 1 to 4 divided doses with dosage increased 1 milligram/kilogram every 3 to 4 days. The dail imipramine should not exceed 5 milligrams/kilogram/day, and children receiving doses of 3.5 milligra or more should be closely monitored (Taketomo et al, 1992).

2) Adolescents should initially receive 30 to 40 milligrams/day. Dosages exceeding 100 mg/day are necessary (Prod Info TOFRANIL(R) tablets, 2005).

1.4.1.B.1.c Nocturnal enuresis

1) Children, aged 6 and over, should initially receive 25 milligrams orally, 1 hour before bedtime. If s response does not occur within 1 week, the dose may be increased by 25 milligrams/day: children u receive a maximum daily dose of 50 milligrams and children over 12 may receive 75 milligrams (Pro 1995b; Taketomo et al, 1992).

2) In early-night bedwetters, it is more effective to give the drug earlier and in divided doses, ie, 25 afternoon and then at bedtime (Prod Info Tofranil(R), 1995b).

3) The daily dose of imipramine should not exceed 2.5 milligrams/kilogram, or 50 milligrams at bedt years of age, or 75 milligrams at bedtime if 12 years of age or older (Prod Info Tofranil(R), 1995b; Ta 1992; Denniston et al, 1994).

4) The optimization of imipramine dose in the treatment of enuresis should be guided by clinical res imipramine/desipramine levels. The use of serum imipramine/desipramine levels may help determin with the drug regimen and outliers. The use of a Bayesian dosing method offers no major advantage method used in combination using serum level data. However, the Bayesian method may be useful possible analytical errors, noncompliance, and non-steady state serum concentrations (Tamayo et a

1.4.1.C Imipramine Pamoate

1.4.1.C.1 Oral route

1.4.1.C.1.a Depression

1) Tofranil-PM(R) should not be used in children because of the increased potential for overdose du capsule potency (75 mg, 100 mg, 125 mg and 150 mg capsule) (Prod Info TOFRANIL-PM(R) capsu

1.4.2 Dosage in Renal Failure

A) Imipramine Hydrochloride

1) No specific dosage adjustment is necessary (Bennett et al, 1994).

B) Imipramine Pamoate

1) No specific dosage adjustment is necessary (Bennett et al, 1994).

1.4.4 Dosage Adjustment During Dialysis

A) Imipramine Hydrochloride

1) HEMODIALYSIS

a) No dosage supplementation is required following hemodialysis or peritoneal dialysis (Bennett et al, 19

2) PERITONEAL DIALYSIS

a) No dosage supplementation is required following hemodialysis or peritoneal dialysis (Bennett et al, 19

B) Imipramine Pamoate

1) HEMODIALYSIS

a) No dosage supplementation is required following hemodialysis or peritoneal dialysis (Bennett et al, 19

2) PERITONEAL DIALYSIS

a) No dosage supplementation is required following hemodialysis or peritoneal dialysis (Bennett et al, 19

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset

1) Initial Response

a) Depression, oral: 7 to 21 days (Prod Info Tofranil(R), 1995a); (Greenblatt & Shader, 1975).

2) Peak Response

a) Depression, oral: 4 to 6 weeks (Eisenberg & Asnis, 1986).

2.2 Drug Concentration Levels

A) Therapeutic Drug Concentration

1) Endogenous depression, greater than 200 ng/mL (IMIPRAMINE plus DESIPRAMINE) (Peselow et al, 1983; G 1977).

2) Prepubertal depressive symptoms, 200 to 225 ng/mL (IMIPRAMINE plus DESIPRAMINE), minimum level of 1 (Preskorn et al, 1983).

3) Hyperactivity, 10 to 54 ng/mL (imipramine only) (Linnoila et al, 1979).

4) Enuresis in children, no correlation (Fritz et al, 1994; Manglick & Buchanan, 1992; DeVane et al, 1984).

a) Some studies have shown levels of 80 to 150 ng/mL (IMIPRAMINE plus DESIPRAMINE) to be effective (I 1980a; Fernandez de Gatta et al, 1984).

5) Ventricular premature depolarizations, 74 to 385 ng/mL (IMIPRAMINE plus desipramine) (Giardina et al, 1983)

6) Diabetic neuropathy, less than 100 nmol/L (IMIPRAMINE plus DESIPRAMINE); 400 to 500 nmol/L required in (Sindrup et al, 1990).

B) Time to Peak Concentration

1) Oral: 1 hour (Gram & Christiansen, 1975).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

Extracorporeal Elimination

2.3.1 Absorption

A) Bioavailability

1) Oral, tablet: 94% to 96% (Heck et al, 1979).

a) The bioavailability of IMIPRAMINE from tablet and syrup form is equivalent (Gagnon et al, 1980).

B) Effects of Food

1) None (Abernethy et al, 1984h).

2.3.2 Distribution

A) Distribution Sites

1) Protein Binding

a) 89% (Kristensen, 1983).

1) Patients with severe burns (35% to 85% BSA) exhibit increased binding during the initial convale 20 days) (Martyn et al, 1984).

2) The free fraction is reduced in cancer patients (Schulz & Luttrell, 1982).

3) The free fraction in rheumatoid arthritis patients is slightly lower than in healthy control subjects ((Kristensen, 1985).

2) OTHER DISTRIBUTION SITES

a) Tissue

1) At steady-state, tissue concentrations are greatest in the lung followed by the brain, the adipose (Sallee & Pollock, 1990a).

B) Distribution Kinetics

1) Volume of Distribution
a) 10 to 20 L/kg (Bennett et al, 1994a; Sallee & Pollock, 1990a).

2.3.3 Metabolism
A) Metabolism Sites and Kinetics
1) Liver, extensive (Gram & Christensen, 1975)(Olivier-Martin et al, 1975).
a) First-pass metabolism occurs with extensive metabolism to conjugated and non-conjugated metaboli
et al, 1975).
b) N-demethylation of imipramine is under pharmacogenic control of CYP2C19 (Morinobu et al, 1997).
c) Hydroxylation may become saturated resulting in drug accumulation (Brosen et al, 1986).
B) Metabolites
1) N-desmethyl metabolite (DESIPRAMINE), active (Drayer, 1976).
a) Patients with recurrent episodes of depression have a significantly lower IMIPRAMINE/DESIPRAMIN
those who do not experience recurrences (1.73) (Tollefson et al, 1985).
b) DESIPRAMINE exists in a 0.3 to 15.0 ratio to IMIPRAMINE in plasma (Nagy & Treiber, 1973).
2) 2-hydroxy IMIPRAMINE, active (Buckley, 1975).
a) Reported to depress cardiac contractility in dogs (Buckley, 1975).
3) 2-hydroxydesipramine, active (DeVane & Jusko, 1981).
a) Serum concentration of the hydroxy metabolites may have some relationship to the drug's toxicity (De
DeVane & Jusko, 1981a).

2.3.4 Excretion
A) Kidney
1) Renal Excretion (%)
a) 0.05 to 0.1% (DESIPRAMINE only) (Gram & Christiansen, 1975).
2) IMIPRAMINE metabolites are excreted in urine (Gram et al, 1971; Crammer et al, 1969).

2.3.5 Elimination Half-life
A) Parent Compound
1) ELIMINATION HALF-LIFE
a) 6 to 18 hours (Benetello et al, 1990a; Sutfin et al, 1984).
1) The half-life of IMIPRAMINE in children ranges from 6 to 15 hours (Rancurello, 1985).
2) In elderly patients the serum half-life ranges from 25 to 30 hours (Benetello et al, 1990a; Abernet
3) The terminal half-life of IMIPRAMINE and the active metabolites is 1.5 to 2.0 times longer followi
administration than that observed following oral administration (Sutfin et al, 1984).
B) Metabolites
1) DESIPRAMINE, 12 to 36 hours (Sutfin et al, 1984).
2) 2-hydroxyimipramine, 6 to 18 hours (Sutfin et al, 1984).
3) 2-hydroxydesipramine, 12 to 36 hours (Sutfin et al, 1984).

2.3.6 Extracorporeal Elimination
A) Hemodialysis
1) Dialyzable: No (Prod Info Tofranil(R), 1995a; Asbach & Schuler, 1974; Bailey et al, 1974; Wright & Cooke
B) Peritoneal
1) Dialyzable: No (Prod Info Tofranil(R), 1995a; Asbach & Schuler, 1974; Bailey et al, 1974; Wright & Cooke

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING
1) Imipramine Hydrochloride
a) Oral (Tablet)
Suicidality and Antidepressant Drugs
Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in child
and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. A
the use of imipramine hydrochloride or any other antidepressant in a child, adolescent, or young adult must b

with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressar placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in a older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observ clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of observation and communication with the prescriber. Imipramine hydrochloride is not approved for use in pedi Info imipramine hcl oral tablets, 2007).

2) Imipramine Pamoate

a) Oral (Capsule)

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in child and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. A the use of imipramine pamoate or any other antidepressant in a child, adolescent, or young adult must balanc clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants comp adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged Depression and certain other psychiatric disorders are themselves associated with increases in the risk of su all ages who are started on antidepressant therapy should be monitored appropriately and observed closely f worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the nee observation and communication with the prescriber. Imipramine pamoate is not approved for use in pediatric TOFRANIL-PM(R) oral capsules, 2007).

3.1 Contraindications

A) Imipramine Hydrochloride

1) coadministration with a MAOI or use within 14 days of discontinuing a MAOI; may cause serious reactions (eg crisis, convulsive seizures, death) (Prod Info imipramine hcl oral tablets, 2007)

2) hypersensitivity to dibenzazepines; risk of cross-sensitivity reactions (Prod Info imipramine hcl oral tablets, 200

3) hypersensitivity to imipramine hydrochloride (Prod Info imipramine hcl oral tablets, 2007)

4) myocardial infarction, during the acute recovery period (Prod Info imipramine hcl oral tablets, 2007)

B) Imipramine Pamoate

1) coadministration with an MAOI or use within 14 days of discontinuing an MAOI; may cause serious reactions (crisis, severe convulsive seizures, death) (Prod Info TOFRANIL-PM(R) oral capsules, 2007)

2) hypersensitivity to dibenzazepines; risk of cross-sensitivity reactions (Prod Info TOFRANIL-PM(R) oral capsule

3) hypersensitivity to imipramine pamoate (Prod Info TOFRANIL-PM(R) oral capsules, 2007)

4) myocardial infarction, during the acute recovery period (Prod Info TOFRANIL-PM(R) oral capsules, 2007)

3.2 Precautions

A) Imipramine Hydrochloride

1) suicidal ideation and behavior or worsening depression, increased risk, particularly in children, adolescents, ar during the first few months of therapy or following changes in dosage (Prod Info imipramine hcl oral tablets, 2007)

2) alcohol, excessive use; increased danger of intentional or unintentional imipramine overdose (Prod Info imipra tablets, 2007)

3) bipolar disorder, in patients at risk; increased risk of precipitation of a mixed/manic episode with only antidepre (Prod Info imipramine hcl oral tablets, 2007)

4) cardiovascular disease, current or history; may cause cardiac conduction defects, arrhythmias, congestive hea myocardial infarction, stoke, and tachycardia (Prod Info imipramine hcl oral tablets, 2007)

5) concurrent use with electroshock therapy; may increase hazards of electroshock therapy (Prod Info imipramine 2007)

6) cyclic-type psychiatric disorders, history; may cause mania or hypomania (Prod Info imipramine hcl oral tablets

7) elderly patients; increased risk of developing cardiac abnormalities (Prod Info imipramine hcl oral tablets, 2007

8) excessive exposure to sunlight; may cause photosensitization (Prod Info imipramine hcl oral tablets, 2007)

9) glaucoma, narrow-angle, history of; due to anticholinergic effects of imipramine hydrochloride (Prod Info imipra tablets, 2007)

10) hepatic function, significantly impaired (Prod Info imipramine hcl oral tablets, 2007)

11) hyperthyroidism or concurrent use of thyroid medications; may increase risk of cardiovascular toxicity (Prod I oral tablets, 2007)

12) intraocular pressure, increased; exacerbation of condition due to cholinergic antagonism (Prod Info imipramir 2007)

13) neutrophil depression, pathological, may occur (Prod Info imipramine hcl oral tablets, 2007)

14) renal function, significantly impaired (Prod Info imipramine hcl oral tablets, 2007)

15) schizophrenia; may activate psychosis (Prod Info imipramine hcl oral tablets, 2007)

16) seizure disorder, history; may lower the convulsive threshold (Prod Info imipramine hcl oral tablets, 2007)

17) surgery, elective (Prod Info imipramine hcl oral tablets, 2007)

18) urinary retention, history of; due to anticholinergic effects of imipramine hydrochloride (Prod Info imipramine h 2007)

B) Imipramine Pamoate

1) suicidal ideation and behavior or worsening depression; increased risk, particularly in children, adolescents, ar during the first few months of therapy or following changes in dosage (Prod Info TOFRANIL-PM(R) oral capsules,

2) alcohol, excessive use; increased danger of intentional or unintentional imipramine overdose (Prod Info TOFR

capsules, 2007)
3) bipolar disorder; increased risk of precipitation of a mixed/manic episode with only antidepressant treatment (F
TOFRANIL-PM(R) oral capsules, 2007)
4) cardiovascular disease, current or history; may increase risk of tachycardia, congestive heart failure, cardiac c
arrhythmias, myocardial infarction (MI), and stroke (Prod Info TOFRANIL-PM(R) oral capsules, 2007)
5) concurrent use with electroshock therapy; may increase hazards of electroshock therapy (Prod Info TOFRANI
capsules, 2007)
6) elderly patients; may increase risk of ECG changes (Prod Info TOFRANIL-PM(R) oral capsules, 2007)
7) glaucoma, history of narrow-angle; exacerbation of condition due to cholinergic antagonism (Prod Info TOFRA
capsules, 2007)
8) hyperthyroidism or concurrent use of thyroid medications; may cause cardiac toxicity (Prod Info TOFRANIL-PM
2007)
9) intraocular pressure, increased; exacerbation of condition due to cholinergic antagonism (Prod Info TOFRANIL
capsules, 2007)
10) mania/hypomania; risk of disease activation (Prod Info TOFRANIL-PM(R) oral capsules, 2007)
11) schizophrenia; may activate psychosis (Prod Info TOFRANIL-PM(R) oral capsules, 2007)
12) seizure disorder, history; may lower the convulsive threshold (Prod Info TOFRANIL-PM(R) oral capsules, 200
13) surgery, elective (Prod Info TOFRANIL-PM(R) oral capsules, 2007)
14) urinary retention, history of; exacerbation of condition due to cholinergic antagonism (Prod Info TOFRANIL-P
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

Otic Effects

Psychiatric Effects

Renal Effects

Reproductive Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

Abnormal ECG

Cardiac dysrhythmia

Cardiogenic shock

Cardiomyopathy

Cardiovascular finding

Dead - sudden death

Hypertension

Hypotension

Myocarditis

Vasoconstriction

3.3.1.A Abnormal ECG

1) Summary

a) ECG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include INCF RATE, PROLONGED PR INTERVAL, INTRAVENTRICULAR CONDUCTION DELAYS, INCREASED CC INTERVAL (QTc), and FLATTENED T WAVES (Marshall & Forker, 1982ak).

2) In one comparative study, phenelzine and mianserin were less likely than imipramine or amitriptyline to pr cardiac conduction, in patients without cardiac disease. Prolongation of the PR interval was observed with im amitriptyline but not with phenelzine or mianserin. There was a trend towards prolongation of the QRS compl tricyclics, as well as the QTc interval; no QRS changes were observed with phenelzine or mianserin and ther phenelzine to decrease the QTc interval, whereas mianserin produced no effect on the QTc interval. These d mianserin and phenelzine are less likely than imipramine or amitriptyline to produce heart block in patients wi mianserin appeared to be the least likely of the four agents to induce cardiac conduction abnormalities (McGı

3) Forty-four depressed patients receiving imipramine 3.5 mg/kg/day for 4 weeks demonstrated prolonged P intervals, lowered T-wave amplitude, and increased heart rate compared to a 2 week drug-free period. None developed severe intraventricular conduction abnormalities nor high-grade AV block (Giardina et al, 1979).

4) IMIPRAMINE therapy in the elderly has been associated with increased heart rate and isolated ECG comp (shortening of the QT interval, changes in ST segments, and T waves) (Hayes et al, 1983). Two elderly, depr with preexisting cardiac arrhythmias, had significant increases in PR interval, QRS segment, and QTc interva treatment with oral imipramine 3.5 mg/kg/day. Both patients also had a reduction in atrial and ventricular prer depolarizations during therapy (Bigger et al, 1977b).

3.3.1.B Cardiac dysrhythmia

1) Summary

a) Production and suppression of atrial and ventricular arrhythmias have been reported in patients recei (Marshall & Forker, 1982ak; Raskind et al, 1982; Levin et al, 1985; Williams & Sherter, 1971). Multifocal ventricular contractions occurred in a 62-year-old woman following withdrawal of IMIPRAMINE. The dep preexisting nonspecific intraventricular conduction delay (Regan et al, 1989).

2) ARRHYTHMIAS ADULT

a) A 25-year-old quadriplegic patient receiving oral imipramine 200 mg at bedtime developed a life-threa arrhythmia shortly after achieving therapeutic levels (Levin et al, 1985). This may have occurred because patients frequently have autonomic supersensitivity. Thus the autonomic effects of imipramine may have cardiac arrhythmia.

b) A 37-year-old black male, who was receiving antihypertensive therapy (guanethidine, hydralazine, an experienced cardiac stand still and died following treatment with 25 mg of imipramine TID for 5 days, des discontinuation of all drugs (Williams & Sherter, 1971). In other reports, discontinuation of imipramine us improvement of cardiac arrhythmias although in some cases of AV block, a pacemaker was required (Ra Moorehead & Knox, 1965; Kantor et al, 1975). Arrhythmias, usually supraventricular or VENTRICULAR have also been reported following acute overdose of imipramine (Brown et al, 1972; Lund-Larsen & Sive

c) The cardiovascular effects associated with imipramine therapy were evaluated in 12 men with stable disease who had become depressed following a myocardial infarction or coronary artery bypass-graft su al, 1982). All other drug regimens were kept constant during the course of the study. The mean maximur was 125 mg/day with a mean plasma level (imipramine plus desmethylimipramine) of 194 ng/mL. During imipramine therapy some patients experienced an antiarrhythmic effect from the imipramine, observed a premature ventricular contractions. Other cardiovascular side effects observed in this study included a m PR interval, QT interval, and heart rate, and orthostatic blood pressure changes.

3) ARRHYTHMIAS - PEDIATRIC

a) The cardiovascular status of 23 pediatric patients (ages 5 to 17 years), who were candidates for imipı

(eg, oppositional behavior, conduct disorders, and depression), were evaluated before and after the initia therapy. Each patient was started on 1.5 mg/kg/day which could be increased to a maximum of 5 mg/kg/ divided doses. The follow-up cardiovascular evaluation was conducted 10 to 14 days after clinical improv condition or steady-state serum concentration of between 150 ng/mL and 250 ng/mL. Resting heart rate PR interval lengthened (average 21.2 msec) in all 23 children (p less than 0.001). One child developed M while on imipramine, but this child had a resting PR interval of 176 msec before the initiation of imipramir on these findings the authors support the recommendation that baseline electrocardiogram should be co patients. In addition, patients with a family history of sudden death, a baseline PR interval greater than th for age, or any alterations in intraventricular conduction are candidates for ambulatory Holter monitor wh imipramine therapy (Fletcher et al, 1993).

3.3.1.C Cardiogenic shock

1) An imipramine-provoked paradoxical pheochromocytoma crisis occurred in a 35-year-old male who prese with severe cardiogenic shock after taking two unknown doses of imipramine for headaches. The hypotensio unresponsive to fluids and anatropes (Ferguson, 1994). Subsequent CT scan revealed a pheochromocytoma confirmed with other diagnostic tests. Previous cases reports of the adverse effects of imipramine in patients pheochromocytoma have resulted in hypertensive crises. It appears that imipramine should be avoided or us patients with known or suspected pheochromocytoma.

3.3.1.D Cardiomyopathy

1) CONGESTIVE CARDIOMYOPATHY was reported in a 50-year-old male after receiving tricyclic antidepre period (amitriptyline/perphenazine for 6 months, then imipramine 150 mg/day for 4 years). The patient experi onset of weakness, shortness of breath, and pedal edema over 2 months prior to admission. Evaluation reve and interstitial edema on chest X-ray and EKG revealed bilateral enlargement. The patient improved somewh furosemide and hydralazine but remained severely disabled (functional class 3) (Howland et al, 1983). A caus relationship was not definitely established in this case.

3.3.1.E Cardiovascular finding

1) Summary

a) Some of the following adverse effects have not been associated with imipramine but have occurred w antidepressants. These include MYOCARDIAL INFARCTION, STROKE, HEART BLOCK, precipitation o HEART FAILURE, ECG CHANGES, ORTHOSTATIC HYPOTENSION, HYPERTENSION, and TACHYC Tofranil(R), 1995). ECG effects reported in patients receiving therapeutic doses of tricyclic antidepressar INCREASED HEART RATE, PROLONGED PR INTERVAL, INTRAVENTRICULAR CONDUCTION DEL INCREASED CORRECTED QT INTERVAL (QTc), and FLATTENED T WAVES (Marshall & Forker, 198 shock, vasoconstriction, vasospasm of the hands and feet (ACROCYANOSIS), and myocarditis have ea in 1 to 2 patients (Appelbaum & Kapoor, 1983; Anderson & Morris, 1988; Ferguson, 1994; Morrow et al,

2) Two authors reported that tricyclic antidepressants when given in therapeutic doses are essentially free of cardiovascular effects in patients without cardiovascular disease and may improve the status of patients with arrhythmias (Glassman & Bigger, 1981; Roose et al, 1987a). The development of second degree atrioventric significantly greater in patients with preexisting bundle-branch block than in patients with normal electrocardio hypotension occurred more frequently in patients with conduction abnormalities (Roose et al, 1987a).

3.3.1.F Dead - sudden death

1) According to one study, the use of higher-dose tricyclic antidepressants (TCAs) was associated with an in SUDDEN CARDIAC DEATH, while lower doses did not increase this risk. In a cohort study including 481,744 cases of sudden cardiac death occurring in a community setting, researchers found that compared to non-us of TCAs was associated with a dose-related increase in the risk of sudden cardiac death. For doses lower tha (mg) (amitriptyline or its equivalent), the rate ratio was 0.97 (95% CI, 0.72 to 1.29), however this increased to 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 TCA mg or higher (amitriptyline or its equivalent) had a 41% increased rate of sudden cardiac death (rate ratio, 1.4 1.95). However, TCAs taken in doses of less than 100 mg (amitriptyline or its equivalent) were not associated risk of sudden cardiac death in the entire cohort or in any subgroups, including persons with treated cardiova Use of selective serotonin reuptake inhibitors was not associated with an increased risk of sudden cardiac de 0.95; 95% CI, 0.42 to 2.15) (Ray et al, 2004).

2) An 8-year-old boy died of cardiac arrest that was attributed to imipramine toxicity. Although there were no taken more than the prescribed dose, the dose at time of death (6.9 milligrams/kilogram/day (mg/kg/day)) wa excess of the recommended dose of 5 mg/kg/day. One month after his dose had been raised to 100 mg twice (approximately a year after starting treatment), he complained of his heart hurting and of being dizzy. Two mo dextroamphetamine 5 mg/day was added to his regimen and was raised to 10 mg/day one month later. Two initial cardiac episode, he again complained of his heart hurting. One month later, while playing basketball, he arrest. On autopsy (20 hours after death), highly elevated venous and ventricular levels of imipramine and its desipramine, were the only abnormalities found (Varley, 2000).

3.3.1.G Hypertension

1) A 57-year-old female treated with 150 mg/day of imipramine for 12 days developed hypertension (Hessov pressure before therapy was noted to be 140/90 mmHg and 3 days after initiating imipramine for endogenous blood pressure rose to 150/110 mmHg. Nine days after initiating therapy the blood pressure had risen to 175/

no associated changes in the EKG. Twenty-four hour urinary excretion of noradrenaline-adrenaline and vanill
was normal. Dosage reduction failed to lower blood pressure and so the drug was discontinued. After 3 week
pressure was close to or at controlled levels.
2) Imipramine, 75 mg at bedtime, produced a rise in diastolic blood pressure in 18 enuretic boys (mean age
diastolic pressure increased by 8 +/- 6 mmHG and standing by 10 +/- 12 mmHG (Lake et al, 1979).

3.3.1.H Hypotension

1) Summary: ORTHOSTATIC HYPOTENSION has been reported in patients receiving imipramine (Glassma
Koehl & Wenzel, 1971; Glassman et al, 1979). Elderly depressed patients (n=45) may be at an increased risk
ORTHOSTATIC HYPOTENSION if they have preexisting severe heart disease, impaired left ventricular funct
concurrent cardiovascular medications. Another factor, that requires further assessment, was increased forea
Individuals with increased forearm resistance had a greater frequency of imipramine-induced orthostatic hypo
with normal or low forearm resistance. Patients were receiving therapeutic doses of imipramine (Glassman et
2) A 9-year-old white female treated with imipramine 25 mg twice daily for 9 days developed POSTURAL HY
the fifth day of therapy, the child developed decreased appetite, dry mouth, and constipation. During the sixth
therapy, she developed WEAKNESS, and DIZZINESS upon standing, pallor, diaphoresis, vomiting when pro
rapid heart rate. Physical exam revealed a supine pulse rate of 120/min with supine blood pressure of 100/70
pressure was noted to fall to 80/50 mmHg and pulse rate increased to 170/min, and the patient also became
sweated profusely. Upon standing, blood pressure dropped to 60/0 mmHg with pulse increasing to greater th
association with a SYNCOPAL ATTACK. An ECG revealed a FIRST DEGREE AV BLOCK. Discontinuation o
resulted in improvement of the patient's condition over the 7 day hospital course with subsequent normalizati
& Wenzel, 1971).
3) A study of 44 depressed adults receiving therapeutic doses of imipramine (average 245 mg/day in males,
females) demonstrated a significant decrease in blood pressure upon standing; average decrease during imi
was 26.1 mmHg during therapy and 10.9 mmHg prior to therapy. This decrease was independent of age, pla
preexisting heart rate (Glassman et al, 1979).
4) Forty-five elderly patients (mean age 63.6) were initially treated with 25 mg/day imipramine with dose bein
mg/day (Branconnier et al, 1983). Cardiovascular function was assessed 3 times during the course of the stu
day 7 and day 28). On day 7 and day 28 the patient exhibited a significant orthostatic change in diastolic bloo
increase in heart rate compared to pretreatment.
5) The cardiovascular effects of imipramine, doxepin, and placebo were compared in 24 depressed patients
The tricyclic antidepressants had no effects on left ventricular ejection fraction but did cause orthostatic chan
pressure. The imipramine therapy was associated with a reduction in premature ventricular contractions, whi
consistently seen in the placebo and doxepin treated patients. Based on the results of this study it would app
patients with preexisting heart disease, without any severe impairment of myocardial performance, can be tre
imipramine or doxepin without an adverse effect on ventricular rhythm or hemodynamic function (Veith et al,

3.3.1.I Myocarditis

1) A 54-year-old female developed myocarditis and hepatitis after restarting imipramine therapy. The patient
later secondary to the myocarditis. It could not be determined if this rare hypersensitivity reaction was directly
imipramine, its desipramine metabolite, or the combination of imipramine and desipramine (Morrow et al, 198

3.3.1.J Vasoconstriction

1) A 37-year-old female, developed severe and prolonged episodes of vasospasm of the hands within 10 da
discontinuation of her amitriptyline therapy and the initiation of 150 mg/day imipramine. Vasospasm reoccurre
rechallenge (Appelbaum & Kapoor, 1983).
2) ACROCYANOSIS of the hands and feet occurred in an 11-year-old girl following imipramine therapy (25 r
approximately 10 weeks) for nocturnal enuresis (Anderson & Morris, 1988). The patient developed initial sym
after initiation of treatment (painful swelling of metacarpophalangeal joints of the feet). Examination after 10 v
revealed cold, blue and moist hands and feet which blanched on pressure. LIVEDO RETICULARIS was obse
forearms. Withdrawal of imipramine resulted in resolution of symptoms in 3 days.

3.3.2 Dermatologic Effects

3.3.2.A Discoloration of skin

1) HYPERPIGMENTATION was described in 4 women (53 to 75 years old) receiving imipramine 150 to 375
years (Ming et al, 1999). Hyperpigmentation began after 2 to 11 years of use. Coloration was described as sl
women and as dark brown or golden brown in the other 2. The site of the reaction was in the face, chest, arm
woman also had a darkening of her iris. The pigmentation disappeared over 6 to 12 months in 2 of the wome
discontinue imipramine.
2) A 46-year-old male was treated with imipramine 75 to 100 mg three times/day for 9 years and developed
pigmentation of his face, neck, and fingers (Hare, 1970). Characteristically the skin of the nose and ears was
the patient had normal skin folds with no ophthalmological disturbances.
3) A 48-year-old white female developed a slate-gray discoloration in sun-exposed areas, predominately her
both hands, and eyes, after receiving imipramine 150 mg/day for five years (Hashimoto et al, 1991). These di
became lighter after discontinuation of the imipramine therapy and returned to normal within one year.

3.3.3 Endocrine/Metabolic Effects

Acute intermittent porphyria

Anticholinergic adverse reaction

Galactorrhea

Hyperthyroidism

Hypoglycemia

Syndrome of inappropriate antidiuretic hormone secretion

3.3.3.A Acute intermittent porphyria

See Drug Consult reference: DRUGS CONSIDERED UNSAFE- ACUTE PORPHYRIAS

3.3.3.B Anticholinergic adverse reaction

1) IMIPRAMINE HYDROCHLORIDE may produce a slightly higher incidence of anticholinergic side effects t
salt due to higher peak concentrations with this salt form; however, this has not been proven. Any dissimilarit
when changed from one salt form to the other is most likely psychological, and is probably due to changes in
between the two products (ie hydrochloride salt - tablet, pamoate salt - capsule (Prod Info Tofranil PM(R), 19
Tofranil(R), 1990; Pers Comm, 1982a).

3.3.3.C Galactorrhea

1) A 34-year-old female treated with imipramine 75 to 100 mg/day for 6 months developed spontaneous gala
Discontinuation of imipramine resulted in subsiding of the LACTATION which recurred when therapy with imi
resumed. During imipramine therapy, it was noted that the patient had low levels of serum serotonin and urin
The author postulated that the mechanism for the galactorrhea was similar to that seen with reserpine which
of the normal hypothalamic inhibition of pituitary prolactin secretion (Klein, 1964).

3.3.3.D Hyperthyroidism

1) A case of a 9.5-year-old female was treated with 25 mg/day oral imipramine for enuresis and also receive
thyroid therapy; the patient demonstrated increased restlessness, hyperkineticism, nervousness, easy fatigab
and warm skin. Physical exam revealed a resting heart rate of 120 beats/min with deep tendon reflexes noted
without clonus. Lab values revealed a thyroxine level of 9.2 mg/dL and a triiodothyronine uptake of 31.9%. EI
sinus tachycardia with ST-T wave changes and basal metabolic rate was elevated by 33%. Discontinuing imi
continuing the same dose of thyroid resulted in the child becoming euthyroid (Colantonio & Orson, 1974).

3.3.3.E Hypoglycemia

1) A 50-year-old male treated with 200 mg/d of imipramine developed severe hypoglycemia (Shrivastava & E
Six days after starting imipramine therapy the patient complained of fatigue, dizziness, loss of weight, and inc
On laboratory examination, he was found to have a nonfasting serum glucose of 57 mg/dL with all other lab v
normal limits. Imipramine therapy was discontinued and his serum glucose returned to 79 mg/dL and sympto
Following an unintentional rechallenge the man began complaining of weakness and dizziness one week late
serum glucose was 34 mg/dL. Following discontinuation of the imipramine therapy his serum glucose returne
2) Imipramine may increase an individual's sensitivity to insulin-induced hypoglycemia, but does not affect th
regulatory response of ACTH and cortisol (Kathol et al, 1991).

3.3.3.F Syndrome of inappropriate antidiuretic hormone secretion

1) Imipramine was associated with SIADH in a 78-year-old woman during therapy for major depression. The
imipramine 25 to 50 mg orally daily for approximately 3 months prior to admission. HYPONATREMIA was ob
admission and subsided during a 9 day interval without imipramine therapy. The patient subsequently develo
bupropion and upon rechallenge with imipramine (Liskin et al, 1984).
2) A 73-year-old thin and frail white female was admitted to a psychiatric unit for evaluation after deliberate ir
cleaning fluid (Colgate, 1993). She was diagnosed with severe depression and started on paroxetine therapy
the paroxetine was discontinued because the depression was getting worse. A single session of electroconvu
tried and then she was started on imipramine syrup, 25 mg twice daily. The dose was increased to 125 mg pe
divided doses, and diazepam was used in doses up to 10 mg/day to control her agitation. Over the next few v
condition improved, but she did fall and sustained a fractured left femur neck. Her mental condition continued
her mobility deteriorated and she suffered several more falls. Physical examination revealed a profound orthc
blood pressure (40 mmHg) and she had hyponatremia (124 mmol/l) and a low serum osmolality (266 mOsm/
intoxication was ruled out and a diagnosis of inappropriate secretion of antidiuretic hormone was made. The i
was then held. Over the next ten days her serum sodium levels returned to the normal range.

3.3.4 Gastrointestinal Effects

Colitis

Xerostomia

3.3.4.A Colitis

1) ISCHEMIC COLITIS, requiring surgical intervention, has been reported in one patient following the ingesti quantity of imipramine (Patel et al, 1992). The individual was a 38-year-old female with a past medical history hospitalized following an ingestion of unspecified quantity of imipramine. Her serum imipramine level was 1,0 micrograms/milliliter. Over the next few days her abdomen became increasingly distended with rebound tend absence of bowel sounds. Laparotomy revealed a necrotic ascending and transverse colon which was subse and the patient's condition improved.

3.3.4.B Xerostomia

1) XEROSTOMIA is frequently associated with imipramine therapy in usual therapeutic doses (150 mg/day). mouth is often associated with gum shrinkage, inflammation of the oral cavity, stomatitis, cracking of the lips mouth, pseudomembrane formation, hairy tongue with white or black or bald beefy red tongue, ill-fitting dentu and oral moniliasis. Discontinuation of the drug and/or treatment with pilocarpine (5 mg four times/day) usuall increase of salivation (Pollack, 1964; Winer & Bahn, 1967).

2) Imipramine, 75 mg every day, given to 12 volunteers in a placebo controlled study caused a significant re secretion rate (Sheth et al, 1979a).

3) A comparison of 5 different antidepressants on salivary flow reveals that amitriptyline and doxepin had the salivation and desipramine the least (Blackwell et al, 1980). Imipramine and nortriptyline were intermediate a in their effects.

3.3.5 Hematologic Effects

3.3.5.A Hematology finding

1) Summary

a) Some of the following adverse effects have not been associated with imipramine but have occurred w antidepressants. These include BONE MARROW DEPRESSION including AGRANULOCYTOSIS, EOS PURPURA, and THROMBOCYTOPENIA (Prod Info Tofranil(R), 1995). IMIPRAMINE-induced agranuloc about 10 cases have been reported (Gravenor et al, 1986).

2) A 59-year-old white female treated with imipramine 50 mg three times per day for 2 months developed ag which was fatal. The patient died 2 weeks after discontinuing imipramine (Hnatko, 1965).

3) A 55-year-old male treated with 25 mg/day of IMIPRAMINE developed asymptomatic eosinophilia. The pa cell count was noted to be 19,650 which gradually decreased in association with an eosinophil count of 693 (300). All through the course the patient remained asymptomatic and well. Following discontinuation of the dru recovered with the eosinophilia subsiding (Penick & Carrier, 1967).

3.3.6 Hepatic Effects

3.3.6.A Hepatotoxicity

1) Summary

a) Hepatotoxicity induced by imipramine (hepatic necrosis) occurs infrequently. The mechanism by whic reaction occurs in unknown, but may be a hypersensitivity reaction. Elevations in bilirubin, alkaline phosp transaminases, and other liver function tests can occur within one to two weeks of the start of therapy. C include pruritus, jaundice, icterus, rashes (erythematous maculopapular, desquamation, xanthelasma an and splenomegaly. Most cases improve following discontinuation of therapy. However, a few patients co severe that they either died or required a liver transplant (Hynes, 1965; Powell et al, 1968; Grace, 1970; 1982; Morrow et al, 1989; Schaefer et al, 1990).

2) High, single-daily dosing of imipramine may be more hazardous to the liver than divided doses. A 33-year receiving 300 mg (6 mg/kg) of imipramine at bedtime along with thiothixene 10 mg and developed an elevatic (Moskovitz et al, 1982). Prior to the hospitalization for worsening mental status she had been receiving 200 to imipramine in divided doses. On day 26 of the single daily dosage of imipramine therapy, liver function tests following subjective complaints by the patient. The test revealed an elevation in liver enzymes. No baseline li were obtained at the time of hospitalization, but a previous liver function test taken one month after the initiati therapy was normal. Antihepatitis A and B antibodies and HAA tests were negative. The imipramine therapy and the thiothixene therapy was continued. Two weeks following the discontinuation of the imipramine therap returned to normal.

3) A 11-year-old boy developed fulminant HEPATIC FAILURE seven days after being started on imipramine for enuresis (Schaefer et al, 1990). Histologically, the liver showed massive HEPATOCELLULAR NECROSIS proliferation and loss of parenchymal volume. Mild amounts of acute and chronic inflammation were found in Hepatocellular necrosis occurred predominantly in the pericentral areas with focal hemorrhage encircling the damage was so extensive a liver transplant was required.

4) A rare hypersensitivity reaction to imipramine is the development of myocarditis and HEPATITIS (Morrow

3.3.7 Immunologic Effects

3.3.7.A Cross sensitivity reaction

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

3.3.8 Musculoskeletal Effects

Fracture of bone, Nonvertebral

Hip fracture

Myasthenia gravis

3.3.8.A Fracture of bone, Nonvertebral

1) In a prospective, population-based, cohort study (n=7983) with a mean follow-up of 8.4 years, there was a nonvertebral fracture in adult participants older than 55 years of age (mean age of 77.5 years) who were curr tricyclic antidepressant (TCA), including amitriptyline, clomipramine, dosulepine, doxepine, imipramine, mapr nortriptyline, and opipramol, compared to those who were not exposed to antidepressants. Current TCA use with an increased risk of nonvertebral fracture (hazard ratio (HR), 1.6; 95% confidence interval (CI), 1.08 to 2 with no antidepressant use. Current TCA use was also associated with an increased risk of nonvertebral frac CI, 1.02 to 2.5) compared with past antidepressant use (n=1217). Duration of TCA use of greater than 6 mon associated with an increased risk of fractures when compared with no antidepressant use and with past antid Fractures of the hip (most frequent), wrist, humerus, and pelvis were reported (Ziere et al, 2008).

3.3.8.B Hip fracture

1) An increased incidence of hip fracture was reported in elderly patients receiving psychotropic agents. This control evaluation of 1021 patients with hip fractures and 5606 control patients. An increased risk of hip fractu with the use of hypnotic/anxiolytic agents with a long elimination half-life (greater than 24 hours), tricyclic anti antipsychotic agents. Current users were defined as subjects who had received a prescription in the 30 day p admission date for the initial hospitalization. The long half-life hypnotic/anxiolytic agents studied were lorazep chlordiazepoxide, and barbiturates (excluding phenobarbital). The tricyclic antidepressants included amitripty imipramine; antipsychotic agents evaluated were thioridazine, haloperidol, chlorpromazine, and perphenazine contrast, shorter-acting hypnotic/anxiolytic agents (half-life of 24 hours or less) were not associated with an in fracture in these patients. The most frequently used agents in this category were diphenhydramine, hydroxyz hydrate. The increased risk of hip fracture observed in this study was directly related to the doses of the drug confounding by dementia did not alter the results. Additional studies are needed to confirm these results in th populations and to evaluate the effects of other psychotropic drugs that have less pronounced sedative effect 1987).

3.3.8.C Myasthenia gravis

See Drug Consult reference: DRUG-INDUCED MYASTHENIA GRAVIS

3.3.9 Neurologic Effects

Akathisia

Central nervous system finding

Cerebral ischemia

Gilles de la Tourette's syndrome

Impaired psychomotor performance

Myoclonus

Seizure

Suicidal thoughts

Tremor

3.3.9.A Akathisia

1) One patient developed akathisia while receiving imipramine therapy and 4 others developed the same wh desipramine, trazodone, or tranylcypromine. The imipramine patient was a 54-year-old female who was treat and imipramine for depression. After titrating the dose of imipramine to 150 mg/day, the patient complained o feeling in her legs and the inability to remain still. Propranolol 10 mg three times daily was started, and the sy completely within several hours of the first dose. Discontinuation of the propranolol resulted in a recurrence o within 24 hours (Zubenko et al, 1987).

3.3.9.B Central nervous system finding

1) Summary

a) Some of the following adverse effects have not been associated with imipramine but have occurred w antidepressants. These include NUMBNESS, TINGLING, PARESTHESIAS of the extremities, ATAXIA, T EXTRAPYRAMIDAL SYMPTOMS, PERIPHERAL NEUROPATHY, SEIZURES, EEG CHANGES, CONF STATES with HALLUCINATIONS especially in the elderly, DISORIENTATION, DELUSIONS, FORGETF ANXIETY, RESTLESSNESS, AGITATION, INSOMNIA, NIGHTMARES, HYPOMANIA, and exacerbation (Prod Info Tofranil(R), 1995; Davies et al, 1971). PARANOIA, AGGRESSIVE BEHAVIOR (Rampling, 19 Petti, 1979), psychomotor impairment (Clayton et al, 1977a), delirium (Godwin, 1983), myoclonus (Garve 1987), akathisia (Zubenko et al, 1987), and Tourette's syndrome (Parraga & Cochran, 1992) have been use of imipramine; SUICIDAL IDEATION is a potential side effect of imipramine (Prod Info Tofranil(R), 19 1992). LEARNING IMPAIRMENT in a social context is NOT seen with tricyclic antidepressants (Gillis, 19

3.3.9.C Cerebral ischemia

1) A 59-year-old male treated with usual therapeutic doses of imipramine for mild depression developed cere attacks (Brechter, 1968). Two weeks after starting drug therapy PARESTHESIA over the entire left side of his with short attacks of SPEECH DISTURBANCES. The drug was discontinued but PARESIS continued to prog involvement and total stenosis of the medial cerebral artery. Although no definite cause and effect relationshi the author postulated that tricyclic antidepressants may cause recurrent ischemic attacks in persons with par the cerebral arteries.

3.3.9.D Gilles de la Tourette's syndrome

1) Two children experienced tics or Tourette's syndrome that may have been precipitated by imipramine (Pa 1992). Motor (throat clearing, head shaking) and vocal tics (stuttering, echolalia, palilalia, profane utterances) boys two weeks after treatment with imipramine (75 to 100 mg/day) for attention deficit hyperactivity disorder concurrent depression. The tics remained despite discontinuation of the imipramine. Remission of the tics wa through the use of haloperidol and thioridazine.

3.3.9.E Impaired psychomotor performance

1) A placebo-controlled study of healthy male volunteers demonstrated DETERIORATION OF DRIVING SKI received 25 mg imipramine three times a day compared with 10 who received placebo and 10 who were cont 1977a).

3.3.9.F Myoclonus

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

3.3.9.G Seizure

1) Summary

a) Imipramine has been shown to decrease the convulsive threshold (Misurec & Nahunek, 1969) and ha documented to cause seizure disorders including the occurrence of GRAND MAL TONIC-CLONIC SEIZ with or without seizure histories. Three reports have cited cases in pediatric patients (Fromm et al, 1972; Petti & Campbell, 1975b). However, cases of grand mal seizures occurring in younger adults (30 years o reported (Fromm et al, 1972; Kaufmann, 1974). Discontinuation of the tricyclic antidepressant and/or inst anticonvulsant therapy usually results in control of seizures.

2) A 25-year-old female that had been treated with 4 weeks therapy of imipramine (150 mg/day) and cloraze developed a seizure following the abrupt discontinuation of clorazepate therapy (Simons, 1983). Since the se solely contributed to the abrupt discontinuation of the clorazepate therapy, the author feels that all patients re prescriptions for antidepressant and benzodiazepines should avoid the abrupt discontinuation of the benzodi See Drug Consult reference: COMPARATIVE INCIDENCE OF SEIZURES FROM ANTIDEPRESSANTS

3.3.9.H Suicidal thoughts

1) Adult and pediatric patients being treated with antidepressants for major depressive disorder who experie anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psycho restlessness), hypomania, or mania may be at risk of suicidal ideation and behavior (SUICIDALITY). This sar to treating patients with other psychiatric and nonpsychiatric disorders. If these symptoms are observed, ther reevaluated and it may be necessary to discontinue medications when symptoms are severe, sudden in onse of the patient's initial symptoms. Patients and their caregivers should be provided with the Medication Guide f this drug (Anon, 2004).

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

3.3.9.I Tremor

1) Imipramine-induced TREMOR occurred in a 61-year-old male. Following doses of 75 mg daily for 3 days, developed a marked action tremor of the upper extremities which was smooth and rhythmic (6 to 9 cycles pe interfered with routine activities. The tremor did not worsen when the dose of imipramine was increased to 15 Propranolol (20 mg twice a day) produced attenuation of the tremor within 25 to 48 hours (Kronfol et al, 1983

2) Some patients with panic disorder imipramine therapy may develop a jitteriness syndrome (Yeragani et al condition is characterized by jitteriness, restlessness, trouble sitting still, insomnia, increased energy, increas possible decreased serum iron level. Whether iron supplementation will prevent or treat this syndrome remai

3.3.11 Otic Effects

3.3.11.A Ototoxicity

1) TINNITUS has been reported in 4 patients: a 37-year-old female, a 30-year-old fem old male, all receiving 50 to 150 mg imipramine daily. Tinnitus disappeared when the imipramine dose was re females and the male required a change in therapy (Racy & Ward-Racy, 1980).

2) Five additional reports of tinnitus secondary to imipramine therapy have been published (Tandon et al, 19 had no history of tinnitus or other otologic abnormalities. All patients developed tinnitus during the second or treatment, with doses of 150 to 250 mg daily of imipramine (combined plasma imipramine-desipramine levels 450 ng/mL). The tinnitus subsided spontaneously within 2 to 4 weeks without any specific treatment in all pat imipramine was maintained in 3 patients and increased in 2). Based upon a chart review of 475 patients treat University of Michigan Medical Center, the authors indicate that approximately 1% of patients receiving tricyc develop tinnitus.

3) A 38 year-old depressed female develop ringing in her ears one week after the dose of imipramine was in mg/day (Laird & Lydiard, 1989). She had no history of ear problems and denied using aspirin or other salicyla medication was continued since the tinnitus was only mildly bothersome and no abnormalities could be found physical examination. The dose of imipramine was increased to 150 mg/day during the second week. The tin approximately six weeks and then diminished without any changes in drug therapy.

3.3.12 Psychiatric Effects

Aggressive behavior

Delirium

Psychotic disorder

Sleep disorder

3.3.12.A Aggressive behavior

1) A 26-year-old male treated with a single oral dose of imipramine for cataplexy developed a feeling of aggr increased intensely over the next half hour with the patient struggling to keep control. The patient was noted staggering, and feelings of drunkenness. It was noted that the patient had previously received diazepam and (Rampling, 1976). In addition, increased aggression was reported in 2 depressed boys, ages 12 and 6 years, therapy (Pallmeyer & Petti, 1979).

2) Four cases of rapid onset untoward aggressiveness was associated with the use of tricyclic antidepressar cases the aggressive behavior coincided with the reintroduction of the tricyclic antidepressant. The mechanis paradoxical response of rapid onset and qualitative characteristics of their reaction are consistent with a prob in the reticular formation which is the rational for their usefulness in cataplexy (Rampling, 1978).

3.3.12.B Delirium

1) Summary

a) Risk factors for the development of tricyclic-induced delirium include high tricyclic serum concentratio organic brain disease, and concomitant neuroleptic therapy (Godwin, 1983).

2) A 31-year-old hospitalized female developed delirium during imipramine therapy; the patient had no know (Godwin, 1983). Initially she presented with a hypomanic reaction (characterized by restlessness, hyperactivi lability of mood, and insomnia) that later developed into the delirium reaction (disorientation to time and place speech, periods of blank stares, periods of unresponsiveness, visual distortions, hallucinations) while on stan imipramine therapy. Plasma imipramine concentrations were in the low end of the therapeutic range. Thus, in delirium may occur in some patients as an idiosyncratic reaction unrelated to imipramine serum concentratior

3.3.12.C Psychotic disorder

1) Summary

a) Psychotic reactions following doses of imipramine ranging from 75 to 600 mg/day have been reportec included DISORIENTATION, AGITATION, CONFUSION, RESTLESSNESS, INSOMNIA, tremor, ATAXI HALLUCINATIONS, PARANOIA and other abnormal manifestations. Some data suggests that these effe more frequently in elderly patients and/or those receiving higher doses. Discontinuation of the drug resul and disappearance of the symptoms (Kane & Keeler, 1964; Ananth, 1973; Wilson et al, 1974; Schulterbr Prod Info Tofranil(R), 1995).

2) A high number of geriatric patients on tricyclic antidepressant therapy have developed confusional reactio as restlessness, sleep disturbances, FORGETFULNESS, agitation, disorientation, and DELUSIONS. This rea appear to be dose-related and is possibly due to the central anticholinergic effects of these drugs. These epis reported to develop within the first 2 weeks of drug therapy and are usually self-limiting, lasting from 3 to 20 d reduction of dosage or discontinuation of the drug appears to result in resolution of these confusional reactior (Davies et al, 1971).

3.3.12.D Sleep disorder

1) Imipramine can markedly suppress REM sleep (REM time, REM activity, and number of REM periods) in adults (Shain et al, 1990).

3.3.13 Renal Effects

3.3.13.A Nephrotoxicity

1) A 65-year-old white male was treated with doses of up to 100 mg three times/day of imipramine for 24 day developed RENAL DAMAGE (Sathananthan & Gershon, 1973c). The patient developed symptoms of anorex confusion, disorientation, and tremulousness in association with elevated BUN (80 mg/dL) and creatinine (2.5 Urine output fell to 725 mL/day despite a fluid intake of approximately 2.5 L. Discontinuation of imipramine re improvement of this clinical condition and abnormal laboratory values returning to normal by the third day.

3.3.14 Reproductive Effects

3.3.14.A Sexual dysfunction

1) ERECTILE DYSFUNCTION and EJACULATORY DELAY or loss has been reported in depressed and nor minimum daily dose of 75 mg. Pain on ejaculation (Couper-Smartt & Rodham, 1973; Simpson et al, 1965; Gr Aizenberg et al, 1991) and loss of libido (Jenkins et al, 1976) as well as increased libido has been reported (S 1965).

2) The occurrence of sexual dysfunction associated with antidepressant therapy is frequent. Decreases in se occurs in 8% of males and 16% of females treated with placebo, 80% of males and 57% of females treated w and 50% of males and 27% of females treated with imipramine (Harrison et al, 1985). Sexual dysfunctions re DECREASE IN LIBIDO, excitement, and orgasm and a delay in ejaculation. Similar results have been reporte by the same group of investigators (Harrison et al, 1986).

3) Other investigators feel that long-term treatment with imipramine has no negative effect on sexual functior 1994). Instead they feel that the presence of depressive symptoms is associated with diminished libido or dec pleasure. An evaluation of 90 patients with a major depressive disorder treated with imipramine found no rela imipramine and sexual function in the total group or the females alone. The number of males included in the s inadequate to draw any conclusions regarding population.

4) A 51-year-old male was treated with an initial dose of 75 mg/day which was reduced to oral imipramine 25

weeks and developed erectile IMPOTENCE at the higher dose. Potency rapidly returned upon decreasing the 25 mg/day (Greenberg, 1965).
5) ANORGASMIA has been reported in a woman treated with imipramine therapy and disappeared when de was substituted for the imipramine (Sovner, 1983).
See Drug Consult reference: DRUG-INDUCED SEXUAL DYSFUNCTION

3.3.15 Respiratory Effects

3.3.15.A Acute respiratory distress syndrome

1) A 15-year-old was admitted to the emergency department following the ingestion of 5 grams (150 mg/kg) approximately 45 minutes prior to arrival (Flaherty et al, 1986). Within 5 hours of ingestion the patient develop hypoxemia, increased QS/QT, and decreased lung compliance. At that time a diagnosis of adult respiratory d (ARDS) was made. Positive end-expiratory pressure (PEEP) resulted in an improvement in lung compliance, shunting. Whether or not the development of adult respiratory distress syndrome ARDS was a direct result of overdose or the development of bradycardia, hypoxemia, metabolic acidosis, hypotension or physostigmine t unknown.

3.3.16 Other

Drug tolerance - finding

Withdrawal sign or symptom

3.3.16.A Drug tolerance - finding

1) Tolerance to the therapeutic effects of IMIPRAMINE therapy has been reported in a small number of patie Baldessarini, 1985). Usually these patients initially respond to therapy and then weeks to months later they re continued antidepressant therapy. Remission can usually be regained by increasing the dose of the medicati medication. The exact mechanism for the development of this tolerance is not known.

3.3.16.B Withdrawal sign or symptom

1) Withdrawal symptoms have been associated with the discontinuation of tricyclic antidepressant therapy a to 55% of the patients. These symptoms frequently occur within the first 24 to 48 hours after cessation of ther withdrawal period is characterized by general somatic malaise (muscle aches, coryza, excessive sweating), g (nausea, vomiting, diarrhea, and abdominal pain), motor restlessness, and/or neuropsychiatric symptoms (dr irritability, agitation, and recurrence of depressed mood). Restarting imipramine therapy generally improves th prevent the occurrence of this withdrawal reaction, the imipramine therapy should be withdrawn gradually, wh (Sathananthan & Gershon, 1973a; Stern & Mendels, 1980; Petti & Law, 1981; Shrivastava & Itil, 1985; Prod I 1995).
2) Children withdrawn from high-dose imipramine therapy over 3 to 10 days may develop a withdrawal syndr 1981). The syndrome is characterized by nausea, vomiting, decreased appetite, tearfulness, headaches, agit It is thought that this withdrawal syndrome may be the result of a cholinergic rebound following the discontinu anticholinergic medications. Extending the duration of the tapering period may be helpful in avoiding the occu syndrome, but there is no clinical evidence to support this theory.
3) A 53-year-old woman, with a 25-year history of unipolar depression but no evidence of bipolar illness, dev cycling bipolar disorder following abrupt discontinuation of her long-term tricyclic antidepressant therapy (Jon The bipolar illness presented as hypomania 2 days after stopping drug therapy. The hypomanic period was fo depression and subsequent fluctuation between mania and depression, each lasting from 2 to 8 weeks.
4) Multifocal premature ventricular contractions (PVCs) occurred in a 62-year-old woman following withdrawa The depressed women had preexisting nonspecific intraventricular conduction delay (Regan et al, 1989). Imip daily) was tapered over a 4-day period, and then doxepin was initiated at a dose of 50 mg at bedtime. PVCs a observed the day following discontinuance of imipramine. Reinitiation of imipramine therapy (100 mg daily) pr sinus rhythm with only occasional uniform PVCs, and no couplets, multiforms, runs, or pauses. It was felt tha drug resulted in rebound irritability with resultant aberrant rhythms. Tricyclic antidepressants should be withdr with frequent EKG monitoring, in patients with a preexisting conduction defects. In patients with no suspected defect, monitoring for signs of ectopy should be undertaken during withdrawal.
5) Withdrawal of imipramine therapy used to treat postpsychotic depression after six months in six schizophr resulted in DEPRESSIVE RELAPSES (Siris et al, 1989). All six patients had benefit from the initial addition o their fluphenazine decanoate and benztropine therapy. After six months the dose of imipramine was decreas weekly intervals without the patient knowledge until it was discontinued. All six patients had experienced recu depressive-like state and three manifested a coincident exacerbation of psychotic symptoms. While only one maintained on all three drugs experienced a depressive-like relapse.

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy
1) Australian Drug Evaluation Committee's (ADEC) Category: C (Batagol, 1996)

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

See Drug Consult reference: PREGNANCY RISK CATEGORIES

2) Crosses Placenta: Yes

3) Clinical Management

a) Due to reported teratogenic effects, use of imipramine during pregnancy should be avoided if possible, es first trimester. The dangers of failure to treat major depression, however, are obvious, and in each case these weighed against the potential for teratogenic effects. If pregnancy occurs during treatment, the patient should possible consequences to the fetus.

4) Literature Reports

a) Imipramine has been associated with teratogenic effects, however, a clear causal relationship has not bee the large cohort study (Heinonen et al, 1977), of 19 mother-child pairs exposed to imipramine in the first trime malformations were reported, suggesting an increased risk of teratogenic effects.

b) A review of the Finnish register of congenital malformations for 1964 to 1972 revealed 3 possible cases of effects (2 cleft lips, 1 CNS anomaly) that were related to the use of an imipramine/chloropyramine combinatio Heikkila & Saxen, 1973).

c) Neonatal intoxication and withdrawal symptoms may be observed with maternal use of imipramine. Sympt the neonate include cyanosis, respiratory distress, vasomotor instability, irritability, hypokinesia, convulsions, increased respiratory rate, autonomic dysfunction, hypoactivity, and belly dance movements of the abdomen (Anon, 1983; Shrand, 1982).

d) Several infants have been described who developed transient respiratory and neurological symptoms sho possibly in relation to maternal imipramine. Of 3 infants whose mothers had used imipramine throughout the infants developed postnatal symptoms of irritability, restlessness, inconsolable crying, tachypnea, cyanosis, h fasciculations, and tremors. One infant developed signs of heart failure despite a normal electrocardiogram, a to 180 per minute, and absence of a congenital cardiac malformation. One infant experienced laryngeal spas difficulties (Eggermont et al, 1972).

e) Based on data collected through the Motherisk Program, there appear to be no differences in cognitive fu temperament and general behavior in children exposed to imipramine throughout gestation when compared t et al, 2002). However, among infants who were exposed to either fluoxetine or tricyclic antidepressants thoug those born to mothers with uncontrolled depressive symptoms showed lower cognitive and language achieve born to mothers who were well-controlled (Nulman et al, 2002).

B) Breastfeeding

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

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

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

3) Clinical Management

a) Imipramine and its metabolite, desipramine, appear in breast milk in low concentrations. The potential for the nursing infant has not been evaluated. When the maternal dose is high, exposure of the infant to the drug minimized by limiting the number of feeds per day (Bennett, 1996).

4) Literature Reports

a) The amount of imipramine and desipramine available to an infant is small. The amount of imipramine mea milk was 4 to 29 ng/mL and desipramine was 17 to 35 ng/mL; a milk:plasma ratio of 1 has been suggested (S 1979).

5) Drug Levels in Breastmilk

a) Parent Drug

1) Milk to Maternal Plasma Ratio

a) 1 (Briggs et al, 1998)

b) Active Metabolites

1) desipramine (Sallee & Pollock, 1990)

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Food Combinations

Drug-Tobacco Combinations

Intravenous Admixtures

3.5.1 Drug-Drug Combinations

Acecainide

Acenocoumarol

Ajmaline

Alprazolam

Amiodarone

Amisulpride

Amobarbital

Amphetamine

Amprenavir

Anisindione

Aprindine

Aprobarbital

Arbutamine

Arformoterol

Arsenic Trioxide

Astemizole

Atazanavir

Atomoxetine

Azimilide

Belladonna

Belladonna Alkaloids

Bepridil

Bethanidine

Bretylium

Bupropion

Butabarbital

Butalbital

Butalbital

Cannabis

Carbamazepine

Chloral Hydrate

Chloroquine

Chlorotrianisene

Cimetidine

Cisapride

Citalopram

Clarithromycin

Clonidine

Clorgyline

Conjugated Estrogens

Darifenacin

Dexfenfluramine

Dexmethylphenidate

Dextroamphetamine

Dicumarol

Dienestrol

Diethylpropion

Diethylstilbestrol

Diltiazem

Disopyramide

Disulfiram

Dofetilide

Dolasetron

Droperidol

Duloxetine

Enflurane

Epinephrine

Erythromycin

Esterified Estrogens

Estradiol

Estriol

Estrone

Estropipate

Eterobarb

Ethinyl Estradiol

Etilefrine

Fenfluramine

Fenfluramine

Flecainide

Fluconazole

Fluoxetine

Fluvoxamine

Formoterol

Fosamprenavir

Foscarnet

Fosphenytoin

Gatifloxacin

Gemifloxacin

Grepafloxacin

Guanadrel

Guanethidine

Guanfacine

Halofantrine

Haloperidol

Halothane

Heptabarbital

Hexobarbital

Hydroquinidine

Ibutilide

Iobenguane I 131

Iproniazid

Isocarboxazid

Isoflurane

Isradipine

Ketoconazole

Labetalol

Levomethadyl

Lidoflazine

Linezolid

Lisdexamfetamine

Lorcainide

Lumefantrine

Mazindol

Mephentermine

Mephobarbital

Mesoridazine

Mestranol

Methamphetamine

Methohexital

Methoxamine

Methylphenidate

Mibefradil

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

Propranolol

Propylhexedrine

Quetiapine

Quinestrol

Quinidine

Quinidine

Rasagiline

Risperidone

Ritonavir

Ropivacaine

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

Verapamil

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 ant agents, including acecainide (Chow et al, 1984), amiodarone (Faggiano et al, 1996), azimilide (Corey et al, 1 (Gilman et al, 1985), ibutilide (Rodriguez et al, 2001), sematilide (Singh, 1996), dofetilide (Allen et al, 2002), a & Runge, 2001). Even though no formal drug interaction studies have been done, the coadministration of Cla antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not (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 antidepres recommended.

7) Probable Mechanism: additive QT prolongation

8) Literature Reports

a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include incre prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flat (Marshall & Forker, 1982ab).

b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, s antidepressants, is not recommended. Dofetilide should be stopped for at least 2 days before any interac initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yam 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 anticoagul 1970c; Williams et al, 1976c). Considerable interindividual differences may be found (Pond et al, 1975c).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: In patients receiving tricyclic antidepressants and oral anticoagulant therapy, the pr ratio or INR (international normalized ratio) should be closely monitored with the addition and withdrawal of th and should be periodically reassessed during concurrent therapy. Achieving a stable drug regimen which pro level of anticoagulation may be difficult in patients on this combination, and frequent adjustments of the antic 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 incre levels and an increase in the plasma half-life of dicumarol, although the effect was not consistent in all su 1975b). This effect was not observed with warfarin.
b) A single oral dose of bishydroxycoumarin after 8 days of nortriptyline resulted in a significantly prolon decreased volume of distribution of the coumarin anticoagulant in 6 healthy volunteers (Vesell et al, 197(mechanism of action was suggested to be reduced bishydroxycoumarin metabolism and/or altered coum
c) Drug dosing was studied in 16 patients on long-term anticoagulant therapy who used concurrent TCA 1976b). TCAs affected the stability of anticoagulant control leading to frequent changes in the doses of a 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 inte recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadm Ia antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is n (Prod Info Elavil(R), 1999g; Prod Info Quinaglute(R), 1999; Marshall & Forker, 1982n).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic agent and a tricyclic anti 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 imi desipramine (Brosen & Gram, 1989). Inhibition of this enzyme system can result in a 35% decrease in im clearance and 85% decrease in desipramine clearance. Demethylation of imipramine by the cytochrome unaffected by this interaction. Until more information is available all patients having quinidine added to dr containing imipramine or desipramine should be monitored for increased antidepressant serum concentr potential toxicity.
b) An increased incidence in sudden death was observed in six out of 53 patients with cardiac disease r amitriptyline, compared to 0 out of 53 in the control group. It was recommended that amitriptyline be avo with underlying cardiac disease except when depression was debilitating and no other drugs were helpfu Coull et al, 1970).
c) In a placebo controlled study, imipramine 3.5 mg/kg was administered daily for seven patients with se and titrated doses to obtain therapeutic plasma concentrations. Two patients displayed premature atrial c and premature ventricular depolarizations before therapy. On patient had 33 premature atrial depolarizat premature ventricular depolarizations (PVD) per hour, which decreased to 0.4 PAC and zero PVC per ho The other patient had 12 PAD and 169 PVD per hour before treatment and 1.8 PAD and 28.1 PVD per h The authors also cautioned that the incidence of cardiotoxicity may increase if tricyclic antidepressants a with Type I antiarrhythmics. It was also recommended that quinidine and procainamide not be used to tre of a tricyclic overdose. The similarities between these agents may exacerbate the cardiotoxicity (Kantor e

3.5.1.D Alprazolam

1) Interaction Effect: increased imipramine plasma concentrations
2) Summary: Imipramine steady state plasma concentrations increased an average of 31% when used conc alprazolam at doses up to 4 mg/day. The clinical significance of this increase is unknown. A decrease in the i should be considered for patients who are being treated with alprazolam and imipramine concurrently and wh increase in side effects such as dry eyes and mouth, constipation, decreased urination, or arrhythmias (Prod (TM) orally disintegrating tablet, 2003).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concomitant use of alprazolam and imipramine may increase the plasma concentra imipramine. The clinical significance of this increase is unknown. If signs or symptoms of increased imipramir as blurred vision, dry mouth, constipation, urinary retention, or arrhythmias are noticed, a downward dosage imipramine should be considered.

7) Probable Mechanism: unknown

3.5.1.E Amiodarone

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

2) Summary: Cases of QTc prolongation and/or torsades de pointes have been reported with all Class III ant agents, including acecainide (Chow et al, 1984), amiodarone (Faggiano et al, 1996), azimilide (Corey et al, 1 (Gilman et al, 1985), ibutilide (Rodriguez et al, 2001), sematilide (Singh, 1996), dofetilide (Allen et al, 2002), a & Runge, 2001). Even though no formal drug interaction studies have been done, the coadministration of Cla antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not (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 antidepres recommended.

7) Probable Mechanism: additive QT prolongation

8) Literature Reports

a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include incre prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flat (Marshall & Forker, 1982ab).

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

3.5.1.F 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 1999), haloperidol (O'Brien et al, 1999), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001 (Owens, 2001b), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003). Even though no formal drug studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recomm Pamelor(R), 2001; Marshall & Forker, 1982t).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

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

3.5.1.G Amobarbital

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

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

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant do required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum con 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 pa treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were e metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Comp epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), s area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipran half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of h and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar eff expected with any combination of TCA and barbiturate.

3.5.1.H Amphetamine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A sin also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been n (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most co not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs f moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) o Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral t Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension ar
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained i amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXE 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 o antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transde 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mm of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure return normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Fle Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transie clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desiprami 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depressior although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant dru depression, with one exception, indicated little advantage of drug over placebo and did not appear to be conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.I Amprenavir

1) Interaction Effect: increased tricyclic serum concentrations and potential toxicity (anticholinergic effects, se cardiac arrhythmias)
2) Summary: Coadministered amprenavir may increase serum concentrations of tricyclic antidepressants, ca risk of arrhythmias or other serious adverse effects. Currently no interaction study has been conducted. Ampr metabolized by cytochrome P450 3A4 enzymes in addition to being a CYP3A4 inhibitor, and tricyclics may pa this pathway for metabolism. Plasma concentrations of the tricyclic should be closely monitored and dose adj 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 concentrations of the tricyclic should be closely monitored and dose adjustments made accordingly. Also mon 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.J Anisindione

1) Interaction Effect: increased risk of bleeding
2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagul 1970k; Williams et al, 1976k). Considerable interindividual differences may be found (Pond et al, 1975k).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: In patients receiving tricyclic antidepressants and oral anticoagulant therapy, the pr ratio or INR (international normalized ratio) should be closely monitored with the addition and withdrawal of th and should be periodically reassessed during concurrent therapy. Achieving a stable drug regimen which pro level of anticoagulation may be difficult in patients on this combination, and frequent adjustments of the antic

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 levels and an increase in the plasma half-life of dicumarol, although the effect was not consistent in all su 1975j). This effect was not observed with warfarin.
b) A single oral dose of bishydroxycoumarin after 8 days of nortriptyline resulted in a significantly prolon decreased volume of distribution of the coumarin anticoagulant in 6 healthy volunteers (Vesell et al, 197(mechanism of action was suggested to be reduced bishydroxycoumarin metabolism and/or altered coum
c) Drug dosing was studied in 16 patients on long-term anticoagulant therapy who used concurrent TCA 1976j). TCAs affected the stability of anticoagulant control leading to frequent changes in the doses of ar Inhibition of coumarin metabolism was the postulated mechanism.

3.5.1.K Aprindine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class I antiarrhythmics have been shown to prolong the QTc interval at the recommended ther Even though no formal drug interaction studies have been done, the coadministration of Class I antiarrhythmi known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Prod Info Tambo acetate, 1998; Larochelle et al, 1984; Scagliotti et al, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class I antiarrhythmic and a tricyclic antidepress recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include increa prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flat (Marshall & Forker, 1982q).
b) A 68-year-old man suffering from agitated major depression was begun on a dose of desipramine 12 produced a subtherapeutic serum level of 442 nmol/L (therapeutic range = 500 to 1000 nmol/L). An increa mg daily produced excellent clinical response with no side effects. He developed atrial fibrillation and flut mg daily was added to his therapy, and desipramine was discontinued. His arrhythmia was suppressed v propafenone 150 mg twice daily and 300 mg at bedtime. Desipramine 150 mg daily was again begun, at experienced dry mouth, sedation, and shakiness; the desipramine serum level was measured at 2092 nr desipramine was discontinued for five days, the side effects ceased, and desipramine therapy was resur The desipramine serum level was measured at 1130 nmol/L (Katz, 1991).

3.5.1.L Aprobarbital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased me TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen s reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressa
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant do required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum con 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 pa treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were e metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Comp epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), s area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipran half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of h and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effe expected with any combination of TCA and barbiturate.

3.5.1.M Arbutamine

1) Interaction Effect: unreliable arbutamine test results
2) Summary: Because tricyclic antidepressants may affect heart rate, arbutamine should not be administered receiving a tricyclic antidepressant, since arbutamine test results may be unreliable (Prod Info GenESA(R), 1
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable

6) Clinical Management: Arbutamine should not be administered to a patient receiving tricyclic antidepressar
7) Probable Mechanism: alteration of heart rate by the tricyclic antidepressant

3.5.1.N Arformoterol

1) Interaction Effect: an increased risk of cardiovascular excitation
2) Summary: Concurrent administration of arformoterol with a tricyclic antidepressant (TCA) may lead to pote arformoterol's adrenergic effects on the cardiovascular system. Therefore, extreme caution is advised if arfor administered to patients who are being treated with a TCA (Prod Info BROVANA(TM) inhalation solution, 200 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 warra arformoterol is administered concurrently with a tricyclic antidepressant (TCA) as the cardiovascular effects o be potentiated by TCAs (Prod Info BROVANA(TM) inhalation solution, 2006).
7) Probable Mechanism: potentiation of cardiovascular effects

3.5.1.O 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 arseni pharmacodynamic interactions can occur between arsenic trioxide and potentially arrhythmogenic agents suc antidepressants that prolong the QT interval (Prod Info Trisenox(R), 2000a). Even though no formal drug inte have been done, the coadministration of arsenic trioxide and other drugs known to prolong the QTc interval, i antidepressants, is not recommended (Prod Info Elavil(R), 1999l; Marshall & Forker, 1982ai).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of arsenic trioxide and other drugs that may prolong 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 r amitriptyline, compared to zero out of 53 in the control group using a hospital based information system. recommended that amitriptyline not be used in patients with underlying cardiac disease except when dep 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 pointe complete heart block has been reported. Over 460 ECG tracings from 40 patients with refractory or relap with arsenic trioxide were evaluated for QTc prolongation. Sixteen of 40 patients (40%) had at least one QTc interval greater than 500 msec. Prolongation of the QTc was observed between 1 and 5 weeks afte infusion, and then returned towards baseline by the end of 8 weeks after arsenic trioxide infusion. In thes evaluations, women did not experience more pronounced QT prolongation than men, and there was no (Prod Info Trisenox(R), 2000).

3.5.1.P 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 th Even though no formal drug interaction studies have been done, the coadministration of astemizole and othe prolong the QTc interval, including tricyclic antidepressants, is not recommended (Prod Info Elavil(R), 1999m 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 interva 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 prese Forker, 1982aj). Electrocardiogram effects reported in patients receiving therapeutic doses of tricyclic an include increased heart rate, prolonged PR interval, intraventricular conduction delays, increased correct (QTc) and flattened T waves.

3.5.1.Q Atazanavir

1) Interaction Effect: increased plasma concentrations of tricyclic antidepressants (drowsiness, hypotension,
2) Summary: Coadministration of atazanavir and tricyclic antidepressants has not been studied. However, th of atazanavir and tricyclic antidepressants has the potential to produce serious and/or life-threatening advers Reyataz(TM), 2003).
3) Severity: major
4) Onset: unspecified

5) Substantiation: theoretical
6) Clinical Management: If atazanavir and tricyclic antidepressants are used concomitantly, monitor patient f and symptoms of tricyclic antidepressant toxicity (hypotenstion, akathisia, anticholinergic effects, sedation, cc arrhythmias).
7) Probable Mechanism: unknown

3.5.1.R 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-hy In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhib such as imipramine. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers imipramine, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with im
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by imipran

3.5.1.S 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 ant agents, including acecainide (Chow et al, 1984), amiodarone (Faggiano et al, 1996), azimilide (Corey et al, 1 (Gilman et al, 1985), ibutilide (Rodriguez et al, 2001), sematilide (Singh, 1996), dofetilide (Allen et al, 2002), a & Runge, 2001). Even though no formal drug interaction studies have been done, the coadministration of Cla antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not (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 antidepres recommended.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include incre prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flat (Marshall & Forker, 1982ab).
b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, s antidepressants, is not recommended. Dofetilide should be stopped for at least 2 days before any intera initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yam 2003).

3.5.1.T Belladonna
1) Interaction Effect: excessive anticholinergic activity (severe dry mouth, constipation, decreased urination, sedation, blurred vision)
2) Summary: The anticholinergic activity of the active alkaloids present in belladonna may predispose the pa anticholinergic activity if taken with tricyclic antidepressants. Belladonna contains L-hyoscyamine, atropine, a with a total alkaloid content of at least 0.3% in the leaves and 0.5% in the roots (Blumenthal et al, 1998). Bec typically available as a homeopathic preparation, the clinical severity of the interaction with tricyclic antidepre 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, ur tachycardia, decreased sweating, mydriasis, blurred vision, elevated temperature, muscular weakness, and s effects are noted, belladonna should be discontinued immediately. In severe cases, paralytic ileus, confusion agitation, delusions, delirium, and paranoia may be encountered as well as tachycardia, dysrhythmia, and hy severe cases, immediate medical attention should be obtained.
7) Probable Mechanism: additive anticholinergic effect

3.5.1.U Belladonna Alkaloids
1) Interaction Effect: excessive anticholinergic activity (severe dry mouth, constipation, decreased urination, sedation, blurred vision)
2) Summary: The anticholinergic activity of the active alkaloids present in belladonna may predispose the pa anticholinergic activity if taken with tricyclic antidepressants. Belladonna contains L-hyoscyamine, atropine, a with a total alkaloid content of at least 0.3% in the leaves and 0.5% in the roots (Blumenthal et al, 1998). Bec typically available as a homeopathic preparation, the clinical severity of the interaction with tricyclic antidepre 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, ur tachycardia, decreased sweating, mydriasis, blurred vision, elevated temperature, muscular weakness, and s effects are noted, belladonna should be discontinued immediately. In severe cases, paralytic ileus, confusion agitation, delusions, delirium, and paranoia may be encountered as well as tachycardia, dysrhythmia, and hy severe cases, immediate medical attention should be obtained.
7) Probable Mechanism: additive anticholinergic effect

3.5.1.V 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-r (Prod Info Vascor(R), 2000). Tricyclic antidepressants (TCAs) have been shown to prolong the QTc interval a recommended therapeutic dose (Marshall & Forker, 1982w).
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, incl antidepressants, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.W Bethanidine

1) Interaction Effect: decreased antihypertensive effectiveness
2) Summary: Antidepressants inhibit the uptake of bethanidine at its site of action in the adrenergic neuron. T may last for several days after discontinuation of the antidepressant (Skinner et al, 1969a; Avery, 1973; Feag
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The combination of bethanidine and imipramine, as well as other tricyclic antidepres should be avoided. An alternative antihypertensive agent 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 2 of 8 adult hypertensive patients who receive debrisoquine concurrently with a tricyclic antidepressant. In 24 control patients given the same drugs wit antidepressants, blood pressure control was achieved in 18. Withdrawal of antidepressant therapy in sev resulted in postural hypotension that necessitated a reduction in dosage of bethanidine or debrisoquine (1969).

3.5.1.X 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 ant agents, including acecainide (Chow et al, 1984), amiodarone (Faggiano et al, 1996), azimilide (Corey et al, 1 (Gilman et al, 1985), ibutilide (Rodriguez et al, 2001), sematilide (Singh, 1996), dofetilide (Allen et al, 2002), a & Runge, 2001). Even though no formal drug interaction studies have been done, the coadministration of Cla antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not (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 antidepres recommended.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include incre prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flat (Marshall & Forker, 1982ab).
b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, s antidepressants, is not recommended. Dofetilide should be stopped for at least 2 days before any interac initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yam 2003).

3.5.1.Y Bupropion

1) Interaction Effect: increased imipramine plasma level
2) Summary: Bupropion was reported to decrease clearance and increase plasma levels of imipramine and i metabolite desipramine in a 64-year-old woman (Shad & Preskorn, 1997a). Coadministration of bupropion wi metabolized by the cytochrome P450 2D6 isoenzyme, such as imipramine, should be approached with cautic initiated at the lower end of the dose range of imipramine. If bupropion is added to the treatment regimen of a

receiving imipramine, a decrease in the dose of imipramine should be considered (Prod Info Wellbutrin XL(TM
Zyban(R), 2000).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: When imipramine is given with bupropion, monitor for signs of imipramine toxicity o
imipramine plasma concentrations. Coadministration of imipramine with bupropion should be approached wit
should be initiated at the lower end of the dose range of imipramine. If bupropion is added to the treatment re
already receiving imipramine, consider decreasing the dose of imipramine.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated imipramine metabolism
8) Literature Reports
a) Bupropion was reported to decrease clearance and increase plasma levels of imipramine and its prim
desipramine in a 64-year-old woman. This patient was treated with imipramine for 8 years prior to additio
therapy. Estimated imipramine clearance decreased from 1.7 mL/min without bupropion to 0.73 mL/min
Additional studies are needed to confirm this observation (Shad & Preskorn, 1997).

3.5.1.Z Butabarbital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased me
TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence
(Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen s
reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressa
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant do
required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum con
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 pa
treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were ex
metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Comp
epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), s
area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipram
half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of h
and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effe
expected with any combination of TCA and barbiturate.

3.5.1.AA Butalbital

1) Interaction Effect: decreased efficacy of imipramine
2) Summary: A 44-year old female on imipramine therapy experienced a relapse of her depressive disorder
a butalbital-containing product for headaches. Her imipramine concentration decreased by approximately 50%
attributed to an induction of cytochrome P450 1A2 enzymes caused by butalbital (Garey et al, 1997a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Imipramine serum levels should be measured one week after the addition of butalbi
dosage adjustments should be based on the results of the imipramine level and on the patient's response.
7) Probable Mechanism: induction of imipramine metabolism by butalbital
8) Literature Reports
a) A 44-year old woman was admitted to a psychiatric unit for an exacerbation of her depression. At the
antidepressant regimen included imipramine 300 mg daily, with an imipramine concentration of 174 ng/m
desipramine concentration of 134 ng/mL. These levels were considered within the normal range, and we
her past concentrations. Because of recurring headaches, she was prescribed a product containing buta
required 8 tablets (butalbital 400 mg) daily to control her headaches. The patient progressed well until tw
hospital stay, when she again experienced a relapse of her depressive disorder. Concentrations at this ti
imipramine 48 ng/mL and desipramine 122 ng/mL. Butalbital was the most reasonable explanation for th
imipramine levels, so it was discontinued and imipramine was increased to 325 mg daily. However, furth
documenting a return to normal imipramine concentrations were futile, since the patient restarted the but
product from her stockpile at home (Garey et al, 1997).

3.5.1.AB Butalbital

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

3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant do required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum con 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 pa treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were ex metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Comp epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), s area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipran half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of h and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effe expected with any combination of TCA and barbiturate.

3.5.1.AC Cannabis

1) Interaction Effect: tachycardia and delirium
2) Summary: Concomitant tetrahydrocannabinol and tricyclic antidepressant therapy has increased the hear 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 h closely.
7) Probable Mechanism: possibly due to beta-adrenergic effect of cannabis coupled with the anticholinergic antidepressants
8) Literature Reports
a) A 21-year-old female receiving oral nortriptyline 30 milligrams at bedtime for 9 months developed ma tachycardia (160 beats/minute) within 30 minutes of smoking a cannabis cigarette. The patient's heart ra beats/minute before smoking the cannabis. She had used cannabis many times before starting the nortri effects (Hillard & Vieweg, 1983).
b) Four cases of tachycardia, cognitive changes, and delirium have been reported in adolescent males t tricyclic antidepressants who smoked marijuana. One of the four cases was evaluated by a physician, th accounts of the event. The toxic effects were considered by the reporters to have resulted from a drug in they occurred with lower doses of marijuana than are common in other reports of marijuana toxicity (usu mg). In case 1, a 16-year-old male taking nortriptyline 75 mg/day presented with tachycardia (130 beats/ confusion, and short-term memory loss 30 minutes after smoking one marijuana cigarette. Symptoms re spontaneously after 24 hours. In case 2, and 18-year-old male taking desipramine 200 mg/day presente smoking marijuana with symptoms of edginess, severe dry mouth, lightheadedness, confusion, short-ter impairment, and tachycardia (110 beats/minute). Symptoms resolved within 48 hours. Case 3, a 15-year desipramine 150 mg/day and sertraline 50 mg/day, reported mood lability, irritability, and a racing heart a marijuana cigarettes which resolved after 16 hours. Case 4, a 16-year-old male taking desipramine and hallucinations, confusion, mild shortness of breath, and elevated heart rate after smoking marijuana. This than the effect he experienced prior to taking desipramine (Wilens et al, 1997).

3.5.1.AD Carbamazepine

1) Interaction Effect: decreased imipramine effectiveness
2) Summary: In a retrospective study of 36 children suffering from hyperactivity secondary to attention deficit antidepressant levels (imipramine and its metabolite desipramine) were decreased by 50% in children receivi compared to levels obtained with imipramine alone (Brown et al, 1990a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for clinical efficacy of the imipramine therapy and for any signs of toxicity of Serum levels of both agents should be considered when either agent is added or discontinued, with appropria adjustments made accordingly.
7) Probable Mechanism: increased imipramine metabolism
8) Literature Reports
a) In a retrospective study, of 36 children with attention deficit hyperactivity disorder, the average plasma imipramine was significantly lower in patients treated with carbamazepine concurrently. The average dos was 1.3 mg/kg in patients receiving imipramine alone, compared to an imipramine dose of 1.8 mg/kg in p both imipramine and carbamazepine. The plasma level of imipramine, desipramine, and total tricyclic ant plasma levels were significantly lower in patients treated with carbamazepine concurrently. The dose of i need to be increased if carbamazepine is added to therapy and the dose of imipramine may need to be carbamazepine is stopped (Brown et al, 1990).
b) Combination therapy with carbamazepine decreases steady-state total serum concentrations of imipr

concentrations of desipramine. Thirteen patients were treated with imipramine 2 mg/kg/day for 3 weeks, carbamazepine 400 mg/day was added. The ratios of total concentrations of imipramine to desipramine and two weeks after carbamazepine intake (0.7 +/- 0.41 versus 0.63 +/- 0.36; p greater than 0.05). Free imipramine and desipramine were elevated after the addition of carbamazepine. Despite lowever imipran desipramine total concentrations, the combination treatment with carbamazepine in depressed patients i tolerated. Dosage increase of imipramine does not appear to be necessary in the depressed patients inc (Szymura-Oleksiak et al, 2001).

3.5.1.AE Chloral Hydrate

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Chloral hydrate and tricyclic antidepressants have been shown to prolong the QTc interval at th therapeutic dose (Young et al, 1986; Marshall & Forker, 1982m). Even though no formal drug interaction stud 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 chloral hydrate and a tricyclic antidepressant is no
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AF 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 tachy fibrillation, and torsades de pointes. Because tricyclic antidepressants may also prolong the QT interval and i arrhythmias, the concurrent administration of chloroquine and tricyclic antidepressants is not recommended ((R), 1999; Marshall & Forker, 1982y).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of chloroquine and a tricyclic antidepressant is not re
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AG Chlorotrianisene

1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, a
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or de estrogens (Somani & Khurana, 1973e), with paradoxical loss of antidepressant effect yet tricyclic toxicity beir simultaneously (Prange, 1972e). The effects of the interaction appear to be estrogen dose-related (Khurana, be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started o (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 down estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, d may be required.
7) Probable Mechanism: unknown
8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. I depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received place imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estr daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The ter received placebo did not improve over the six weeks of the study. The ten patients taking estrogen and i demonstrated a significantly greater improvement in symptoms than did the ten patients taking imipramir after two weeks, the five patients who received imipramine and high-dose estrogen had not improved as patients receiving imipramine and low-dose estrogen. The only side effect reported was drowsiness, whi the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two wee for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the pr estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl e daily did not improve as much as ten patients receiving only imipramine. Also, the patients on the combi side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972d).

b) A case reported demonstrated an interaction in a 32-year-old female taking conjugated estrogens 2.5 imipramine 100 mg (Khurana, 1972d). The patient developed lethargy, tremors, and signs of depersonal years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient bec had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing th side-effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA 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 begin there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients'

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

d) The effects of oral contraceptives on clomipramine were studied in 42 women between the ages of 18 three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with ora Over the four-week study, three control patients (two due to side-effects) and five in the experimental gro side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of ser concentrations. No difference in serum concentrations was noted between the groups. However, this res 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 antidep concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjug 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estro discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution withi Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily wh amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 m developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours follo discontinuation of the antidepressant (Krishnan et al, 1984d).

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

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 19 are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the cer system resulting in an antidepressant effect (Oppenheim, 1983b).

3.5.1.AH Cimetidine

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

2) Summary: Concomitant cimetidine and imipramine therapy has resulted in inhibition of the metabolism of leading to prolonged half-life and elevated serum concentrations (Miller & Macklin, 1983a; Wells et al, 1986a; 1984b) and adverse effects (Miller & Macklin, 1983a; Sutherland et al, 1987; Wells et al, 1986a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Imipramine levels should be considered within the first few days of starting or disco cimetidine. An alternative H2 blocker that does not appear to impair the metabolism of imipramine, such as ra famotidine, might be considered.

7) Probable Mechanism: decreased imipramine metabolism

8) Literature Reports

a) In a case report, a 32-year-old woman concurrently on cimetidine 300 mg four times daily for abdomi exhibited severe anticholinergic side effects and orthostatic hypotension with the addition of imipramine, (Miller & Macklin, 1983). Upon rechallenge, imipramine pharmacokinetics with and without cimetidine we concurrent administration of cimetidine 300 mg four times daily and imipramine 100 mg daily, steady stat life for imipramine was 44 hours and plasma clearance 210 mL/minute. The ratio of imipramine to desipr calculated to be 2.6 (normal ratio 1 to 1.2). Upon discontinuation of cimetidine the elimination half-life of i decreased to 23 hours and the plasma clearance increased to 355 mL/minute. The patient was able to c without complaints of anticholinergic side effects without cimetidine. Cimetidine also was reported to incr bioavailability of oral imipramine doses in six healthy volunteers, in addition to impairing imipramine clea increasing the desipramine area under the curve (Abernethy et al, 1984a).

b) Six healthy young (24 to 25 year-old) volunteers participated in four randomly sequenced clinical trial effects of cimetidine administration on the pharmacokinetics of imipramine. Each clinical trial was separa week. Trial 1: 12.5 mg of imipramine was infused over 30 minutes. Trial 2: 300 mg of cimetidine was adm every six hours, starting 12 hours prior to the imipramine dose (12.5 mg intravenously infused over 30 m continued for 96 hours after the imipramine dose. Trial 3: 50 mg of imipramine was administered orally fo overnight fast, with the fast continued for three hours following administration of the drug. Trial 4: Cimetic administered as described in trial 2 and 50 mg imipramine was administered oral as described in trial 3. half-life for imipramine was significantly increased (15.5 hours to 22.1 hours) during cimetidine therapy ir administration group and increased (15.3 hours to 20.7 hours), but not significantly, in the oral administra Absolute bioavailability for orally administered imipramine nearly doubled (40% to 75%) during cimetidine on these results patients receiving concurrent cimetidine and imipramine therapy should have a 50% to 6 imipramine dose in order to avoid potential imipramine toxicity or should have their plasma imipramine/d monitored closely (Abernethy & Kerzner, 1984b).

c) Concomitant administration of cimetidine and imipramine was reported to result in psychosis (in the p sensorium) in a 38-year-old woman with major depression. Discontinuation of both drugs resulted in reso and depression within 72 hours. However, it is unclear if this patient's psychotic features were induced s combination of these two agents (Miller et al, 1987).

d) The impaired elimination of these tricyclic antidepressants is rather rapid and new steady state serum

would be expected to be achieved in three to five days after initiation of cimetidine therapy. It is suggeste doses be adjusted downward by 50% when cimetidine is given concurrently with further adjustments in c determined by plasma level monitoring (Wells et al, 1986).

e) Using microsomes from 4 human livers, cimetidine was shown to inhibit the demethylation of imipram hydroxylation of desmethylimipramine (Spina & Koike, 1986).

3.5.1.AI 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 fibrillation, torsades de pointes, and QT prolongation. Because tricyclic antidepressant agents also may prolo and increase the risk of arrhythmias, the concurrent administration of cisapride with a drug from this class is c (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.AJ Citalopram

1) Interaction Effect: an increase in the bioavailability and half-life of desipramine, the major metabolite of im

2) Summary: Imipramine pharmacokinetics were not influenced by citalopram when the two were coadminist Celexa(TM), 2002; Gram et al, 1993a). However, citalopram may increase exposure to desipramine, the majo imipramine. Clinical events have not been reported and, in an isolated report, citalopram was successfully su paroxetine in a patient who had experienced elevated tricyclic antidepressant levels during paroxetine treatm an inhibitor of cytochrome P450 2D6 enzymes, and imipramine, a tertiary amine, is converted to a secondary (desipramine) by N-demethylation. The secondary amine then undergoes hydroxylation, a process which is c oxidative enzymes of the CYP2D6 system (Taylor, 1995).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Caution is indicated in the coadministration of tricyclic antidepressants and citalopra monitoring tricyclic antidepressant concentration and/or dose adjustment when there is a change in therapy c citalopram. However, citalopram may be preferred over paroxetine when tricyclic antidepressants are coadmi

7) Probable Mechanism: inhibition of desipramine metabolism, the major metabolite of imipramine

8) Literature Reports

a) Eight healthy male volunteers completed three phases of an interaction study to determine the effects imipramine and citalopram. All subjects were extensive metabolizers of sparteine, indicating normal cyto enzyme activity. Each subject received citalopram 40 mg alone as a single daily dose for 10 days, imipra single oral dose, and a single oral dose of imipramine 100 mg coadministered on day 7 of citalopram the weeks separated each treatment phase. Results showed that the concurrent administration of citalopram resulted in a 50% increase in the desipramine area under the concentration-time curve (AUC) and a simi 2-hydroxy-desipramine AUC. Also, the desipramine half-life was approximately seven hours longer wher citalopram (27 hours vs. 20 hours). The AUC and half-life of imipramine were not affected by citalopram These results showed that citalopram is an inhibitor of cytochrome P450 2D6 hepatic enzymes, since mo antidepressants rely on this system for metabolism (Gram et al, 1993).

b) A case report describes a 45-year-old white female with major depressive disorder and dysthymia. Th several trials of antidepressants from all available drug classes, as well as electroconvulsive therapy. Th medications included pindolol, desipramine, clonazepam, and olanzapine. Paroxetine was initiated and t mg/day occurred over 3 months. The patient developed light-headedness, ataxia, and increased confusi titration. Desipramine serum levels were 1810 ng/mL (therapeutic range 75-300 ng/mL). After decreasing desipramine 200 mg, the serum desipramine level was still 1665 ng/mL. The reduction in side effects we the paroxetine dose was decreased to 30 mg/day and desipramine dose was decreased to 150 mg/day. dosage reduction of both drugs the patient's serum desipramine level was 1153 ng/mL. Paroxetine was d desipramine dose was decreased to 100 mg/day in divided doses. Citalopram was initiated and titrated t the next two months the patient's desipramine level decreased to 195 ng/mL. Depressive symptoms also Desipramine toxicity is presumed to be caused by hepatic cytochrome P450 2D6 (CYP2D6) isoenzyme I paroxetine. The author concludes that the switch to citalopram likely is responsible for diminished desipra levels, although alternative explanations should not be discounted (Ashton, 2000).

3.5.1.AK 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 inter recommended therapeutic dose (Prod Info Biaxin(R), 2002; Marshall & Forker, 1982o). Even though no forma studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong th 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 t
such as clarithromycin, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AL Clonidine

1) Interaction Effect: decreased antihypertensive effectiveness
2) Summary: Concomitant clonidine and tricyclic antidepressant (TCA) therapy may impair the antihypertens
clonidine (Prod Info Catapres(R), 1996). Tricyclic antidepressants increase the release of noradrenaline, pres
re-uptake blockade. Clonidine reduces the release of noradrenaline by stimulating pre-synaptic alpha-2 adrer
whose function is to inhibit noradrenaline release (Briant et al, 1973a; Hicks et al, 1981; Hui, 1983; Glass et a
Mianserin, a tetracyclic antidepressant, was not shown to exhibit the impairment of clonidine's antihypertensi
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 do
may be required. An alternative class of antihypertensive agents or an alternative class of antidepressants m
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 res
blind placebo controlled study showed that the introduction of the tricyclic antidepressant led to the loss
control in four of the five subjects within two weeks. The rise in the arterial pressure was more prominent
position than in the erect. The average blood pressure increase in the desipramine period compared to t
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 er
determine the effects of desipramine on central adrenergic function. Patients were given a clonidine infus
3 weeks of treatment with desipramine. Results showed that the sedative and hypotensive effects of clor
significantly inhibited after three weeks of treatment with desipramine. This interaction was also seen at
not reach clinical significance. The authors concluded that the effects that were observed during the stuc
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 excis
carcinoma. Pain management of amitriptyline 75 mg nightly and sodium valproate 500 mg three times da
after slow-release morphine only had a limited effect. A clonidine spinal intrathecal injection of 75 microg
when it was felt that the patient had become tolerant to opioid treatment. Within five minutes, the patient
severe pain, which resolved within 30 minutes after diamorphine was given. Two mechanisms for this int
postulated. In the first, the pain could have been the result of a clonidine-cholinergic interaction. In the se
augmentation of serotoninergic transmission may have unmasked an effect of clonidine at central recept
nociception (Hardy & Wells, 1988).

3.5.1.AM Clorgyline

1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus
changes)
2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concur
and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982e; Spig
Brodribb et al, 1994e; Neuvonen et al, 1993b). Serotonin syndrome is a rare but potentially fatal condition of
hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Ste
Consequently, coadministration of TCAs and MAOIs is contraindicated in most cases. If TCAs and MAOIs mu
concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and trany
monitor patients closely (Schuckit et al, 1971e; White & Simpson, 1984d).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of a tricyclic antidepressant, such as imipramine with an monoam
inhibitor (MAOI), such as clorgyline is contraindicated. If imipramine is replacing treatment with clorgyline, a n
weeks should elapse after clorgyline is discontinued before therapy with imipramine begins (Prod Info imipran
oral tablet, 2003). There is no specific washout period for replacing imipramine treatment with clorgyline. How
advisable to gradually taper the tricyclic antidepressant dosage before starting treatment with the MAOI (Rem
7) Probable Mechanism: altered catecholamine uptake and metabolism
8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (T
considered an absolute contraindication in the past and still is listed as such by the manufacturers (Prod
hydrochloride oral tablet, 2003). Reports of excitation, hyperpyrexia, convulsions, and possible death hav
to the combination (Lockett & Milner, 1965b; Brachfeld et al, 1963a; Winston, 1971b; Schuckit et al, 197
1965a; Spiker & Pugh, 1976b). The mechanism may relate to the combined inhibition of catecholamine r
central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965b).

b) The development of serotonin syndrome due to administration of a TCA after MAOI therapy has beer
double-blind, crossover study examining the effects of clorgyline and clomipramine for the treatment of o
compulsive disorder, two subjects developed severe reactions characteristic of serotonin syndrome. Dur

patients had received clorgyline therapy, followed by a washout period of approximately four weeks and clomipramine therapy. After taking the first 100 mg dose of clomipramine, one patient developed coarse in both legs, hyperreflexia, diaphoresis, and arrhythmia. Another patient developed a similar reaction afte with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's sympto several hours later, and both patients were later treated successfully with clomipramine without adverse 1982d).

c) A 76-year old woman who had been taking clomipramine 50 mg daily for several months was switche 300 mg daily. The patient experienced somnolence, confusion, and fever which then progressed to furth impairment, muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were describe diagnostic criteria for serotonin syndrome and were resolved a few days later after discontinuing all antid medications (Spigset et al, 1993e).

d) A 39-year old woman with bipolar disorder developed serotonin syndrome after imipramine was adde The patient was taking moclobemide 300 mg twice daily when imipramine was started at 50 mg daily, fol dosage increases of imipramine to 200 mg and a reduction of moclobemide dosage to 150 mg twice dail the increase in imipramine to 200 mg per day, the patient developed symptoms of serotonin syndrome, i shivering, confusion, fever, and spasms in the extremities. The patient was treated with chlorpromazine a 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 isocarboxazid and amitriptyline. In all three cases the patients had been given MAOIs and TCAs alone w complications. It was only when the drugs were used in combination that symptoms of mania emerged, s 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 pl 34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sw by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulatio death (Tackley & Tregaskis, 1987c).

g) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsi TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 15 or its equivalent, 45 mg phenelzine, or 60 mg isocarboxazid) b) oral administration c) avoidance of clomi imipramine, desipramine, and tranylcypromine in any combination, and d) close monitoring of patients (K Winston, 1971b; Schuckit et al, 1971d; White & Simpson, 1984c; Rom & Benner, 1972a). The combinati in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to t and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991b). Alternatively previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some s that the combination of amitriptyline and isocarboxazid is preferred (Perry et al, 1991b). Numerous studie refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TC 1977b; Schuckit et al, 1971d; Ashcroft, 1975b).

3.5.1.AN Conjugated Estrogens

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

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

3) Severity: minor

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment down estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, d 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. I depressed female prisoners were randomly assigned to four treatment groups. Ten patients received pla imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estr daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and in demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramin after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, whi the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two wee for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the pr estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl e daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combin side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972b).

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg a daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab v

Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the sid from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1972b).

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the begir there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the c matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' clomipramine. It was proposed that there was no significant difference in side-effects between the groups groups were matched after patients had dropped out of the study. Had the patients been matched prior t different conclusions may have been drawn (Beaumont, 1973a).

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with ora Over the four-week study, three control patients (two due to side-effects) and five in the experimental gro side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of se concentrations. No difference in serum concentrations was noted between the groups. However, this res 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 antidep concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjug 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estro discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution withi Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily wh amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 m developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours follo discontinuation of the antidepressant (Krishnan et al, 1984b).

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

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 19 are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the cer system resulting in an antidepressant effect (Oppenheim, 1983a).

3.5.1.AO Darifenacin

1) Interaction Effect: increased imipramine exposure and potentially increased adverse effects

2) Summary: Concomitant use of darifenacin and imipramine may result in substantially increased exposure its active metabolite desipramine. The mean maximum concentration (Cmax) and area under the concentrati (AUC) of imipramine increased 57% and 70%, respectively, when used together with darifenacin 30 mg once state. Note: The recommended dose of darifenacin is 7.5 or 15 mg once daily. The AUC of desipramine, the a of imipramine, increased 3.6-fold. Caution should be used with the coadministration of darifenacin and CYP2 a narrow therapeutic window, such as tricyclic antidepressants, including imipramine (Prod Info Enablex, 200

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Use caution with the coadministration of darifenacin and other CYP2D6 substrates therapeutic window, such as imipramine. Monitor for imipramine toxicity.

7) Probable Mechanism: competitive inhibition of CYP2D6-mediated imipramine metabolism

3.5.1.AP Dexfenfluramine

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

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

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

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

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen
coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained i
amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXE
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 o
antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transde
2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i
such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mm
of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure return
normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Fle
Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g
four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transie
clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desiprami
1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc
therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depressior
although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant dru
depression, with one exception, indicated little advantage of drug over placebo and did not appear to be
conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.AQ Dexmethylphenidate

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

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen
coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained i
amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXE
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 o
antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transde
2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i
such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mm
of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure return
normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Fle
Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g
four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transie
clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desiprami
1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc
therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depressior
although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant dru
depression, with one exception, indicated little advantage of drug over placebo and did not appear to be
conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.AR Dextroamphetamine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte
enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A sin

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

3.5.1.AS Dicumarol

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

3.5.1.AT Dienestrol

1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, a
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or de
estrogens (Somani & Khurana, 1973g), with paradoxical loss of antidepressant effect yet tricyclic toxicity beir
simultaneously (Prange, 1972g). The effects of the interaction appear to be estrogen dose-related (Khurana,
be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started o
(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 down estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, d 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. I depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received place imipramine (150 milligrams/day) and placebo, 5 patients received imipramine (150 milligrams/day) and e micrograms/day), while 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (25 mic 10 patients that received placebo did not improve over the 6 weeks of the study. The 10 patients taking e imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients takin alone. However, after 2 weeks, the 5 patients that received imipramine and high-dose estrogen had not i as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsine affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period o required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed residual estrogen in the high-dose group. In another group, 5 women received imipramine 150 milligrams estradiol 50 micrograms daily did not improve as much as 10 patients receiving only imipramine. Also, th combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange,

b) A case reported by (Khurana, 1972f) demonstrated an interaction in a 32-year-old female taking conj 2.5 milligrams and imipramine 100 milligrams. The patient developed lethargy, tremors, and signs of dep After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. the estrogen, the side-effects abated. Some investigators have proposed that the side effects resulted fr 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 begin there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' clomipramine. It was proposed that there was no significant difference in side-effects between the groups groups were matched after patients had dropped out of the study. Had the patients been matched prior t 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 a three women took clomipramine 25 milligrams at bedtime while 19 took clomipramine 25 milligrams at be contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimenta side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of se concentrations. No difference in serum concentrations was noted between the groups. However, this res 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 antidep concurrently. A 24-year-old patient receiving clomipramine 120 milligrams/day for anorexia nervosa and estrogens 1.25 milligrams/day for amenorrhea developed restless legs and a constant desire to move co Estrogen was discontinued and benztropine 2 milligrams was administered, resulting in marked reductio within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogens milligrams/day who was prescribed amitriptyline 50 milligrams/day for depression. Within hours of amitrip was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared af amitriptyline. Positive rechallenge at one week with doxepin 100 milligrams, with resolution following disc doxepin. A third case of akathisia was reported in a 35-year-old patient who received conjugated estroge milligrams/day and amitriptyline 50 milligrams/day. Akathisia developed within a few hours after taking th amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al,

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

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 19 are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the cer system resulting in an antidepressant effect (Oppenheim, 1983c).

3.5.1.AU Diethylpropion

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

dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) o Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral t Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension ar
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained i amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXE 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 c antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transde 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mm of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure return normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Fle Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transie clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desiprami 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depressior although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant dru depression, with one exception, indicated little advantage of drug over placebo and did not appear to be conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.AV Diethylstilbestrol
1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, a
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or de estrogens (Somani & Khurana, 1973k), with paradoxical loss of antidepressant effect yet tricyclic toxicity bein simultaneously (Prange, 1972k). The effects of the interaction appear to be estrogen dose-related (Khurana, be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started o (Krishnan et al, 1984k).
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment down estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, d 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. I depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received place imipramine (150 milligrams/day) and placebo, 5 patients received imipramine (150 milligrams/day) and e micrograms/day), while 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (25 mic 10 patients that received placebo did not improve over the 6 weeks of the study. The 10 patients taking e imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients takin alone. However, after 2 weeks, the 5 patients that received imipramine and high-dose estrogen had not i as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsine affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period o required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed residual estrogen in the high-dose group. In another group, 5 women received imipramine 150 milligrams estradiol 50 micrograms daily did not improve as much as 10 patients receiving only imipramine. Also, th combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange,
b) A case reported by (Khurana, 1972j) demonstrated an interaction in a 32-year-old female taking conju 2.5 milligrams and imipramine 100 milligrams. The patient developed lethargy, tremors, and signs of dep After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. U the estrogen, the side-effects abated. Some investigators have proposed that the side effects resulted fr 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 begin there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the c

matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' clomipramine. It was proposed that there was no significant difference in side-effects between the groups groups were matched after patients had dropped out of the study. Had the patients been matched prior t 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 a three women took clomipramine 25 milligrams at bedtime while 19 took clomipramine 25 milligrams at be contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimenta side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of ser concentrations. No difference in serum concentrations was noted between the groups. However, this res 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 antidep concurrently. A 24-year-old patient receiving clomipramine 120 milligrams/day for anorexia nervosa and estrogens 1.25 milligrams/day for amenorrhea developed restless legs and a constant desire to move co Estrogen was discontinued and benztropine 2 milligrams was administered, resulting in marked reductio within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogens milligrams/day who was prescribed amitriptyline 50 milligrams/day for depression. Within hours of amitrip was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared af amitriptyline. Positive rechallenge at one week with doxepin 100 milligrams, with resolution following disc doxepin. A third case of akathisia was reported in a 35-year-old patient who received conjugated estroge milligrams/day and amitriptyline 50 milligrams/day. Akathisia developed within a few hours after taking th amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al,

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

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 19 are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the cer system resulting in an antidepressant effect (Oppenheim, 1983e).

3.5.1.AW Diltiazem

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

2) Summary: Diltiazem decreased imipramine oral clearance by 35% (statistically significant) compared to pl randomized, crossover study in 12 healthy subjects (Hermann et al, 1992c). Diltiazem increased imipramine l 30% compared to placebo which was also significant; the clinical significance of this is not known.

3) Severity: minor

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Monitor for anticholinergic side effects of imipramine if diltiazem is added to therapy imipramine may be appropriate. Conversely, if diltiazem is discontinued, monitor continued clinical efficacy of adjust dosage accordingly.

7) Probable Mechanism: decreased imipramine clearance

8) Literature Reports

a) Imipramine serum concentrations may be altered if administered concomitantly with diltiazem. Follow imipramine 100 mg/day on day 4 of a 7 day course of diltiazem 90 mg/q8h during a controlled study, the imipramine decreased by 35% resulting in a significant increase (35%) in the peak serum concentration. failed to occur when the drug was given to those receiving placebo. Monitor drug levels for effectiveness when adding or decreasing diltiazem dosages (Hermann et al, 1992b).

3.5.1.AX 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 inte recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadm Ia antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is n (Prod Info Elavil(R), 1999g; Prod Info Quinaglute(R), 1999; Marshall & Forker, 1982n).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic agent and a tricyclic anti 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 imi desipramine (Brosen & Gram, 1989). Inhibition of this enzyme system can result in a 35% decrease in im clearance and 85% decrease in desipramine clearance. Demethylation of imipramine by the cytochrome unaffected by this interaction. Until more information is available all patients having quinidine added to dr containing imipramine or desipramine should be monitored for increased antidepressant serum concentr potential toxicity.

b) An increased incidence in sudden death was observed in six out of 53 patients with cardiac disease r

amitriptyline, compared to 0 out of 53 in the control group. It was recommended that amitriptyline be avo with underlying cardiac disease except when depression was debilitating and no other drugs were helpfu Coull et al, 1970).

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

3.5.1.AY Disulfiram

1) Interaction Effect: increased bioavailability of imipramine

2) Summary: Increased elimination half-life, higher peak plasma levels, and decreased total body clearance when administered during disulfiram therapy have been demonstrated (Ciraulo et al, 1985). The clinical signif finding is unknown.

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor the patient for excessive adverse effects to imipramine.

7) Probable Mechanism: disulfiram-induced inhibition of imipramine hepatic metabolism

8) Literature Reports

a) Two healthy men who had been detoxified for 14 days participated in a study to determine the effect pharmacokinetics of imipramine and desipramine. Doses of imipramine 12.5 mg were administered intra to disulfiram 500 mg daily therapy and after 14 days of therapy with disulfiram. The protocol for desipram same but was performed only in one subject. For imipramine, the area under the concentration-time curv by 32.5% and 26.8% after disulfiram administration in patient 1 and patient 2, respectively. The eliminati also increased by 18.3% and 13.6%, respectively, while the total body imipramine clearance decreased respectively. Desipramine showed a 32.3% increase in the AUC when administered with disulfiram. The also increased by 19.8% and the total body clearance decreased 24.3% (Ciraulo et al, 1985).

3.5.1.AZ 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 ant agents, including acecainide (Chow et al, 1984), amiodarone (Faggiano et al, 1996), azimilide (Corey et al, 1 (Gilman et al, 1985), ibutilide (Rodriguez et al, 2001), sematilide (Singh, 1996), dofetilide (Allen et al, 2002), a & Runge, 2001). Even though no formal drug interaction studies have been done, the coadministration of Cla antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not (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 antidepres recommended.

7) Probable Mechanism: additive QT prolongation

8) Literature Reports

a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include incre prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flat (Marshall & Forker, 1982ab).

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

3.5.1.BA 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 recommended therapeutic dose (Marshall & Forker, 1982b). Even though no formal drug interaction studies h the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as c recommended (Prod Info Elavil(R), 1999a; 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 as tricyclic antidepressants, is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BB 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. formal drug interaction studies have been done, the coadministration of droperidol and other drugs known to interval, including tricylclic antidepressants is not recommended (Prod Info Inapsine(R), 2002; Marshall & For

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of droperidol and tricyclic antidepressants is not reco

7) Probable Mechanism: additive cardiac effects

3.5.1.BC Duloxetine

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

2) Summary: The coadministration of duloxetine with a tricyclic antidepressant is likely to increase bioavailab agent, increasing the risk of adverse events. Duloxetine is a moderately potent inhibitor of CYP2D6. When a CYP2D6 substrate desipramine 50 mg and duloxetine 60 mg twice daily were coadministered, the desipramir 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 (TCA therapy with duloxetine and a TCA is unavoidable, plasma concentrations of the tricyclic should be closely m adjustments made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008). Also, monito 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.BD Enflurane

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

2) Summary: Enflurane may prolong the QT interval in some patients (Owens, 2001). Because tricyclic antid also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of enflurane a antidepressants is not recommended (Marshall & Forker, 1982a). Concomitant administration of amitriptyline 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 patie 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 anesthesia have been documented (Sprague & Wolf, 1982). The first patient, a 42-year old female, was 100 mg daily. Anesthesia was induced with fentanyl, enflurane, and nitrous oxide. Approximately three h anesthesia was induced, clonic movements of the patient's right hand and forearm were noted. Enflurane was 1% at the time. Changes in ventilation did not affect the involuntary movements, so enflurane was d replaced with halothane 1%. The movements decreased in frequency and amplitude and subsequently c approximately one minute. The second case report involved a 39-year old male who was taking amitripty Anesthesia was maintained with enflurane 1% to 2%, and intermittent clonic movements started in the ri approximately one hour into the surgery. Enflurane was discontinued and halothane was instituted, whic involuntary movements to disappear in approximately two minutes. No further movements were seen du three hours of anesthesia.

3.5.1.BE 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 c drugs to volunteers on tricyclic antidepressants. Arrhythmias and other severe adverse effects have also bee 1980; Avery, 1973a; Boakes et al, 1973a; Boakes, 1973; Mitchell et al, 1970; Stone et al, 1964a). Local use (anesthesia) of epinephrine in concentrations of 1:100,000 or less is less likely to precipitate clinically significa 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 enhanced in the presence of tricyclic antidepressants (TCAs). Concomitant use should be avoided. If these d together, careful monitoring and a dose reduction of the sympathomimetic is required. Patients should be inst 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 (epineph norepinephrine, phenylephrine, and isoproterenol) before and after imipramine (25 mg three times daily f showed an increased pressor response to epinephrine (2- to 4-fold), norepinephrine (4- to 8-fold), and ph 3-fold) after imipramine, but no difference was observed in the response to isoproterenol. Thus, the incre response appeared to occur only for alpha adrenergic effects. All four subjects demonstrated changes in with epinephrine and imipramine consisting of sinus arrhythmia in three subjects and multiple ectopic be rhythm in the fourth subject (Boakes et al, 1973).

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

3.5.1.BF 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 s (Oberg & Bauman, 1995a). Erythromycin has demonstrated QTc prolongation in combination with other drug QT interval (Prod Info PCE(R), 1997). Tricyclic antidepressants have been shown to prolong the QTc interval recommended therapeutic dose (Marshall & Forker, 1982g). Caution is advised with coadministration of drug 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 concomita 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 pat were maintained on desipramine (n equal to 5), imipramine (n equal to 1), doxepin (n equal to 1), or doxe All patients received erythromycin stearate 250 mg four times daily for six days while maintaining their us regimen. No change in the antidepressant or active metabolite concentrations was seen during coadmini erythromycin (Amsterdam & Maislin, 1991).

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

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

3.5.1.BG Esterified Estrogens

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

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

3) Severity: minor

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment down estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, d 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 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received pla imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estr daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and in demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramin after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, whi the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two wee

for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the pr
estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl e
daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combin
side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972b).

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

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the begir
there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the c
matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients'
clomipramine. It was proposed that there was no significant difference in side-effects between the groups
groups were matched after patients had dropped out of the study. Had the patients been matched prior t
different conclusions may have been drawn (Beaumont, 1973a).

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18
three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with ora
Over the four-week study, three control patients (two due to side-effects) and five in the experimental gro
side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of ser
concentrations. No difference in serum concentrations was noted between the groups. However, this res
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 antidep
concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjug
1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estro
discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution withi
Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily wh
amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless,
inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case
reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 m
developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours follo
discontinuation of the antidepressant (Krishnan et al, 1984b).

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

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 19
are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result
and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the cer
system resulting in an antidepressant effect (Oppenheim, 1983a).

3.5.1.BH Estradiol

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

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

3) Severity: minor

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment down
estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, d
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. I
depressed female prisoners were randomly assigned to four treatment groups. Ten patients received pla
imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estr
daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10
received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and in
demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramin
after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as
patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, whi
the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two wee
for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the pr
estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl e
daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combin
side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972b).

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

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the begin there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the c matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' clomipramine. It was proposed that there was no significant difference in side-effects between the groups groups were matched after patients had dropped out of the study. Had the patients been matched prior t different conclusions may have been drawn (Beaumont, 1973a).

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with ora Over the four-week study, three control patients (two due to side-effects) and five in the experimental gro side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of se concentrations. No difference in serum concentrations was noted between the groups. However, this res 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 antidep concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjug 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estro discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution withi Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily wh amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 m developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours follo discontinuation of the antidepressant (Krishnan et al, 1984b).

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

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 19 are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the cer system resulting in an antidepressant effect (Oppenheim, 1983a).

3.5.1.BI Estriol

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

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

3) Severity: minor

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment down estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, d 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. I depressed female prisoners were randomly assigned to four treatment groups. Ten patients received pla imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estr daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and in demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramin after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, whi the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two wee for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the pr estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl e daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combin side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972b).

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg a daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab v Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the sid

from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1972b).

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the begin there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' clomipramine. It was proposed that there was no significant difference in side-effects between the groups groups were matched after patients had dropped out of the study. Had the patients been matched prior t different conclusions may have been drawn (Beaumont, 1973a).

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with ora Over the four-week study, three control patients (two due to side-effects) and five in the experimental gro side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of se concentrations. No difference in serum concentrations was noted between the groups. However, this res 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 antidep concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjug 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estro discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution withi Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily wh amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 m developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours follo discontinuation of the antidepressant (Krishnan et al, 1984b).

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

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 19 are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the cer system resulting in an antidepressant effect (Oppenheim, 1983a).

3.5.1.BJ Estrone

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

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

3) Severity: minor

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment down estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, d 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. I depressed female prisoners were randomly assigned to four treatment groups. Ten patients received pla imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estr daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and in demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramin after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, whi the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two we for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the pr estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combin side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972b).

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

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the begin there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the

matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' clomipramine. It was proposed that there was no significant difference in side-effects between the groups groups were matched after patients had dropped out of the study. Had the patients been matched prior t different conclusions may have been drawn (Beaumont, 1973a).

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with ora Over the four-week study, three control patients (two due to side-effects) and five in the experimental gro side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of ser concentrations. No difference in serum concentrations was noted between the groups. However, this res 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 antidep concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjug 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estro discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily wh amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 m developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours follo discontinuation of the antidepressant (Krishnan et al, 1984b).

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

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 19 are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the cer system resulting in an antidepressant effect (Oppenheim, 1983a).

3.5.1.BK Estropipate

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

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

3) Severity: minor

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment down estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, d 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. I depressed female prisoners were randomly assigned to four treatment groups. Ten patients received pla imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estr daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and in demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramin after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, whi the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two we for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the pr estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combin side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972b).

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

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the begin there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' clomipramine. It was proposed that there was no significant difference in side-effects between the groups groups were matched after patients had dropped out of the study. Had the patients been matched prior t different conclusions may have been drawn (Beaumont, 1973a).

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with ora Over the four-week study, three control patients (two due to side-effects) and five in the experimental gro side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of se concentrations. No difference in serum concentrations was noted between the groups. However, this res 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 antidep concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjug 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estro discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution withi Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily wh amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 m developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours follo discontinuation of the antidepressant (Krishnan et al, 1984b).

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

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 19 are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the cer system resulting in an antidepressant effect (Oppenheim, 1983a).

3.5.1.BL Eterobarb

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

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

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant do required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum con 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 pa treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were e metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Comp epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), s area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipram half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of h and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar eff expected with any combination of TCA and barbiturate.

3.5.1.BM Ethinyl Estradiol

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

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or d estrogens (Somani & Khurana, 1973i), with paradoxical loss of antidepressant effect yet tricyclic toxicity being simultaneously (Prange, 1972i). The effects of the interaction appear to be estrogen dose-related (Khurana, 1 of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on e (Krishnan et al, 1984i).

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment down estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, d 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. I depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received place imipramine (150 milligrams/day) and placebo, 5 patients received imipramine (150 milligrams/day) and e micrograms/day), while 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (25 mic 10 patients that received placebo did not improve over the 6 weeks of the study. The 10 patients taking e imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients takin

alone. However, after 2 weeks, the 5 patients that received imipramine and high-dose estrogen had not i
as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsine
affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period o
required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed
residual estrogen in the high-dose group. In another group, 5 women received imipramine 150 milligram
estradiol 50 micrograms daily did not improve as much as 10 patients receiving only imipramine. Also, th
combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange,
b) A case report demonstrated an interaction in a 32-year-old female taking conjugated estrogens 2.5 m
imipramine 100 milligrams (Khurana, 1972h). The patient developed lethargy, tremors, and signs of depe
After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams
became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. U
the estrogen, the side-effects abated. Some investigators have proposed that the side effects resulted fr
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 begir
there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the
matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients'
clomipramine. It was proposed that there was no significant difference in side-effects between the groups
groups were matched after patients had dropped out of the study. Had the patients been matched prior t
different conclusions may have been drawn (Beaumont, 1973e).
d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18
three women took clomipramine 25 milligrams at bedtime while 19 took clomipramine 25 milligrams at be
contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimenta
side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of se
concentrations. No difference in serum concentrations was noted between the groups. However, this res
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 antidep
concurrently. A 24-year-old patient receiving clomipramine 120 milligrams/day for anorexia nervosa and
estrogens 1.25 milligrams/day for amenorrhea developed restless legs and a constant desire to move co
Estrogen was discontinued and benztropine 2 milligrams was administered, resulting in marked reductio
within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogens
milligrams/day who was prescribed amitriptyline 50 milligrams/day for depression. Within hours of amitrip
was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared af
amitriptyline. Positive rechallenge at one week with doxepin 100 milligrams, with resolution following disc
doxepin. A third case of akathisia was reported in a 35-year-old patient who received conjugated estroge
milligrams/day and amitriptyline 50 milligrams/day. Akathisia developed within a few hours after taking th
amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al,
f) The absolute bioavailability of imipramine increased in women who received low-dose oral contracept
micrograms or less of ethinyl estradiol) from 27 to 44% (p less than 0.05) as evident by an increase in th
plasma concentration time curve (Abernethy et al, 1984e).
g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 19
are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result
and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the cer
system resulting in an antidepressant effect (Oppenheim, 1983d).

3.5.1.BN 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 o
drugs to volunteers on tricyclic antidepressants. Arrhythmias and other severe adverse effects have also bee
1980; Avery, 1973a; Boakes et al, 1973a; Boakes, 1973; Mitchell et al, 1970; Stone et al, 1964a). Local use (
anesthesia) of epinephrine in concentrations of 1:100,000 or less is less likely to precipitate clinically significa
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
enhanced in the presence of tricyclic antidepressants (TCAs). Concomitant use should be avoided. If these d
together, careful monitoring and a dose reduction of the sympathomimetic is required. Patients should be inst
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 (epineph
norepinephrine, phenylephrine, and isoproterenol) before and after imipramine (25 mg three times daily f
showed an increased pressor response to epinephrine (2- to 4-fold), norepinephrine (4- to 8-fold), and ph
3-fold) after imipramine, but no difference was observed in the response to isoproterenol. Thus, the incre
response appeared to occur only for alpha adrenergic effects. All four subjects demonstrated changes in
with epinephrine and imipramine consisting of sinus arrhythmia in three subjects and multiple ectopic be
rhythm in the fourth subject (Boakes et al, 1973).
b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found th

receiving a local anesthetic with norepinephrine (1:25,000) had severe reactions (severe headaches, che subarachnoid hemorrhage). The drug history was incomplete, but at least three had been taking a tricycl at the time (Anon, 1972).

3.5.1.BO Fenfluramine

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

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

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

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

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained i amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXE 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 c antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transde 2006).

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

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transi clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desiprami 1990).

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

3.5.1.BP Fenfluramine

1) Interaction Effect: an increased risk of imipramine toxicity (sedation)

2) Summary: When fenfluramine was added to imipramine therapy, the blood concentration of imipramine pl was dramatically increased in a 55-year old female. The increased blood levels caused the patient to fall asle (Fogelson, 1997a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: If fenfluramine is used in combination with imipramine, the patient should be monitc sedation, hypertension and dysrhythmias.

7) Probable Mechanism: inhibition of imipramine metabolism

8) Literature Reports

a) A 55-year old female patient was maintained on imipramine 350 mg daily for several years, with imipr desipramine blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with fenflu three times daily, the patient fell asleep while driving. The imipramine plus desipramine level was 704 mc may have inhibited the cytochrome p450 isoenzyme responsible for metabolizing imipramine (Fogelson,

b) A study was conducted in 15 patients with DSM-III major depression who failed to respond to treatme desipramine given for at least four weeks. Fenfluramine 40 mg to 120 mg daily for two weeks was then a transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plas desipramine (Price et al, 1990a).

3.5.1.BQ Flecainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class I antiarrhythmics have been shown to prolong the QTc interval at the recommended ther Even though no formal drug interaction studies have been done, the coadministration of Class I antiarrhythmi known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Prod Info Tambo acetate, 1998; Larochelle et al, 1984; Scagliotti et al, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class I antiarrhythmic and a tricyclic antidepress recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include incre prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flat (Marshall & Forker, 1982q).
b) A 68-year-old man suffering from agitated major depression was begun on a dose of desipramine 12 produced a subtherapeutic serum level of 442 nmol/L (therapeutic range = 500 to 1000 nmol/L). An incre mg daily produced excellent clinical response with no side effects. He developed atrial fibrillation and flut mg daily was added to his therapy, and desipramine was discontinued. His arrhythmia was suppressed v propafenone 150 mg twice daily and 300 mg at bedtime. Desipramine 150 mg daily was again begun, at experienced dry mouth, sedation, and shakiness; the desipramine serum level was measured at 2092 nr desipramine was discontinued for five days, the side effects ceased, and desipramine therapy was resur The desipramine serum level was measured at 1130 nmol/L (Katz, 1991).

3.5.1.BR 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 fluconaz al, 1999). Several tricyclic antidepressants (TCAs) have been shown to prolong the QTc interval at the recom therapeutic dose (Marshall & Forker, 1982x). Even though no formal drug interaction studies have been done 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 re
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BS Fluoxetine

1) Interaction Effect: tricyclic antidepressant toxicity (dry mouth, urinary retention, sedation) and an increase cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and fluoxetine have been shown to prolong the QTc interval a recommended therapeutic dose (Prod Info Prozac(R), 2001; Marshall & Forker, 1982h). Even though no form studies have been done which demonstrate QT prolongation, the coadministration of tricyclic antidepressants known to prolong the QTc interval, such as fluoxetine, is not recommended (Prod Info Elavil(R), 1999d). In ac use of fluoxetine and TCAs such as desipramine, nortriptyline, and imipramine has resulted in significant incr concentrations (Preskorn et al, 1994a; Preskorn et al, 1994a; Aranow et al, 1989a; Downs et al, 1989a; Gooc & 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 rec
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 addition of fluoxetine, the ratio of antidepressant level to dose increased by 109% to 486% in the patient developed clinical symptoms (anticholinergic effects, constipation, urinary hesitancy, sedation, unstable the increased levels (Aranow et al, 1989).
b) Fluoxetine statistically and clinically significantly increased desipramine concentrations in 18 healthy fluoxetine (20 mg daily) was added to desipramine (50 mg daily), the mean maximum concentration of d increased by 278% and the area under the concentration-time curve increased by 342%. Desipramine tr concentrations continued to be 198% above baseline three weeks after fluoxetine was discontinued. The compared pharmacokinetics of desipramine when combined with sertraline. The impact of sertraline was 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 w was added. Desipramine serum levels ranged from 109 to 150 ng/mL with oral doses of 300 mg at bedti fluoxetine therapy. Following the addition of oral fluoxetine 20 mg daily to the regimen, the desipramine s increased to 212 ng/mL within five days. The fluoxetine dose was increased to 40 mg/day three days late desipramine serum level was 419 ng/mL after four days. A worsening of depression and severe fatigue c increases in desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose t

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 a memory while receiving fluoxetine 40 mg daily and desipramine 150 mg daily for five weeks; fluoxetine w and the blood levels of desipramine decreased from 938 to 48 ng/mL with resolution of clinical symptoms 1989).
e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant Prior to fluoxetine therapy, the patient's measured levels of desipramine had ranged from 148 to 160 ng/ of 300 mg daily. Five weeks after the addition of fluoxetine 20 mg daily, she reported anticholinergic sym and confusion with a desipramine level of 527 ng/mL. The desipramine dose was lowered to 200 mg/day later, the level was 244 ng/mL; the patient reported decreased energy, impaired short-term memory, and speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced to adverse effects resolved in six days. Eight days later, the desipramine level was 122 ng/mL (Downs et al
f) Concomitant administration of fluoxetine and desipramine was reported to result in an increased desip new onset of delirium in a 69-year-old male within 10 days of the addition of fluoxetine to the patient's reg al, 1990).

3.5.1.BT Fluvoxamine

1) Interaction Effect: imipramine toxicity (dry mouth, urinary retention, sedation)
2) Summary: Addition of fluvoxamine to imipramine or desipramine therapy can result in significantly increas antidepressant plasma levels and signs of tricyclic toxicity (Spina et al, 1992a; Spina et al, 1993aa; Spina et a Fluvoxamine significantly increases imipramine half-life and reduces clearance (Spina et al, 1993a). The add fluvoxamine to imipramine or desipramine therapy may result in greatly increased tricyclic antidepressant pla tricyclic toxicity (Spina et al, 1992a; Spina et al, 1993aa). A bidirectional effect is suggested, in which fluvoxa imipramine concentrations (by interfering with N-demethylation), and imipramine increases fluvoxamine level 1993a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients for signs of imipramine and fluvoxamine toxicity; lower doses of on may be required with concomitant therapy.
7) Probable Mechanism: decreased imipramine metabolism
8) Literature Reports
a) The pharmacokinetics of combined imipramine and fluvoxamine were studied in healthy volunteers (S After a 7-day course of fluvoxamine, imipramine half-life was significantly increased (from 23 to 41 hours decreased (from 1.02 to 0.28 L/h/kg).
b) The addition of fluvoxamine to imipramine or desipramine in four patients was reported to result in gre tricyclic antidepressant plasma levels (Spina et al, 1992). Three of four patients showed signs of tricyclic of fluvoxamine 100 mg daily for 10 days on plasma concentrations of imipramine was studied in seven d on maintenance therapy (Spina et al, 1993a). Imipramine plasma levels were three to four times higher d coadministration. One patient complained of anticholinergic effects, along with tremor and confusion. The this drug interaction was inhibition of demethylation of imipramine. A pharmacokinetic study in healthy vo demonstrated a significantly increased imipramine half-life and reduced clearance (Spina et al, 1993).
c) Metabolism of tricyclic antidepressants coadministered with fluvoxamine was studied in eight depress patients received imipramine) (Hartter et al, 1993). Fluvoxamine was found to interfere with N-demethyla The combination of fluvoxamine and imipramine led to increased plasma levels of imipramine and decrea concentrations of the N-demethylated imipramine metabolite desimipramine. In addition, TCA-fluvoxamin apparently raised plasma levels of fluvoxamine.

3.5.1.BU Formoterol

1) Interaction Effect: an increased risk of cardiovascular excitation
2) Summary: Concurrent administration of formoterol with a tricyclic antidepressant (TCA) may lead to poten formoterol's adrenergic effects on the cardiovascular system. Therefore, extreme caution is advised if formote to patients who are being treated with a TCA (Prod Info FORADIL(R) AEROLIZER(R) inhalation powder, 200 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 warra formoterol is administered concurrently with a tricyclic antidepressant (TCA) as the cardiovascular effects of f potentiated by TCAs (Prod Info FORADIL(R) AEROLIZER(R) inhalation powder, 2006).
7) Probable Mechanism: potentiation of cardiovascular effects

3.5.1.BV Fosamprenavir

1) Interaction Effect: increased tricyclic agent serum concentrations and potential toxicity (anticholinergic effe confusion, cardiac arrhythmias)
2) Summary: Coadministration of fosamprenavir with a tricyclic antidepressant may provoke increased serum the tricyclic antidepressant, causing a potential risk of arrhythmias or other serious adverse effects. Fosampr of amprenavir, an inhibitor of the CYP3A4 isoenzyme in addition to being a CYP3A4 substrate. Tricyclic agen

depend on the CYP3A4 pathway for metabolism. Plasma concentrations of the tricyclic agent should be close 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 unavoida concentrations of the tricyclic agent should be closely monitored. Also monitor patients for signs and symptor toxicity (anticholinergic effects, sedation, confusion, cardiac arrhythmias) (Prod Info LEXIVA(R) oral solution,
7) Probable Mechanism: inhibition of CYP3A4-mediated tricyclic agent metabolism

3.5.1.BW 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 tachyca fibrillation, and torsades de pointes. Because tricyclic antidepressants may also prolong the QT interval and i arrhythmias, the concurrent administration of foscarnet and tricyclic antidepressants is not recommended (Pr (R), 1998; Marshall & Forker, 1982u).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of foscarnet and tricyclic antidepressants is not recor
7) Probable Mechanism: additive cardiac effects

3.5.1.BX 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 occur with fosphenytoin (Prod Info Cerebyx(R), 1999). A few case reports have indicated that imipramine inhi metabolism resulting in increased serum phenytoin concentration (Petti & Campbell, 1975; Perucca & Richer antidepressants (TCAs) may lower the seizure threshold in epileptic patients stabilized on anticonvulsants. Tl because phenytoin is an enzyme inducer, the metabolism of antidepressants may be increased resulting in re 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 patient begins to exhibit signs of toxicity (tremor, nystagmus, ataxia, hyperreflexia); lower doses of phenytoin 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.BY 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 tachy fibrillation, and torsades de pointes. Although pharmacokinetic studies between gatifloxacin and other drugs v QT interval have not been performed, an additive effect cannot be excluded. Therefore, the concurrent admir 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 re
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BZ 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 interva antidepressants, have not been performed, gemifloxacin should be used cautiously when given concurrently 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 ge tricyclic antidepressants, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CA 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 prolongatio interval. On an outpatient basis, grepafloxacin is contraindicated with other drugs that are known to also prolo interval or cause torsades de pointes, including tricyclic antidepressants. When appropriate cardiac monitorin such as in the hospitalized patient, these two agents should be coadministered with caution (Prod Info Raxar

3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The concurrent use of grepafloxacin and tricyclic antidepressants is contraindicated appropriate cardiac monitoring can be assured, such as in the hospitalized patient.
7) Probable Mechanism: additive cardiac effects

3.5.1.CB Guanadrel
1) Interaction Effect: decreased antihypertensive effectiveness
2) Summary: Tricyclic antidepressants inhibit the uptake of guanethidine and possibly guanadrel into the adr resulting in an inhibition of its antihypertensive effect (Mitchell et al, 1967; Ober & Wang, 1973). When a patie concomitant tricyclic antidepressant and guanadrel therapy, caution should be exercised when the tricyclic ar 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 do may be required. An alternative class of antihypertensive agents such as angiotensin-converting enzyme inhi considered.
7) Probable Mechanism: decreased uptake of guanadrel into adrenergic neurons

3.5.1.CC Guanethidine
1) Interaction Effect: decreased antihypertensive effectiveness
2) Summary: Tricyclic antidepressants inhibit the uptake of guanethidine, and possibly guanadrel, into the ac resulting in an inhibition of the antihypertensive effect (Gulati et al, 1966; Mitchell et al, 1967a; Ober & Wang, al, 1964).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Blood pressure should be monitored for an appropriate clinical response; higher do guanethidine may be required. An alternative class of antihypertensive agents, such as angiotensin-convertir might be considered.
7) Probable Mechanism: decrease uptake of guanethidine into adrenergic neurons

3.5.1.CD Guanfacine
1) Interaction Effect: decreased antihypertensive effectiveness
2) Summary: Concomitant clonidine and tricyclic antidepressant (TCA) therapy may impair the antihypertens clonidine. Since the mechanism of action of guanfacine is similar to clonidine, patients stabilized on guanfaci monitored for a hypertensive response when TCA (i.e. desipramine or imipramine) therapy is started (Briant e 1983b). A case has been reported of a patient maintained on guanfacine who developed an increase in blooc imipramine was added to therapy. When imipramine was discontinued, her blood pressure returned to baseli Feely, 1991a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Blood pressure should be monitored for an appropriate clinical response; higher do may be required. An alternative class of antihypertensive agents, such as an angiotensin-converting enzyme considered.
7) Probable Mechanism: unknown
8) Literature Reports
a) A case of a hypertensive female who was maintained on guanfacine 2 mg daily with mean blood pres mm Hg was reported (Buckley & Feely, 1991). After amitriptyline 75 mg daily was begun, her mean bloo 150/100 mm Hg; upon discontinuation of the amitriptyline, the blood pressure returned to 136/91 mm Hg was given imipramine 50 mg daily and experienced similar changes in loss of blood pressure control; up of imipramine, the blood pressure again returned to 137/90 mm Hg.
b) Concomitant clonidine and tricyclic antidepressant therapy may impair the antihypertensive effects of the mechanism of action of guanfacine is similar to clonidine, patients stabilized on guanfacine should be hypertensive response when desipramine therapy is started (Briant et al, 1973b; Hui, 1983a).

3.5.1.CE 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 tachy fibrillation, and torsades de pointes. Because tricyclic antidepressants may also prolong the QT interval and i arrhythmias, the concurrent administration of halofantrine and tricyclic antidepressants is not recommended ((R), 1998; Marshall & Forker, 1982aa).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable

6) Clinical Management: The concurrent administration of halofantrine and a tricyclic antidepressant is not re
7) Probable Mechanism: additive cardiac effects

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

3.5.1.CG 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 ant also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of halothane a antidepressants is not recommended (Marshall & Forker, 1982p).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Because of the potential for additive QT interval prolongation, the concurrent admin halothane and tricyclic antidepressants is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CH Heptabarbital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased me TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen s reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressa
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant do required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum con 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 pa treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were ex metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Comp epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), s area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipram half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of h and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effe expected with any combination of TCA and barbiturate.

3.5.1.CI Hexobarbital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased me TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence (Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen s reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressa
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant do required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum con

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 pa treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were ex metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Comp epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), s area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipram half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of h and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effe expected with any combination of TCA and barbiturate.

3.5.1.CJ 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 inte recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadm Ia antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is n (Prod Info Elavil(R), 1999g; Prod Info Quinaglute(R), 1999; Marshall & Forker, 1982n).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic agent and a tricyclic anti 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 imi desipramine (Brosen & Gram, 1989). Inhibition of this enzyme system can result in a 35% decrease in im clearance and 85% decrease in desipramine clearance. Demethylation of imipramine by the cytochrome unaffected by this interaction. Until more information is available all patients having quinidine added to d containing imipramine or desipramine should be monitored for increased antidepressant serum concentr potential toxicity.
b) An increased incidence in sudden death was observed in six out of 53 patients with cardiac disease r amitriptyline, compared to 0 out of 53 in the control group. It was recommended that amitriptyline be avo with underlying cardiac disease except when depression was debilitating and no other drugs were helpfu Coull et al, 1970).
c) In a placebo controlled study, imipramine 3.5 mg/kg was administered daily for seven patients with se and titrated doses to obtain therapeutic plasma concentrations. Two patients displayed premature atrial c and premature ventricular depolarizations before therapy. On patient had 33 premature atrial depolarizat premature ventricular depolarizations (PVD) per hour, which decreased to 0.4 PAC and zero PVC per ho The other patient had 12 PAD and 169 PVD per hour before treatment and 1.8 PAD and 28.1 PVD per h The authors also cautioned that the incidence of cardiotoxicity may increase if tricyclic antidepressants a with Type I antiarrhythmics. It was also recommended that quinidine and procainamide not be used to tre of a tricyclic overdose. The similarities between these agents may exacerbate the cardiotoxicity (Kantor e

3.5.1.CK 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 ant agents, including acecainide (Chow et al, 1984), amiodarone (Faggiano et al, 1996), azimilide (Corey et al, 1 (Gilman et al, 1985), ibutilide (Rodriguez et al, 2001), sematilide (Singh, 1996), dofetilide (Allen et al, 2002), a & Runge, 2001). Even though no formal drug interaction studies have been done, the coadministration of Cla antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not (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 antidepres recommended.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include incre prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flat (Marshall & Forker, 1982ab).
b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, s antidepressants, is not recommended. Dofetilide should be stopped for at least 2 days before any interac initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yam 2003).

3.5.1.CL Iobenguane I 131

1) Interaction Effect: false-negative results of scintigraphy
2) Summary: Imipramine, which selectively blocks the active transport of catecholamines into storage vesicle myocardial uptake of iobenguane I-131 and increases the rate of loss of iobenguane I-131 from the liver, thus scintigraphy (Sisson et al, 1987).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Imipramine should be discontinued prior to any procedure using iobenguane I-131.
7) Probable Mechanism: reduction of iobenguane I-131 uptake

3.5.1.CM Iproniazid

1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus changes)
2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concu and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982o; Spig Brodribb et al, 1994m; Neuvonen et al, 1993g). Serotonin syndrome is a rare but potentially fatal condition of hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Ste TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clom desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971n; White & Simpson, 198
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of a tricyclic antidepressant (TCA) and a monoamine oxidase inhi should be done only with close monitoring and where the clinical benefit outweighs the potential risk. Other a therapy should first be considered. Consider using a 14 day washout period between treatment with both me clinically necessary, avoid large doses and use agents other than imipramine, clomipramine, desipramine, ar
7) Probable Mechanism: altered catecholamine uptake and metabolism
8) Literature Reports

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

b) Administration of a TCA after MAOI therapy may result in the development of serotonin syndrome. In crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-com two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipram taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both leg diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hou 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 fo prior to switching to moclobemide 300 mg daily. The patient experienced somnolescence, confusion, an progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patie were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days l 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 p 34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sw by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulatio death (Tackley & Tregaskis, 1987h).

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

3.5.1.CN Isocarboxazid

1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus changes)
2) Summary: The concurrent administration of isocarboxazid and imipramine is contraindicated (Prod Info M Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MA has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982g; Spigset et al, 1 al, 1994g; Neuvonen et al, 1993c). Serotonin syndrome is a rare but potentially fatal condition of serotonergic characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991d). MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, d tranylcypromine, and monitor patients closely (Schuckit et al, 1971g; White & Simpson, 1984f).
3) Severity: contraindicated

4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of imipramine and isocarboxazid is contraindicated. In patients to isocarboxazid therapy from a dibenzazepine-related entity, allow at least a one-week medication-free inter initiate isocarboxazid at one-half of the normal dose for at least the first week of therapy. Also allow one week between the discontinuation of isocarboxazid and the administration of another MAO inhibitor or dibenzazepi
7) Probable Mechanism: altered catecholamine uptake and metabolism
8) Literature Reports
a) Concomitant administration of monoamine oxidase inhibitors (MAOI) with tricyclic antidepressants (TC considered an absolute contraindication in the past and still is listed as such by the manufacturers. Repo hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner et al, 1963b; Winston, 1971c; Schuckit et al, 1971f; Sargent, 1965b; Spiker & Pugh, 1976c). The mechar the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catec metabolism (Sjoqvist, 1965c).
b) The development of serotonin syndrome was reported due to administration of a TCA after MAOI the blind, crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessiv disorder, two subjects developed severe reactions characteristic of serotonin syndrome. During the study received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent c therapy. After taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerk hyperreflexia, diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first do motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolve later, and both patients were later treated successfully with clomipramine without adverse effects (Insel e
c) A drug interaction was reported when a 76-year old woman who had been taking clomipramine 50 mg months was switched to moclobemide 300 mg daily. The patient experienced somnolescence, confusion then progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The symptoms were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a after discontinuing all antidepressant medications (Spigset et al, 1993g).
d) A 39-year old woman with bipolar disorder developed serotonin syndrome after imipramine was adde The patient was taking moclobemide 300 mg twice daily when imipramine was started at 50 mg daily, fol dosage increases of imipramine to 200 mg and a reduction of moclobemide dosage to 150 mg twice dail the increase in imipramine to 200 mg per day, the patient developed symptoms of serotonin syndrome, i shivering, confusion, fever, and spasms in the extremities. The patient was treated with chlorpromazine a 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 isocarboxazid and amitriptyline. In all three cases the patients had been given MAOIs and TCAs alone w complications. It was only when the drugs were used in combination that symptoms of mania emerged, s 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 pl 34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sw by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulatio death (Tackley & Tregaskis, 1987d).
g) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsi TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 15 or its equivalent, 45 mg phenelzine, or 60 mg isocarboxazid) b) oral administration c) avoidance of clomi imipramine, desipramine, and tranylcypromine in any combination, and d) close monitoring of patients (K Winston, 1971c; Schuckit et al, 1971f; White & Simpson, 1984e; Rom & Benner, 1972b). The combinatio in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to t and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991c). Alternatively previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some s that the combination of amitriptyline and isocarboxazid is preferred (Perry et al, 1991c). Numerous studie refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TC 1977c; Schuckit et al, 1971f; Ashcroft, 1975c).

3.5.1.CO 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 anti also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of isoflurane a antidepressants is not recommended (Marshall & Forker, 1982v).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Because of the potential for additive QT interval prolongation, the concurrent admin isoflurane and a tricyclic antidepressants is not recommended.
7) Probable Mechanism: additive effect on QT prolongation

3.5.1.CP 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 tachyca

fibrillation, and torsades de pointes. Because tricyclic antidepressants may also prolong the QT interval and i
arrhythmias, the concurrent administration of isradipine with a tricyclic antidepressant is not recommended (F
(R), 2000; Marshall & Forker, 1982z).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of isradipine and a tricyclic antidepressant is not rec
7) Probable Mechanism: additive cardiac effects

3.5.1.CQ Ketoconazole
1) Interaction Effect: decreased clearance and prolonged half-life of imipramine
2) Summary: In a controlled study of six healthy volunteers, coadministration of ketoconazole with a single d
resulted in an increase in imipramine area under the concentration-time curve (AUC) and imipramine half-life
decrease in imipramine clearance. The changes were minor, however, and deemed to be likely clinically insig
considering the wide therapeutic range of imipramine (Spina et al, 1997a).
3) Severity: minor
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, downward dosage adju
imipramine may be necessary.
7) Probable Mechanism: inhibition of imipramine hepatic metabolism
8) Literature Reports
a) A controlled study evaluated oral ketoconazole and the pharmacokinetic effects on oral imipramine a
12 healthy male volunteers. The subjects were divided into two groups and received either a single dose
mg or desipramine 100 mg, both alone and after 10 days of a 14-day regimen of oral ketoconazole 200 r
Coadministration of ketoconazole resulted in significantly increased imipramine area under the concentra
(AUC) values (from 3795 +/- 918 nmol h/L to 4567 +/- 1076 nmol h/L) and significantly decreased imipra
clearance (from 1.16 +/- 0.21 L/hr/kg to 0.96 +/- 0.20 L/hr/kg). Imipramine half-life was also significantly i
coadministration with ketoconazole, from 16.7 +/- 3.3 hours to 19.2 +/- 5.4 hours. The changes in imipra
pharmacokinetics were deemed to be minor considering the therapeutic range of the drug. During coadm
ketoconazole with desipramine, no significant pharmacokinetic changes were observed. The authors cor
ketoconazole inhibits the N-demethylation of imipramine by cytochrome P450 3A4, without affecting the
imipramine and desipramine, which is thought to be mediated through the cytochrome P450 2D6 pathwa
1997).

3.5.1.CR Labetalol
1) Interaction Effect: imipramine toxicity (dry mouth, urinary retention, sedation)
2) Summary: Labetalol decreased imipramine clearance by 38% (statistically significant) compared to placeb
crossover study in 12 healthy subjects (Hermann et al, 1992). Labetalol increased imipramine area under the
time curve (AUC) by 53% compared to placebo, which was also significant. The clinical significance of the ph
interaction is undetermined.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor for anticholinergic side effects of imipramine if labetalol is added to therapy
imipramine may be appropriate. Conversely, if labetalol is discontinued, monitor continued clinical efficacy of
adjust dosage accordingly.
7) Probable Mechanism: decreased imipramine metabolism, increased imipramine AUC

3.5.1.CS Levomethadyl
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Any drug known to have the potential to prolong the QT interval should not be used with levom
pharmacodynamic interactions can occur between levomethadyl and potentially arrhythmogenic agents such
prolong the QT interval (Prod Info Orlaam(R), 2001).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Levomethadyl is contraindicated in patients being treated with imipramine as it may
prolongation and interact with levomethadyl.
7) Probable Mechanism: unknown

3.5.1.CT Lidoflazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and lidoflazine have been shown to prolong the QTc interval a
recommended therapeutic dose (Hanley & Hampton, 1983; Marshall & Forker, 1982r). Even though no forma
studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong tl
such as lidoflazine, is not recommended (Prod Info Elavil(R), 1999i).
3) Severity: major

4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of lidoflazine and tricyclic antidepressants is not reco
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CU Linezolid

1) Interaction Effect: increased risk of serotonin syndrome (hyperthermia, hyperreflexia, myoclonus, mental s
2) Summary: Concomitant use of linezolid and a tricyclic antidepressant, such as imipramine, is contraindica of monitoring for serotonin syndrome. If symptoms occur, consider discontinuation of either one or both of the is a reversible, nonselective inhibitor of monoamine oxidase and may therefore interact with tricyclic antidepr Spontaneous reports of serotonin syndrome associated with the co-administration of linezolid and serotonerg 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 imipramine, is cor unless patient is closely observed for signs and/or symptoms of serotonin syndrome. If concomitant use is cli monitor for signs and symptoms of serotonin syndrome, such as neuromuscular abnormalities (including hyp muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including tachycardi diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation an Serotonin syndrome can be life-threatening. If serotonin syndrome develops, discontinue the offending agent supportive care and other therapy as necessary (Boyer & Shannon, 2005; Prod Info ZYVOX(R) IV injection, o suspension, 2008).
7) Probable Mechanism: linezolid inhibition of monoamine oxidase resulting in an increased concentration of

3.5.1.CV Lisdexamfetamine

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

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained i amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXE 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 o antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transde 2006).

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

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transi clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramin 1990).

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

3.5.1.CW Lorcainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class I antiarrhythmics have been shown to prolong the QTc interval at the recommended ther
Even though no formal drug interaction studies have been done, the coadministration of Class I antiarrhythmi
known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Prod Info Tambo
acetate, 1998; Larochelle et al, 1984; Scagliotti et al, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class I antiarrhythmic and a tricyclic antidepress
recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include incre
prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flat
(Marshall & Forker, 1982q).
b) A 68-year-old man suffering from agitated major depression was begun on a dose of desipramine 12
produced a subtherapeutic serum level of 442 nmol/L (therapeutic range = 500 to 1000 nmol/L). An incre
mg daily produced excellent clinical response with no side effects. He developed atrial fibrillation and flut
mg daily was added to his therapy, and desipramine was discontinued. His arrhythmia was suppressed v
propafenone 150 mg twice daily and 300 mg at bedtime. Desipramine 150 mg daily was again begun, at
experienced dry mouth, sedation, and shakiness; the desipramine serum level was measured at 2092 nr
desipramine was discontinued for five days, the side effects ceased, and desipramine therapy was resur
The desipramine serum level was measured at 1130 nmol/L (Katz, 1991).

3.5.1.CX Lumefantrine

1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Lumefantrine is a CYP2D6 inhibitor and may cause QT interval prolongation. Concomitant use
artemether/lumefantrine and a CYP2D6 substrate (eg, amitriptyline, clomipramine, flecainide, and imipramine
elevated drug levels of the CYP2D6 substrate. As some CYP2D6 substrates can also prolong the QT interva
for additive QT prolongation. Therefore, artemether/lumefantrine should not be coadministered with CYP2D6
possess cardiac effects (Prod Info COARTEM(R) oral tablets, 2009).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Artemether/lumefantrine should not be administered concomitantly with CYP2D6 su
amitriptyline, clomipramine, flecainide, and imipramine, due to the potential additive effect on QT interval prol
Info COARTEM(R) oral tablets, 2009).
7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.CY Mazindol

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte
enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973d; Raisfeld, 1972). A sim
also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been n
(Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most co
not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs f
moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo
therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of
agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects
dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho
could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) o
Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral t
Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension ar
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen
coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained in
amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXE
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 o
antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transde
2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in
such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mm

of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure return normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Fle Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transie clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desiprami 1990).

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

3.5.1.CZ Mephentermine

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

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

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

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

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained i amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXE 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 c antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transde 2006).

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

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transie clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desiprami 1990).

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

3.5.1.DA Mephobarbital

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

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

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dc required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum con 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 pa treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were e metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Comp epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), s area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipran half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of h and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar eff expected with any combination of TCA and barbiturate.

3.5.1.DB 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 oth prolong the QT interval is contraindicated (Prod Info Serentil(R), 2001). Tricyclic antidepressants (TCAs) at th 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 contrain

7) Probable Mechanism: additive effect on QT interval

3.5.1.DC Mestranol

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

2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or de estrogens (Somani & Khurana, 1973i), with paradoxical loss of antidepressant effect yet tricyclic toxicity being simultaneously (Prange, 1972i). The effects of the interaction appear to be estrogen dose-related (Khurana, 1 of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on e (Krishnan et al, 1984i).

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment down estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, d 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. I depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received place imipramine (150 milligrams/day) and placebo, 5 patients received imipramine (150 milligrams/day) and e micrograms/day), while 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (25 mic 10 patients that received placebo did not improve over the 6 weeks of the study. The 10 patients taking e imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients takin alone. However, after 2 weeks, the 5 patients that received imipramine and high-dose estrogen had not i as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsine affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period o required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed residual estrogen in the high-dose group. In another group, 5 women received imipramine 150 milligrams estradiol 50 micrograms daily did not improve as much as 10 patients receiving only imipramine. Also, th combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange,

b) A case report demonstrated an interaction in a 32-year-old female taking conjugated estrogens 2.5 m imipramine 100 milligrams (Khurana, 1972h). The patient developed lethargy, tremors, and signs of depe After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. U the estrogen, the side-effects abated. Some investigators have proposed that the side effects resulted fr 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 begin there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' clomipramine. It was proposed that there was no significant difference in side-effects between the groups groups were matched after patients had dropped out of the study. Had the patients been matched prior t different conclusions may have been drawn (Beaumont, 1973e).

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 three women took clomipramine 25 milligrams at bedtime while 19 took clomipramine 25 milligrams at be contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimenta side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of se concentrations. No difference in serum concentrations was noted between the groups. However, this res 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 antidep

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

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

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 19 are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the cer system resulting in an antidepressant effect (Oppenheim, 1983d).

3.5.1.DD Methamphetamine

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

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

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

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

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained in amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXE 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 o antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transde 2006).

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

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transie clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramin 1990).

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

3.5.1.DE Methohexital

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

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

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant do required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum con 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 pa treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were e metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Comp epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), s area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipran half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of h and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effe expected with any combination of TCA and barbiturate.

3.5.1.DF 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 d drugs to volunteers on tricyclic antidepressants. Arrhythmias and other severe adverse effects have also bee 1980; Avery, 1973a; Boakes et al, 1973a; Boakes, 1973; Mitchell et al, 1970; Stone et al, 1964a). Local use (anesthesia) of epinephrine in concentrations of 1:100,000 or less is less likely to precipitate clinically significa 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 enhanced in the presence of tricyclic antidepressants (TCAs). Concomitant use should be avoided. If these d together, careful monitoring and a dose reduction of the sympathomimetic is required. Patients should be inst 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 (epineph norepinephrine, phenylephrine, and isoproterenol) before and after imipramine (25 mg three times daily f showed an increased pressor response to epinephrine (2- to 4-fold), norepinephrine (4- to 8-fold), and ph 3-fold) after imipramine, but no difference was observed in the response to isoproterenol. Thus, the incre response appeared to occur only for alpha adrenergic effects. All four subjects demonstrated changes in with epinephrine and imipramine consisting of sinus arrhythmia in three subjects and multiple ectopic be rhythm in the fourth subject (Boakes et al, 1973).
b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found th receiving a local anesthetic with norepinephrine (1:25,000) had severe reactions (severe headaches, che subarachnoid hemorrhage). The drug history was incomplete, but at least three had been taking a tricycl at the time (Anon, 1972).

3.5.1.DG Methylphenidate

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

antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transde 2006).

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

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transi clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desiprami 1990).

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

3.5.1.DH Mibefradil

1) Interaction Effect: an increased risk of imipramine toxicity (drowsiness, hypotension, akathisia)

2) Summary: Imipramine is metabolized by cytochrome P450 2D6 and has a high first-pass effect. When mib inhibitor of CYP450 2D6) and imipramine were coadministered, the area under the concentration-time curve (imipramine was increased seven- to eight-fold (Prod Info Posicor(R), 1997).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients for excessive imipramine adverse effects (drowsiness, hypotensior dosage adjustment of imipramine may be necessary.

7) Probable Mechanism: inhibition of imipramine metabolism

3.5.1.DI 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 c drugs to volunteers on tricyclic antidepressants. Arrhythmias and other severe adverse effects have also bee 1980; Avery, 1973a; Boakes et al, 1973a; Boakes, 1973; Mitchell et al, 1970; Stone et al, 1964a). Local use (anesthesia) of epinephrine in concentrations of 1:100,000 or less is less likely to precipitate clinically significa 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 enhanced in the presence of tricyclic antidepressants (TCAs). Concomitant use should be avoided. If these d together, careful monitoring and a dose reduction of the sympathomimetic is required. Patients should be inst 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 (epineph norepinephrine, phenylephrine, and isoproterenol) before and after imipramine (25 mg three times daily f showed an increased pressor response to epinephrine (2- to 4-fold), norepinephrine (4- to 8-fold), and ph 3-fold) after imipramine, but no difference was observed in the response to isoproterenol. Thus, the incre response appeared to occur only for alpha adrenergic effects. All four subjects demonstrated changes in with epinephrine and imipramine consisting of sinus arrhythmia in three subjects and multiple ectopic be rhythm in the fourth subject (Boakes et al, 1973).

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

3.5.1.DJ Moclobemide

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

2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concur and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982c; Spig Brodribb et al, 1994c; Neuvonen et al, 1993a). Serotonin syndrome is a rare but potentially fatal condition of s hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Ste Subsequently, the concomitant use of TCAs and MAOIs is contraindicated in most cases. If TCAs and MAOIs concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and trany monitor patients closely (Schuckit et al, 1971c; White & Simpson, 1984b).

3) Severity: contraindicated

4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Concomitant use of moclobemide and imipramine is contraindicated. If imipramine i
treatment with moclobemide, a minimum of 2 weeks should elapse after moclobemide is discontinued and im
is begun (Prod Info imipramine hydrochloride oral tablet, 2003). However, the manufacturer of moclobemide
short washout period of 2 days after discontinuation of moclobemide and before imipramine is initiated (Prod
2001). There is no specific washout period for replacing imipramine treatment with moclobemide. However, it
gradually taper the tricyclic antidepressant dosage before starting treatment with an 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 (T
considered an absolute contraindication in the past and still is listed as such by the manufacturers. Repo
hyperpyrexia, convulsions, and possible death have been attributed to the combination (Prod Info imipra
oral tablet, 2003; Lockett & Milner, 1965a; Brachfeld et al, 1963; Winston, 1971a; Schuckit et al, 1971b; S
Spiker & Pugh, 1976a). The mechanism may relate to the combined inhibition of catecholamine reuptake
nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965a).

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

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

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

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

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

g) Three patients with bipolar disorder developed manic symptoms while undergoing concurrent therapy
isocarboxazid and amitriptyline. In all three cases the patients had been given MAOIs and TCAs alone w
complications. It was only when the drugs were used in combination that symptoms of mania emerged, s
synergistic effect (de la Fuente et al, 1986).

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

i) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unrespons
TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 15
or its equivalent, 45 mg phenelzine, or 60 mg isocarboxazid) b) oral administration c) avoidance of clomi
imipramine, desipramine, and tranylcypromine in any combination, and d) close monitoring of patients (K
Winston, 1971a; Schuckit et al, 1971b; White & Simpson, 1984a; Rom & Benner, 1972). The combinatio
in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to t
and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991a). Alternativel
previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some s
that the combination of amitriptyline and isocarboxazid is preferred (Perry et al, 1991a). Numerous studie
refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TC
1977a; Schuckit et al, 1971b; Ashcroft, 1975a).

3.5.1.DK 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 avoide
receiving agents that also prolong the QT interval, such as tricyclic antidepressants. Although pharmacokinet
moxifloxacin and other drugs which prolong the QT interval have not been performed, an additive effect cann
Therefore, moxifloxacin should be used with caution when given concurrently with a tricyclic antidepressant (
(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 ar
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.DL Nefopam

1) Interaction Effect: an increased risk of seizures
2) Summary: Nefopam inhibits the neuronal uptake of norepinephrine and serotonin and increases the risk o especially in patients with a history of a convulsive disorder. Tricyclic antidepressants also lower the seizure t Therefore, the manufacturer of nefopam advises caution in patients on concurrent tricyclic antidepressant the 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 p nefopam and a tricyclic antidepressant. An alternative analgesic may be considered.
7) Probable Mechanism: additive lowering of seizure threshold

3.5.1.DM Nialamide

1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus changes)
2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concur and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982k; Spig Brodribb et al, 1994j; Neuvonen et al, 1993e). Serotonin syndrome is a rare but potentially fatal condition of s hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Ste TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clom desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971j; White & Simpson, 198
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of a tricyclic antidepressant (TCA) and a monoamine oxidase inhi should be done only with close monitoring and where the clinical benefit outweighs the potential risk. Other a therapy should first be considered. If deemed clinically necessary, avoid large doses and use agents other th 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 (T considered an absolute contraindication in the past. Reports of excitation, hyperpyrexia, convulsions, and have been attributed to the combination (Lockett & Milner, 1965e; Winston, 1971e; Schuckit et al, 1971i; 1976e). The mechanism may relate to the combined inhibition of catecholamine reuptake into the centra and inhibition of catecholamine metabolism (Sjoqvist, 1965e).

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

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

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

e) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsi TCA alone. The combination may be utilized in one of two ways. Most frequently, the recommendation is previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then sim started (Perry et al, 1991e). Alternatively, in a patient previously receiving a TCA, small doses of the MA added (Schoonover, 1983). Numerous studies in patients with refractory depression or phobic anxiety st successfully used the combination of MAOIs and TCAs (Ponto et al, 1977e; Schuckit et al, 1971i; Ashcro

3.5.1.DN 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 c drugs to volunteers on tricyclic antidepressants. Arrhythmias and other severe adverse effects have also bee 1980; Avery, 1973a; Boakes et al, 1973a; Boakes, 1973; Mitchell et al, 1970; Stone et al, 1964a). Local use (anesthesia) of epinephrine in concentrations of 1:100,000 or less is less likely to precipitate clinically significa 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 enhanced in the presence of tricyclic antidepressants (TCAs). Concomitant use should be avoided. If these d together, careful monitoring and a dose reduction of the sympathomimetic is required. Patients should be inst 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 (epineph norepinephrine, phenylephrine, and isoproterenol) before and after imipramine (25 mg three times daily f showed an increased pressor response to epinephrine (2- to 4-fold), norepinephrine (4- to 8-fold), and ph 3-fold) after imipramine, but no difference was observed in the response to isoproterenol. Thus, the incre response appeared to occur only for alpha adrenergic effects. All four subjects demonstrated changes in with epinephrine and imipramine consisting of sinus arrhythmia in three subjects and multiple ectopic be rhythm in the fourth subject (Boakes et al, 1973).
b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found th receiving a local anesthetic with norepinephrine (1:25,000) had severe reactions (severe headaches, che subarachnoid hemorrhage). The drug history was incomplete, but at least three had been taking a tricycl at the time (Anon, 1972).

3.5.1.DO 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 a recommended therapeutic dose (Prod Info Sandostatin(R), 1999; Marshall & Forker, 1982). Even though no f interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known t 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 reco
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.DP 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 c drugs to volunteers on tricyclic antidepressants. Arrhythmias and other severe adverse effects have also bee 1980; Avery, 1973a; Boakes et al, 1973a; Boakes, 1973; Mitchell et al, 1970; Stone et al, 1964a). Local use (anesthesia) of epinephrine in concentrations of 1:100,000 or less is less likely to precipitate clinically significa 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 enhanced in the presence of tricyclic antidepressants (TCAs). Concomitant use should be avoided. If these d together, careful monitoring and a dose reduction of the sympathomimetic is required. Patients should be inst 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 (epineph norepinephrine, phenylephrine, and isoproterenol) before and after imipramine (25 mg three times daily f showed an increased pressor response to epinephrine (2- to 4-fold), norepinephrine (4- to 8-fold), and ph 3-fold) after imipramine, but no difference was observed in the response to isoproterenol. Thus, the incre response appeared to occur only for alpha adrenergic effects. All four subjects demonstrated changes in with epinephrine and imipramine consisting of sinus arrhythmia in three subjects and multiple ectopic be rhythm in the fourth subject (Boakes et al, 1973).
b) A review of spontaneous reports of adverse reactions to vasoconstrictors in local anesthetics found th receiving a local anesthetic with norepinephrine (1:25,000) had severe reactions (severe headaches, che subarachnoid hemorrhage). The drug history was incomplete, but at least three had been taking a tricycl at the time (Anon, 1972).

3.5.1.DQ Pargyline

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

changes)
2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concu
and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982a; Spig
Brodribb et al, 1994; Neuvonen et al, 1993). Serotonin syndrome is a rare but potentially fatal condition of se
hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Ste
TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clom
desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971a; White & Simpson, 198
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of a tricyclic antidepressant (TCA) and a monoamine oxidase inhi
should be done only with close monitoring and where the clinical benefit outweighs the potential risk. Other a
therapy should first be considered. If deemed clinically necessary, avoid large doses and use agents other th
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 (T
considered an absolute contraindication in the past. Reports of excitation, hyperpyrexia, convulsions, an
have been attributed to the combination (Lockett & Milner, 1965; Winston, 1971; Schuckit et al, 1971; Sp
1976). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central
and inhibition of catecholamine metabolism (Sjoqvist, 1965).
b) Administration of a TCA after MAOI therapy may result in the development of serotonin syndrome. In
crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-com
two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients
clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipram
taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both leg
diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper
symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hou
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 fo
prior to switching to moclobemide 300 mg daily. The patient experienced somnolescence, confusion, an
progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patie
were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days l
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 p
34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sv
by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulatio
death (Tackley & Tregaskis, 1987).
e) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unrespons
TCA alone. The combination may be utilized in one of two ways. Most frequently, the recommendation is
previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then sim
started (Perry et al, 1991). Alternatively, in a patient previously receiving a TCA, small doses of the MAO
added (Schoonover, 1983). Numerous studies in patients with refractory depression or phobic anxiety st
successfully used the combination of MAOIs and TCAs (Ponto et al, 1977; Schuckit et al, 1971; Ashcroft

3.5.1.DR Paroxetine
1) Interaction Effect: imipramine toxicity (dry mouth, sedation, urinary retention)
2) Summary: Paroxetine coadministered with desipramine or imipramine produced higher serum concentrati
antidepressant (TCA) in some patients (Prod Info Paxil CR(TM), 2003; Hartter et al, 1994; Brosen et al, 1993
effect on TCAs may resemble that of fluoxetine (another selective serotonin reuptake inhibitor), which is knov
metabolism (Aranow et al, 1989b; Vaughan, 1988; Goodnick, 1989b). With coadministration, monitor patients
toxicity. Imipramine doses may need to be reduced.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of paroxetine with other drugs that are metabolized by cytochrom
(CYP2D6) should be approached with caution. When paroxetine is coadministered with imipramine, monitor
and symptoms of imipramine toxicity (dry mouth, sedation, urinary retention, blurred vision). Imipramine dose
reduced.
7) Probable Mechanism: decreased cytochrome P450 2D6-mediated imipramine metabolism
8) Literature Reports
a) The effect of paroxetine on desipramine metabolism was studied in nine extensive metabolizers (EM)
metabolizers (PM) of desipramine. Subjects took a single oral dose of desipramine before starting paroxe
dose after 11 days of paroxetine use. After the addition of paroxetine, EMs experienced a 5-fold decreas
desipramine, indicating that paroxetine inhibits oxidation reactions catalyzed by CYP2D6. PMs had a slig
clearance of desipramine with paroxetine. With concurrent administration of desipramine and paroxetine
two drugs may result in a need for dosage adjustments, especially in extensive metabolizers of desipram
1993).

3.5.1.DS Pemoline

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

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

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

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

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained i amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXE 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 o antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transde 2006).

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

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transie clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramin 1990).

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

3.5.1.DT 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 interva recommended therapeutic dose (Lindsay et al, 1990; Marshall & Forker, 1982i). Even though no formal drug have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc 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 re

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.DU Pentobarbital

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

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

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant do required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum con 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 pa treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were ex metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Comp epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), s area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipran half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of h and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effe expected with any combination of TCA and barbiturate.

3.5.1.DV Phendimetrazine

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

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

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

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

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained in amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXE 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 o antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transde 2006).

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

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transie clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramin 1990).

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

3.5.1.DW Phenelzine

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

2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concur and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982r; Spig Brodribb et al, 1994q; Neuvonen et al, 1993i). Serotonin syndrome is a rare but potentially fatal condition of s hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Ste Consequently, coadministration of TCAs and MAOIs is contraindicated in most cases (Prod Info imipramine h tablet, 2003). If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid in clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971t; White &

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of imipramine with an monoamine oxidase inhibitor (MAOI) is con imipramine is replacing treatment with phenelzine, a minimum of 2 weeks should elapse after phenelzine is d therapy with imipramine begins (Prod Info imipramine hydrochloride oral tablet, 2003). The manufacturer of p

recommends that at least 10 days should elapse before imipramine therapy is replaced by phenelzine (Prod
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 (T considered an absolute contraindication in the past and still is listed as such by the manufacturers (Prod hydrochloride oral tablet, 2003). Reports of excitation, hyperpyrexia, convulsions, and possible death hav to the combination (Lockett & Milner, 1965j; Brachfeld et al, 1963f; Winston, 1971j; Schuckit et al, 1971s Spiker & Pugh, 1976j). The mechanism may relate to the combined inhibition of catecholamine reuptake nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965j).

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

c) A drug interaction was reported in a 76-year old woman who had been taking clomipramine 50 mg da months was switched to moclobemide 300 mg daily. The patient experienced somnolence, confusion, ar progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patie were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days l discontinuing all antidepressant medications (Spigset et al, 1993r).

d) A 39-year old woman with bipolar disorder developed serotonin syndrome after imipramine was adde The patient was taking moclobemide 300 mg twice daily when imipramine was started at 50 mg daily, fol dosage increases of imipramine to 200 mg and a reduction of moclobemide dosage to 150 mg twice dail the increase in imipramine to 200 mg per day, the patient developed symptoms of serotonin syndrome, i shivering, confusion, fever, and spasms in the extremities. The patient was treated with chlorpromazine a 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 isocarboxazid and amitriptyline. In all three cases the patients had been given MAOIs and TCAs alone w complications. It was only when the drugs were used in combination that symptoms of mania emerged, s 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 pl 34-year old man. After taking several doses, the patient developed symptoms of nausea and profuse sw pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulation a (Tackley & Tregaskis, 1987i).

g) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unrespons TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 15 or its equivalent, 45 mg phenelzine, or 60 mg isocarboxazid) b) oral administration c) avoidance of clomi imipramine, desipramine, and tranylcypromine in any combination, and d) close monitoring of patients (K Winston, 1971j; Schuckit et al, 1971s; White & Simpson, 1984n; Rom & Benner, 1972e). The combinatio in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to t and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991i). Alternatively previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some s that the combination of amitriptyline and isocarboxazid is preferred (Perry et al, 1991i). Numerous studie refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TC 1977j; Schuckit et al, 1971s; Ashcroft, 1975i).

3.5.1.DX Phenindione

1) Interaction Effect: increased risk of bleeding

2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagul 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 pr ratio or INR (international normalized ratio) should be closely monitored with the addition and withdrawal of th and should be periodically reassessed during concurrent therapy. Achieving a stable dosage regimen which p desired level of anticoagulation may be difficult in patients on this combination, and frequent adjustments of t 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 incre levels and an increase in the plasma half-life of dicumarol, although the effect was not consistent in all su 1975f). This effect was not observed with warfarin.

b) A single oral dose of bishydroxycoumarin after 8 days of nortriptyline resulted in a significantly prolon decreased volume of distribution of the coumarin anticoagulant in 6 healthy volunteers (Vesell et al, 197(

mechanism of action was suggested to be reduced bishydroxycoumarin metabolism and/or altered coum
c) Drug dosing was studied in 16 patients on long-term anticoagulant therapy who used concurrent TCA
1976f). TCAs affected the stability of anticoagulant control leading to frequent changes in the doses of a
Inhibition of coumarin metabolism was the postulated mechanism.

3.5.1.DY Phenmetrazine

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

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

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

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

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen
coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained i
amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXE
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 o
antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transde
2006).

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

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g
four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transie
clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramin
1990).

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

3.5.1.DZ Phenobarbital

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

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

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant do
required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum con
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 pa
treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were e
metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Comp
epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), s
area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipran
half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of h
and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar eff

expected with any combination of TCA and barbiturate.

3.5.1.EA Phenprocoumon

1) Interaction Effect: increased risk of bleeding

2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagul 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 pr ratio or INR (international normalized ratio) should be closely monitored with the addition and withdrawal of th and should be periodically reassessed during concurrent therapy. Achieving a stable drug regimen which pro level of anticoagulation may be difficult in patients on this combination, and frequent adjustments of the antic 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 incre levels and an increase in the plasma half-life of dicumarol, although the effect was not consistent in all su 1975h). This effect was not observed with warfarin.

b) A single oral dose of bishydroxycoumarin after 8 days of nortriptyline resulted in a significantly prolon decreased volume of distribution of the coumarin anticoagulant in 6 healthy volunteers (Vesell et al, 197(mechanism of action was suggested to be reduced bishydroxycoumarin metabolism and/or altered coum

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

3.5.1.EB Phentermine

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

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

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

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

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained in amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXE 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 o antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transde 2006).

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

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transie clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramin 1990).

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

3.5.1.EC 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 c drugs to volunteers on tricyclic antidepressants. Arrhythmias and other severe adverse effects have also bee 1980; Avery, 1973a; Boakes et al, 1973a; Boakes, 1973; Mitchell et al, 1970; Stone et al, 1964a). Local use (anesthesia) of epinephrine in concentrations of 1:100,000 or less is less likely to precipitate clinically significa 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 enhanced in the presence of tricyclic antidepressants (TCAs). Concomitant use should be avoided. If these d together, careful monitoring and a dose reduction of the sympathomimetic is required. Patients should be inst 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 (epineph norepinephrine, phenylephrine, and isoproterenol) before and after imipramine (25 mg three times daily f showed an increased pressor response to epinephrine (2- to 4-fold), norepinephrine (4- to 8-fold), and ph 3-fold) after imipramine, but no difference was observed in the response to isoproterenol. Thus, the incre response appeared to occur only for alpha adrenergic effects. All four subjects demonstrated changes in with epinephrine and imipramine consisting of sinus arrhythmia in three subjects and multiple ectopic be rhythm in the fourth subject (Boakes et al, 1973).

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

3.5.1.ED Phenytoin

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

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

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Consider phenytoin serum levels if a tricyclic antidepressant is added to therapy or begins to exhibit signs of toxicity; lower doses of phenytoin may be required. If phenytoin is added to tricyclic therapy, monitor for clinical efficacy of the tricyclic agent.

7) Probable Mechanism: inhibition of phenytoin metabolism

3.5.1.EE 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 dr the QT interval is contraindicated (Prod Info Orap(R), 1999a). Tricyclic antidepressants (TCAs) at therapeutic QT prolongation (Prod Info Norpramin(R), 2000; Marshall & Forker, 1982ad).

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 tr 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 s patients include prolongation of the QT interval, flattening, notching, and inversion of the T wave, and the waves. Sudden, unexpected deaths have occurred at doses greater than 20 milligrams/day (Prod Info O 1999).

3.5.1.EF 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 inte recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadm Ia antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is n (Prod Info Elavil(R), 1999g; Prod Info Quinaglute(R), 1999; Marshall & Forker, 1982n).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic agent and a tricyclic anti
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 imi
desipramine (Brosen & Gram, 1989). Inhibition of this enzyme system can result in a 35% decrease in im
clearance and 85% decrease in desipramine clearance. Demethylation of imipramine by the cytochrome
unaffected by this interaction. Until more information is available all patients having quinidine added to di
containing imipramine or desipramine should be monitored for increased antidepressant serum concentr
potential toxicity.
b) An increased incidence in sudden death was observed in six out of 53 patients with cardiac disease r
amitriptyline, compared to 0 out of 53 in the control group. It was recommended that amitriptyline be avo
with underlying cardiac disease except when depression was debilitating and no other drugs were helpfu
Coull et al, 1970).
c) In a placebo controlled study, imipramine 3.5 mg/kg was administered daily for seven patients with se
and titrated doses to obtain therapeutic plasma concentrations. Two patients displayed premature atrial c
and premature ventricular depolarizations before therapy. On patient had 33 premature atrial depolarizat
premature ventricular depolarizations (PVD) per hour, which decreased to 0.4 PAC and zero PVC per ho
The other patient had 12 PAD and 169 PVD per hour before treatment and 1.8 PAD and 28.1 PVD per h
The authors also cautioned that the incidence of cardiotoxicity may increase if tricyclic antidepressants a
with Type I antiarrhythmics. It was also recommended that quinidine and procainamide not be used to tre
of a tricyclic overdose. The similarities between these agents may exacerbate the cardiotoxicity (Kantor e

3.5.1.EG 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 inte
recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadm
Ia antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is n
(Prod Info Elavil(R), 1999g; Prod Info Quinaglute(R), 1999; Marshall & Forker, 1982n).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic agent and a tricyclic anti
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 imi
desipramine (Brosen & Gram, 1989). Inhibition of this enzyme system can result in a 35% decrease in im
clearance and 85% decrease in desipramine clearance. Demethylation of imipramine by the cytochrome
unaffected by this interaction. Until more information is available all patients having quinidine added to di
containing imipramine or desipramine should be monitored for increased antidepressant serum concentr
potential toxicity.
b) An increased incidence in sudden death was observed in six out of 53 patients with cardiac disease r
amitriptyline, compared to 0 out of 53 in the control group. It was recommended that amitriptyline be avo
with underlying cardiac disease except when depression was debilitating and no other drugs were helpfu
Coull et al, 1970).
c) In a placebo controlled study, imipramine 3.5 mg/kg was administered daily for seven patients with se
and titrated doses to obtain therapeutic plasma concentrations. Two patients displayed premature atrial c
and premature ventricular depolarizations before therapy. On patient had 33 premature atrial depolarizat
premature ventricular depolarizations (PVD) per hour, which decreased to 0.4 PAC and zero PVC per ho
The other patient had 12 PAD and 169 PVD per hour before treatment and 1.8 PAD and 28.1 PVD per h
The authors also cautioned that the incidence of cardiotoxicity may increase if tricyclic antidepressants a
with Type I antiarrhythmics. It was also recommended that quinidine and procainamide not be used to tre
of a tricyclic overdose. The similarities between these agents may exacerbate the cardiotoxicity (Kantor e

3.5.1.EH Primidone

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased me
TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence
(Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen s
reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressa
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant do
required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum con
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 pa treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were ex metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Comp epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), s area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipran half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of h and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effe expected with any combination of TCA and barbiturate.

3.5.1.EI 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 inte recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadm Ia antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is n (Prod Info Elavil(R), 1999g; Prod Info Quinaglute(R), 1999; Marshall & Forker, 1982n).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic agent and a tricyclic anti 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 imi desipramine (Brosen & Gram, 1989). Inhibition of this enzyme system can result in a 35% decrease in im clearance and 85% decrease in desipramine clearance. Demethylation of imipramine by the cytochrome unaffected by this interaction. Until more information is available all patients having quinidine added to dr containing imipramine or desipramine should be monitored for increased antidepressant serum concentr potential toxicity.

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

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

3.5.1.EJ Procarbazine

1) Interaction Effect: neurotoxicity, seizures

2) Summary: Concomitant tricyclic antidepressant and more potent MAOI use has resulted in hyperpyrexia, c death. Procarbazine has relatively weak MAOI actions, so while the potential for drug interactions between tri antidepressants and procarbazine exists, clinical data are lacking at this time (Schuckit et al, 1971r; White & S 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 c supervision, and then only if other antidepressant class agents have proven unsuccessful. With more potent I recommendations for concurrent use of TCAs have included avoiding large doses of the TCA, using only oral avoiding imipramine, clomipramine, and desipramine. Procarbazine therapy should not begin until seven day 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 monoa inhibitor (Gilman et al, 1985a). Animal studies have indicated that procarbazine is a monoamine oxidase (DeVita et al, 1965) but appears to be a relatively weak MAOI in man (Gilman et al, 1985a). Hypertensiv still result from concomitant administration of tricyclic antidepressants, sympathomimetics, and tyramine (Gilman et al, 1985a; Ponto et al, 1977i).

b) Concomitant administration of monoamine oxidase (MAO) inhibitors with tricyclic antidepressants has an absolute contraindication in the past and still is listed as such by the manufacturers. Reports of excita convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965i; Brach Winston, 1971i; Schuckit et al, 1971q; Sargent, 1965e; Spiker & Pugh, 1976i). Careful examination of su unusual circumstances in most cases such as parenteral administration of a tricyclic. The mechanism ma

combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catechol (Sjoqvist, 1965i).

c) Procarbazine therapy should not begin until 7 days following discontinuation of tricyclic antidepressar following the discontinuation of other MAO inhibitors (AMA Department of Drugs, 1992; Gilman et al, 198

3.5.1.EK 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 Cor Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, are available. Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Marshall & F Case reports have described increased plasma levels and adverse effects when phenothiazines and tricyclic were taken together, likely due to inhibition of their metabolism (Ghaemi & Kirkwood, 1998; Geller et al, 1985 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 re

7) Probable Mechanism: additive effect on QT interval

3.5.1.EL Propafenone

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

2) Summary: Class I antiarrhythmics have been shown to prolong the QTc interval at the recommended ther Even though no formal drug interaction studies have been done, the coadministration of Class I antiarrhythmi known to prolong the QTc interval, including tricyclic antidepressants, is not recommended (Prod Info Tambo acetate, 1998; Larochelle et al, 1984; Scagliotti et al, 1982).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a Class I antiarrhythmic and a tricyclic antidepress recommended.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include incre prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flat (Marshall & Forker, 1982q).

b) A 68-year-old man suffering from agitated major depression was begun on a dose of desipramine 12 produced a subtherapeutic serum level of 442 nmol/L (therapeutic range = 500 to 1000 nmol/L). An incre mg daily produced excellent clinical response with no side effects. He developed atrial fibrillation and flut mg daily was added to his therapy, and desipramine was discontinued. His arrhythmia was suppressed v propafenone 150 mg twice daily and 300 mg at bedtime. Desipramine 150 mg daily was again begun, at experienced dry mouth, sedation, and shakiness; the desipramine serum level was measured at 2092 nr desipramine was discontinued for five days, the side effects ceased, and desipramine therapy was resur The desipramine serum level was measured at 1130 nmol/L (Katz, 1991).

3.5.1.EM Propranolol

1) Interaction Effect: increased imipramine concentrations

2) Summary: One report of 2 cases of children receiving imipramine and propranolol was suggestive of inter metabolism of imipramine with this combination (Gillette & Tannery, 1994). In one case, imipramine levels ros when the propranolol dose was increased following admission to the hospital. No toxicity was noted. The pos compliance prior to admission might have played a role was not considered by the authors, and no rechalleng The other case involved several changes in dose of both drugs. Prospective study is needed to determine the interaction.

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for an enhanced effect of imipramine. A dosage adjustment may be require

7) Probable Mechanism: decreased imipramine metabolism

3.5.1.EN Propylhexedrine

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

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

dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) o Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral t Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension ar
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained i amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXE 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 c antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transde 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mm of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure return normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Fle Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transi clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramin 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depressior although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant dru depression, with one exception, indicated little advantage of drug over placebo and did not appear to be conventional antidepressants in primary depression (Satel & Nelson, 1989).

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

3.5.1.EP Quinestrol

1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, a
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or de estrogens (Somani & Khurana, 1973m), with paradoxical loss of antidepressant effect yet tricyclic toxicity bei simultaneously (Prange, 1972m). The effects of the interaction appear to be estrogen dose-related (Khurana, be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started o (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 down estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, d 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. I depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received place

imipramine (150 milligrams/day) and placebo, 5 patients received imipramine (150 milligrams/day) and e micrograms/day), while 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (25 mic 10 patients that received placebo did not improve over the 6 weeks of the study. The 10 patients taking e imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients takin alone. However, after 2 weeks, the 5 patients that received imipramine and high-dose estrogen had not i as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsine affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period o required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed residual estrogen in the high-dose group. In another group, 5 women received imipramine 150 milligrams estradiol 50 micrograms daily did not improve as much as 10 patients receiving only imipramine. Also, th combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange,

b) A case reported by (Khurana, 1972l) demonstrated an interaction in a 32-year-old female taking conju 2.5 milligrams and imipramine 100 milligrams. The patient developed lethargy, tremors, and signs of dep After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. U the estrogen, the side-effects abated. Some investigators have proposed that the side effects resulted fr 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 begir there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' clomipramine. It was proposed that there was no significant difference in side-effects between the groups groups were matched after patients had dropped out of the study. Had the patients been matched prior t 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 a three women took clomipramine 25 milligrams at bedtime while 19 took clomipramine 25 milligrams at be contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimenta side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of se concentrations. No difference in serum concentrations was noted between the groups. However, this res 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 antidep concurrently. A 24-year-old patient receiving clomipramine 120 milligrams/day for anorexia nervosa and estrogens 1.25milligrams/day for amenorrhea developed restless legs and a constant desire to move co Estrogen was discontinued and benztropine 2 milligrams was administered, resulting in marked reductio within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogens milligrams/day who was prescribed amitriptyline 50 milligrams/day for depression. Within hours of amitrip was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared a amitriptyline. Positive rechallenge at one week with doxepin 100 milligrams, with resolution following disc doxepin. A third case of akathisia was reported in a 35-year-old patient who received conjugated estroge milligrams/day and amitriptyline 50 milligrams/day. Akathisia developed within a few hours after taking th amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al,

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

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 19 are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the cer system resulting in an antidepressant effect (Oppenheim, 1983f).

3.5.1.EQ 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 inte recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadm Ia antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is n (Prod Info Elavil(R), 1999g; Prod Info Quinaglute(R), 1999; Marshall & Forker, 1982n).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic agent and a tricyclic anti 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 imi desipramine (Brosen & Gram, 1989). Inhibition of this enzyme system can result in a 35% decrease in im clearance and 85% decrease in desipramine clearance. Demethylation of imipramine by the cytochrome unaffected by this interaction. Until more information is available all patients having quinidine added to d containing imipramine or desipramine should be monitored for increased antidepressant serum concentr potential toxicity.

b) An increased incidence in sudden death was observed in six out of 53 patients with cardiac disease r

amitriptyline, compared to 0 out of 53 in the control group. It was recommended that amitriptyline be avo with underlying cardiac disease except when depression was debilitating and no other drugs were helpfu Coull et al, 1970).

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

3.5.1.ER Quinidine

1) Interaction Effect: imipramine toxicity (dry mouth, sedation) and an increased risk of cardiotoxicity (QT pro torsades de pointes, cardiac arrest)

2) Summary: Two studies have demonstrated that concomitant use of quinidine and imipramine or desipram increased serum concentrations of these antidepressants (Brosen & Gram, 1989b; Steiner et al, 1987). Due t cardiac effects, the incidence of cardiotoxicity (increased PR interval, QRS complex, and QTc interval) may a tricyclic antidepressants are administered with Type I antiarrhythmics (Kantor et al, 1978b; Bigger et al, 1977

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: The concurrent use of imipramine and quinidine is not recommended. Monitor for in antidepressant side effects with concurrent therapy; lower doses of the tricyclic agent may be required in som monitor the patient for signs and symptoms of additive cardiac effects, including any changes in the EKG.

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

8) Literature Reports

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

b) One study reported the cardiac effects of imipramine in two patients with depression and cardiac arrh week single-blind protocol of imipramine 3.5 mg/kg daily. The PR interval, QRS complex, and QTc interv significantly in both cases, producing EKG changes similar to those of Type I antiarrhythmics (quinidine, disopyramide). Each patient showed a decrease in both atrial and ventricular premature depolarizations The first patient decreased from 33.4 atrial and 30.1 ventricular premature depolarizations per hour to 0. ventricular premature depolarizations per hour. A second patient had 12.3 atrial and 169 ventricular pren depolarizations per hour prior to drug treatment which decreased to 1.8 atrial and 28.1 ventricular prema depolarizations per hour during imipramine therapy. The investigators concluded that the doses of antiar should be adjusted downward when used concurrently with tricyclic antidepressants due to an increased cardiotoxicity (Bigger et al, 1977).

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

3.5.1.ES Rasagiline

1) Interaction Effect: severe CNS toxicity

2) Summary: Concomitant use of rasagiline and tricyclic antidepressants should be avoided. Concurrent adm overlapping therapy with tricyclic antidepressants and non-selective MAOIs has been reported to cause serio fatal, reactions; the mechanisms of these reactions are not fully understood. Signs and symptoms include sev (behavioral and mental status changes, diaphoresis, muscular rigidity, hypertension, and syncope) associate hyperpyrexia and death. Data from clinical studies, where rasagiline-treated patients (n=115) were concomita tricyclic antidepressants, are insufficient to rule out an interaction. At least 14 days should elapse after discon 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. Wa after discontinuing rasagiline before initiating therapy with a tricyclic antidepressant (Prod Info AZILECT(R) o

7) Probable Mechanism: unknown

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

3.5.1.EU Ritonavir
1) Interaction Effect: increased imipramine serum concentrations and potential toxicity (anticholinergic effects confusion, cardiac arrhythmias)
2) Summary: Coadministered ritonavir may increase serum concentrations of imipramine, resulting in imipra Info Norvir(R), 1999). Therapeutic concentration monitoring is recommended for tricyclic antidepressants whe with ritonavir (Prod Info Invirase(R), 2003).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients for signs and symptoms of tricyclic antidepressant toxicity (anticho sedation, confusion, cardiac arrhythmias). Reduce doses of imipramine as required.
7) Probable Mechanism: decreased imipramine metabolism

3.5.1.EV Ropivacaine
1) Interaction Effect: increased plasma levels of ropivacaine
2) Summary: Ropivacaine is metabolized in the liver by the cytochrome P4501A enzyme system to 3-hydrox major metabolite. Drugs which are metabolized by P4501A2 via competitive inhibition, such as imipramine, w interact with the metabolism of ropivacaine. This would result in decreased renal clearance and increased pla concentrations of ropivacaine (Prod Info Naropin(TM), 1996).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Care must be taken to monitor the patient for signs of local anesthetic toxicity with t coadministration of ropivacaine and other drugs which are known to be metabolized by cytochrome P4501A2 inhibition, such as imipramine.
7) Probable Mechanism: inhibition of ropivacaine metabolism

3.5.1.EW S-Adenosylmethionine
1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, ment
2) Summary: A single case has been reported of serotonin syndrome likely resulting from the combination of adenosylmethionine (SAMe) and clomipramine (Iruela et al, 1993a). SAMe was shown to hasten the onset of response of imipramine in a clinical trial involving 40 patients, without serotonergic side effects (Berlanga et a is initiated with SAMe and a tricyclic antidepressant, the patient should be monitored closely for early signs of syndrome. Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized 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 de symptoms sooner than imipramine alone (Berlanga et al, 1992). One case has been reported of serotonin sy resulting from concomitant use of SAMe and clomipramine (Iruela et al, 1993). If SAMe and a tricyclic antidep together, use low doses of each and titrate upward slowly, while monitoring closely for early signs of serotoni 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 s been taking S-adenosylmethionine 100 milligrams (mg) intramuscularly daily and clomipramine 25 mg da which was then increased to 75 mg/day. Within 48-72 hours of the increased clomipramine dosage, she progressively anxious, agitated, and confused. On admission she was verbally unresponsive and stupor

130 beats/minute, respiratory rate 30 breaths/minute, temperature 40.5 degrees Celsius, diarrhea, myoc tremors, rigidity, hyperreflexia, shivering, diaphoresis, and dehydration. Temperature increased to 43 de during her hospital stay, with no documented infection. White blood cell count (WBC) was 13,040 mm3, dehydrogenase was 662 units/liter (U/L), creatine phosphokinase was 8920 U/L, serum potassium 2.7 m (mEq/L), creatinine 1.1 mg/100 milliliter (mL) (laboratory reference values were not provided). A cranial c tomography (CT) scan was normal. The patient was not taking neuroleptics. Serum benzodiazepine and antidepressant levels were normal. Symptoms resolved gradually with 4 days of hydration and supportiv interaction was proposed to be a result of synergistic activity of S-adenosylmethionine and clomipramine 1993).

3.5.1.EX 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 antidepressant, or within two weeks of the discontinuation of a tricyclic antidepressant (Prod Info SEREVENT inhalation powder, 2006). Clinically significant changes in systolic and diastolic blood pressure, pulse rate, ar electrocardiograms have been seen with the use of salmeterol, and these changes may be exacerbated by th antidepressant.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

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

7) Probable Mechanism: potentiation of vascular effects

3.5.1.EY Secobarbital

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

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

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dc required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum con 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 pa treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were e metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Comp epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), s area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipran half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of h and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar eff expected with any combination of TCA and barbiturate.

3.5.1.EZ Selegiline

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

2) Summary: Coadministration of imipramine and selegiline is contraindicated (Prod Info imipramine hydroch 2003; Prod Info EMSAM(R) transdermal patch, 2006). Concomitant tricyclic antidepressants (TCAs) and MA in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to resu termed serotonin syndrome (Insel et al, 1982i; Spigset et al, 1993j; Brodribb et al, 1994i; Neuvonen et al, 199 syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertensi myoclonus, and changes in mental status (Sternbach, 1991e). A minimum of 14 days should elapse after dis selegiline before initiating therapy with imipramine. A time period of 4 to 5 half-lives, approximately 1 week, s discontinuing imipramine prior to initiating therapy with selegiline (Prod Info EMSAM(R) transdermal patch, 2

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concomitant use of imipramine with selegiline is contraindicated. A minimum of 14 elapse after discontinuing selegiline before initiating therapy with imipramine. A time period of 4 to 5 half-lives week, should elapse after discontinuing imipramine prior to initiating therapy with selegiline.

7) Probable Mechanism: altered catecholamine uptake and metabolism

8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (T considered an absolute contraindication in the past and still is listed as such by the manufacturers. Repo

hyperpyrexia, convulsions, and possible death have been attributed to the combination (Prod Info imipra oral tablet, 2003; Lockett & Milner, 1965d; Brachfeld et al, 1963c; Winston, 1971d; Schuckit et al, 1971h; Spiker & Pugh, 1976d). The mechanism may relate to the combined inhibition of catecholamine reuptake nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965d).

b) Coadministration of selegiline with TCAs such as protriptyline or amitriptyline has resulted in severe C hyperpyrexia and death. Combination of selegiline with various other tricyclic antidepressants has cause effects, including hypertension, syncope, and muscular rigidity (Prod Info selegiline hydrochloride oral tal

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

d) A drug interaction occurred in a 76-year old woman who had been taking clomipramine 50 mg daily f prior to switching to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fe progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patie were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days l discontinuing all antidepressant medications (Spigset et al, 1993i).

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

f) Three patients with bipolar disorder developed manic symptoms while undergoing concurrent therapy and amitriptyline. In all three cases the patients had been given MAOIs and TCAs alone without complica when the drugs were used in combination that symptoms of mania emerged, suggesting a synergistic ef et al, 1986c).

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

h) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unrespons TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 15 or its equivalent, 45 mg phenelzine, or 60 mg isocarboxazid) b) oral administration c) avoidance of clomi imipramine, desipramine, and tranylcypromine in any combination, and d) close monitoring of patients (K Winston, 1971d; Schuckit et al, 1971h; White & Simpson, 1984g; Rom & Benner, 1972c). The combinati in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to t and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991d). Alternativel previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some s that the combination of amitriptyline and isocarboxazid is preferred (Perry et al, 1991d). Numerous studie refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TC 1977d; Schuckit et al, 1971h; Ashcroft, 1975d).

3.5.1.FA 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 ant agents, including acecainide (Chow et al, 1984), amiodarone (Faggiano et al, 1996), azimilide (Corey et al, 1 (Gilman et al, 1985), ibutilide (Rodriguez et al, 2001), sematilide (Singh, 1996), dofetilide (Allen et al, 2002), a & Runge, 2001). Even though no formal drug interaction studies have been done, the coadministration of Cla antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not (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 antidepres recommended.

7) Probable Mechanism: additive QT prolongation

8) Literature Reports

a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include incre prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flat (Marshall & Forker, 1982ab).

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

3.5.1.FB 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 I 1999), haloperidol (O'Brien et al, 1999), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001 (Owens, 2001b), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003). Even though no formal drug studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recomm Pamelor(R), 2001; Marshall & Forker, 1982t).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

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

3.5.1.FC Sertraline

1) Interaction Effect: modest elevations in imipramine serum levels or possible serotonin syndrome (hyperter hyperthermia, myoclonus, mental status changes)

2) Summary: There is limited evidence suggesting that sertraline may inhibit tricyclic antidepressant (TCA) m resulting in higher TCA serum concentrations. Sertraline inhibits cytochrome P450 2D6 enzyme activity and r plasma concentrations of coadministered drugs that are metabolized by this pathway, including the tricyclic a (Preskorn et al, 1994c; Lydiard et al, 1993; Prod Info Zoloft(R), 1999). Effects of the interaction may have littl impact, however. Increases in TCA serum levels associated with sertraline coadministration were modest cor found when fluoxetine (another selective serotonin reuptake inhibitor) was combined with desipramine (von M Monitor patients on imipramine-sertraline therapy for TCA toxicity (dry mouth, urinary retention, CNS depress 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 reupt (SSRIs) may result in the inhibition of the TCA metabolism. A few cases of serotonin syndrome have also be concurrent TCA and SSRI therapy. Caution should be observed when drugs in these two classes are used to

7) Probable Mechanism: inhibition of imipramine metabolism

8) Literature Reports

a) Desipramine pharmacokinetics was studied in 18 healthy male volunteers. Study subjects received o (50 mg daily) for 7 days followed by desipramine with sertraline (50 mg daily) for 21 days. When sertralin desipramine therapy, the mean maximum concentration of desipramine increased by 34% and the area concentration-time curve increased by 26%. Trough concentrations of desipramine were close to baselin sertraline was discontinued. The changes in desipramine concentrations were modest and the interactio clinically significant (Preskorn et al, 1994b).

3.5.1.FD 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 ant agents, including acecainide (Chow et al, 1984), amiodarone (Faggiano et al, 1996), azimilide (Corey et al, 1 (Gilman et al, 1985), ibutilide (Rodriguez et al, 2001), sematilide (Singh, 1996), dofetilide (Allen et al, 2002), a & Runge, 2001). Even though no formal drug interaction studies have been done, the coadministration of Cla antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not (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 antidepres recommended.

7) Probable Mechanism: additive QT prolongation

8) Literature Reports

a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include incre prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flat (Marshall & Forker, 1982ab).

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

3.5.1.FE 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 di amiodarone. The use of sparfloxacin is contraindicated with drugs which produce an increase in the QTc inte torsades de pointes, including tricyclic antidepressants. Sparfloxacin is also contraindicated in persons with k 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 pat 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 t sparfloxacin steady-state was 10 msec (2.5%). Of these subjects, 0.7% had a QTc interval greater than steady-state. However, no arrhythmic effects were seen in any of the patients. The magnitude of the QTc increase with repeated administration of sparfloxacin, and the QTc interval returns to baseline within 48 h 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 w for suppurative otitis media and mastoiditis was treated with sparfloxacin due to an allergy to betalactam six of treatment she felt dizzy and lost consciousness. This was attributed to torsades de pointes on the was followed by cardiac arrest which required cardiopulmonary resuscitation. Her pre-treatment electroc QT and QTc intervals of 0.34 and 0.46 seconds, respectively. An electrocardiogram post-arrest revealed intervals of 0.35 and 0.60 seconds, respectively. A 24-hour continuous electrocardiography confirmed nu of torsades de pointes occurring after episodes of sino-auricular block. Sparfloxacin was discontinued an returned to baseline within a week. Upon further testing, it was determined that the patient suffered from long QT syndrome. Due to the onset of symptoms with administration of sparfloxacin and the relief of sy discontinuation of the drug, it is highly probable that sparfloxacin contributed to the torsades de pointes.

3.5.1.FF 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 recommended therapeutic dose (Stramba-Badiale et al, 1997; Marshall & Forker, 1982c). Even though no for interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known t interval, such as spiramycin, is not recommended (Prod Info Elavil(R), 1999b).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of spiramycin and tricyclic antidepressants is not rec

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.FG St John's Wort

1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, ment

2) Summary: Theoretically, since St. John's Wort is thought to inhibit serotonin reuptake and may have mild oxidase inhibitory activity (Singer et al, 1999; Thiede & Walper, 1994), serotonin syndrome could result when taken along with a tricyclic antidepressant. This theoretical risk of serotonin syndrome is also based on case serotonin syndrome resulting from concomitant use of selective serotonin reuptake inhibitors with tricyclic ant (Alderman & Lee, 1996), as well as concomitant use of monoamine oxidase inhibitors with tricyclic antidepres al, 1994a; Spigset et al, 1993b; Tackley & Tregaskis, 1987a). Coadministration of amitriptyline and St. John's the area under the concentration-time curve of amitriptyline and its metabolite nortriptyline (Roots et al, 2000) antidepressants are similarly affected by St. John's Wort, the risk of serotonin syndrome may be reduced, yet the tricyclic antidepressant may also be reduced. To maintain maximal effectiveness of the tricyclic antidepre avoid any potential risk of serotonin syndrome, avoid concomitant use of St. John's Wort and tricyclic antidep

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.FH 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 inter recommended therapeutic dose (Lopez et al, 1987; Marshall & Forker, 1982s). Even though no formal drug in have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc cotrimoxazole, is not recommended (Prod Info Elavil(R), 1999j).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable
6) Clinical Management: The concurrent administration of cotrimoxazole and tricyclic antidepressants is not r
7) Probable Mechanism: additive effects on QT prolongation

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

3.5.1.FJ Tapentadol
1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental s
2) Summary: Concurrent use of tapentadol and a tricyclic antidepressant may result in serotonin syndrome, v threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and d 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-thr called serotonin syndrome. If these agents are used together, monitor the patient closely for symptoms of ser (restlessness, hyperthermia, hyperreflexia, incoordination), especially during treatment initiation and dose inc tapentadol immediate release oral tablets, 2008).
7) Probable Mechanism: additive serotonergic effect

3.5.1.FK 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 ant agents, including acecainide (Chow et al, 1984), amiodarone (Faggiano et al, 1996), azimilide (Corey et al, 1 (Gilman et al, 1985), ibutilide (Rodriguez et al, 2001), sematilide (Singh, 1996), dofetilide (Allen et al, 2002), a & Runge, 2001). Even though no formal drug interaction studies have been done, the coadministration of Cla antiarrhythmics and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is not r (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 antidepres recommended.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) EKG effects reported in patients receiving therapeutic doses of tricyclic antidepressants include incre prolonged PR interval, intraventricular conduction delays, increased corrected QT interval (QTc) and flat (Marshall & Forker, 1982ab).
b) Concurrent use of Class III antiarrhythmic agents, and other drugs that can prolong the QT interval, s antidepressants, is not recommended. Dofetilide should be stopped for at least 2 days before any interac initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yam 2003).

3.5.1.FL 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 may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of telithr tricyclic antidepressants is not recommended (Marshall & Forker, 1982af).
3) Severity: major
4) Onset: unspecified

5) Substantiation: theoretical
6) Clinical Management: Because of the potential for additive QT interval prolongation, the concurrent admin
telithromycin and a tricyclic antidepressants is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.FM 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 recomme
dose (Marshall & Forker, 1982ae). Even though no formal drug interaction studies have been done, the coad
terfenadine and other drugs known to prolong the QTc interval, including tricyclic antidepressants, is contrain
Elavil(R), 1999k; 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 int
tricyclic antidepressants, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.FN Thiopental
1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased me
TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence
(Moody et al, 1977; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen s
reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressa
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dc
required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum con
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 pa
treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were e
metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Comp
epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), s
area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipran
half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of h
and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar eff
expected with any combination of TCA and barbiturate.

3.5.1.FO 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
prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001). Tricyclic antidepressants (TCAs) at th
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 contraindi
7) Probable Mechanism: additive effect on QT interval

3.5.1.FP Tibolone
1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, a
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or de
estrogens (Somani & Khurana, 1973a), with paradoxical loss of antidepressant effect yet tricyclic toxicity beir
simultaneously (Prange, 1972a). The effects of the interaction appear to be estrogen dose-related (Khurana,
be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started o
(Krishnan et al, 1984a).
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment down
estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, d
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. I

depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received place imipramine (150 milligrams/day) and placebo, 5 patients received imipramine (150 milligrams/day) and e micrograms/day), while 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (25 mic 10 patients that received placebo did not improve over the 6 weeks of the study. The 10 patients taking e imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients takin alone. However, after 2 weeks, the 5 patients that received imipramine and high-dose estrogen had not i as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsine affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period o required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed residual estrogen in the high-dose group. In another group, 5 women received imipramine 150 milligrams estradiol 50 micrograms daily did not improve as much as 10 patients receiving only imipramine. Also, th combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange,

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

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the begin there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' clomipramine. It was proposed that there was no significant difference in side-effects between the groups groups were matched after patients had dropped out of the study. Had the patients been matched prior t different conclusions may have been drawn (Beaumont, 1973).

d) The effect of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 a three women took clomipramine 25 milligrams at bedtime while 19 took clomipramine 25 milligrams at be contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimenta side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of se concentrations. No difference in serum concentrations was noted between the groups. However, this res 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 antidep concurrently. A 24-year-old patient receiving clomipramine 120 milligrams/day for anorexia nervosa and estrogens 1.25 milligrams/day for amenorrhea developed restless legs and a constant desire to move co Estrogen was discontinued and benztropine 2 milligrams was administered, resulting in marked reductio within 48 hours. LI Akathisia and disorientation developed in a 55-year-old patient on conjugated estroge milligrams/day who was prescribed amitriptyline 50 milligrams/day for depression. Within hours of amitrip was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared a amitriptyline. Positive rechallenge at one week with doxepin 100 milligrams, with resolution following disc doxepin. A third case of akathisia was reported in a 35-year-old patient who received conjugated estroge milligrams/day and amitriptyline 50 milligrams/day. Akathisia developed within a few hours after taking th amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al,

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

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 19 are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the cer system resulting in an antidepressant effect (Oppenheim, 1983).

3.5.1.FQ Toloxatone

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

2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concu and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982p; Spig Brodribb et al, 1994o; Neuvonen et al, 1993h). Serotonin syndrome is a rare but potentially fatal condition of hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Ste TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clom desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971p; White & Simpson, 198

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

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

considered an absolute contraindication in the past. Reports of excitation, hyperpyrexia, convulsions, an have been attributed to the combination (Lockett & Milner, 1965h; Winston, 1971h; Schuckit et al, 1971o 1976h). The mechanism may relate to the combined inhibition of catecholamine reuptake into the centra and inhibition of catecholamine metabolism (Sjoqvist, 1965h).

b) There is minimal risk of a clinically significant pharmacokinetic interaction between amitriptyline and t MAOI-A (Vandel et al, 1993). Seventeen inpatients being treated for major depressive illness were admi amitriptyline 125 mg once daily for two weeks, and the following two weeks they received amitriptyline 12 toloxatone 600 mg daily. With combined therapy there was a small, nonsignificant increase in amitriptylir 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 unrespons TCA alone. The combination may be utilized in one of two ways. Most frequently, the recommendation is previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then sim started (Perry et al, 1991h). Alternatively, in a patient previously receiving a TCA, small doses of the MA added (Schoonover, 1983). Numerous studies in patients with refractory depression or phobic anxiety st successfully used the combination of MAOIs and TCAs (Ponto et al, 1977h; Schuckit et al, 1971o; Ashcr

d) Serotonin syndrome has been reported with the use of moclobemide, a reversible inhibitor of monoar a TCA. A 39-year old woman with bipolar disorder developed serotonin syndrome after imipramine was a moclobemide. The patient was taking moclobemide 300 mg twice daily when imipramine was started at 5 followed by two dosage increases of imipramine to 200 mg and a reduction of moclobemide dosage to 1 Five days after the increase in imipramine to 200 mg per day, the patient developed symptoms of seroto including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated w and symptoms resolved over the next few days without further complications (Brodribb et al, 1994n).

3.5.1.FR Tramadol

1) Interaction Effect: an increased risk of seizures

2) Summary: Seizures have been reported in patients using tramadol. Some medications, including tricyclic a (TCAs), are known to reduce the seizure threshold. The risk of seizures may be enhanced when imipramine a 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 conc therapy. If possible, avoid this combination, especially in patients with underlying conditions that might predis

7) Probable Mechanism: unknown

3.5.1.FS Tranylcypromine

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

2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concu and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982m; Spi Brodribb et al, 1994l; Neuvonen et al, 1993f). Serotonin syndrome is a rare but potentially fatal condition of se hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Ste Consequently, coadministration of TCAs and MAOIs is contraindicated in most cases. If TCAs and MAOIs mu concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and trany monitor patients closely (Schuckit et al, 1971l; White & Simpson, 1984j).

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of imipramine with a monoamine oxidase inhibitor (MAOI), such a is contraindicated. If imipramine is replacing treatment with tranylcypromine, a minimum of 14 days should el tranylcypromine is discontinued before therapy with imipramine begins (Prod Info imipramine hydrochloride o The manufacturer of tranylcypromine recommends that at least 7 days should elapse before tranylcypromine replaced by imipramine. Similarly, if imipramine therapy is substituted by tranylcypromine, there should be a period. Tranylcypromine should then be given using half the normal starting dosage for, minimally, the first w (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 (T considered an absolute contraindication in the past and still is listed as such by the manufacturers (Prod hydrochloride oral tablet, 2003). Reports of excitation, hyperpyrexia, convulsions, and possible death hav to the combination (Lockett & Milner, 1965f; Brachfeld et al, 1963d; Winston, 1971f; Schuckit et al, 1971k Spiker & Pugh, 1976f). The mechanism may relate to the combined inhibition of catecholamine reuptake 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 crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-com two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipram taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both leg

diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hou 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 fo prior to switching to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fe progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patie were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days l discontinuing all antidepressant medications (Spigset et al, 1993m).

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

e) Three patients with bipolar disorder developed manic symptoms while undergoing concurrent therapy isocarboxazid and amitriptyline. In all three cases the patients had been given MAOIs and TCAs alone w complications. It was only when the drugs were used in combination that symptoms of mania emerged, s 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 pl 34-year old man. After taking several doses, the patient developed symptoms of nausea and profuse sw pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulation a (Tackley & Tregaskis, 1987g).

g) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unrespons TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 15 or its equivalent, 45 mg phenelzine, or 60 mg isocarboxazid) b) oral administration c) avoidance of clomi imipramine, desipramine, and tranylcypromine in any combination, and d) close monitoring of patients (K Winston, 1971f; Schuckit et al, 1971k; White & Simpson, 1984i; Rom & Benner, 1972d). The combinatio one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991f). Alternatively previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some s that the combination of amitriptyline and isocarboxazid is preferred (Perry et al, 1991f). Numerous studie refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TC 1977f; Schuckit et al, 1971k; Ashcroft, 1975f).

3.5.1.FT 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 Cor Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, are available. Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Marshall & F Case reports have described increased plasma levels and adverse effects when phenothiazines and tricyclic were taken together, likely due to inhibition of their metabolism (Ghaemi & Kirkwood, 1998; Geller et al, 1985 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 re

7) Probable Mechanism: additive effect on QT interval

3.5.1.FU 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 inter recommended therapeutic dose (Lopez et al, 1987; Marshall & Forker, 1982s). Even though no formal drug in have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc cotrimoxazole, is not recommended (Prod Info Elavil(R), 1999j).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of cotrimoxazole and tricyclic antidepressants is not r

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.FV 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 therapeutic dose (Prod Info Vivactil(R), 1999; McCue et al, 1989; Munger & Effron, 1988; Mauro et al, 1988; I 1982j; Goldstein & Claghorn, 1980; Buckhardt et al, 1978; Pinder et al, 1977; Thorstrand, 1976; Singh, 1972) formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc inter 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 tricycli and vasopressin, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.FW Venlafaxine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest) effects of both drugs
2) Summary: Tricyclic antidepressants (TCAs) and venlafaxine have been shown to prolong the QTc interval recommended therapeutic dose (Prod Info Effexor(R) XR, 2003; Marshall & Forker, 1982d). Even though no interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known t interval, such as venlafaxine, is not recommended (Prod Info Elavil(R), 1999c). In addition, venlafaxine and tr antidepressants (TCAs) may competitively inhibit each other's metabolism which may increase side effects o 2000; Prod Info Effexor(R) XR, 2003; Ellingrod & Perry, 1994). Venlafaxine increased the AUC, Cmax, and C desipramine by approximately 35%. The AUCs of 2-OH-desipramine increased by 2.5 and 4.5 fold when adm venlafaxine 37.5 mg and 75 mg every 12 hours, respectively. The pharmacokinetics of imipramine and the 2- 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 administra 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 metaboli affected. Venlafaxine increased the area under the concentration-time curve (AUC), maximum concentra minimum concentration (Cmin) of desipramine by approximately 35%. The 2-OH-desipramine AUCs incr (venlafaxine 37.5 mg every 12 hours) and by 4.5-fold (venlafaxine 75 mg every 12 hours). The clinical si finding is unknown (Prod Info venlafaxine extended release oral tablets, 2008).

3.5.1.FX Verapamil

1) Interaction Effect: imipramine toxicity (dry mouth, sedation, urinary retention)
2) Summary: Verapamil decreased imipramine clearance by 25% (statistically significant) compared with pla controlled, single-dose study in 12 healthy volunteers (Hermann et al, 1992a). Imipramine bioavailability was by verapamil (15% greater than with placebo). The clinical significance of this interaction and whether it occu tricyclic antidepressants has yet to be determined.
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor for anticholinergic side effects of imipramine if verapamil is added to therap imipramine may be appropriate. Conversely, if verapamil is discontinued, monitor continued clinical efficacy c adjust dosage accordingly.
7) Probable Mechanism: decreased imipramine clearance

3.5.1.FY Warfarin

1) Interaction Effect: an increased risk of bleeding
2) Summary: Tricyclic antidepressants (TCAs) may increase the half-life and bioavailability of oral anticoagul 1970a; Williams et al, 1976a). Considerable interindividual differences may be found (Pond et al, 1975a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: In patients receiving imipramine and warfarin, closely monitor prothrombin time ratio warfarin doses accordingly.
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 incre levels and an increase in the plasma half-life of dicumarol, although the effect was not consistent in all su 1975). This effect was not observed with warfarin.
b) A single oral dose of bishydroxycoumarin after eight days of nortriptyline resulted in a significantly pro and decreased volume of distribution of the coumarin anticoagulant in six healthy volunteers (Vesell et a mechanism of action was suggested to be reduced bishydroxycoumarin metabolism and/or altered coum
c) Drug dosing was studied in 16 patients on long-term anticoagulant therapy who used concurrent TCA 1976). TCAs affected the stability of anticoagulant control leading to frequent changes in the doses of an Inhibition of coumarin metabolism was the postulated mechanism.

3.5.1.FZ 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 interaction studies have been done, it is recommended that concurrent use with other agents that may prolon avoided (Prod Info GEODON(R) oral capsules, IM injection, 2007; Marshall & Forker, 1982ah).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive QTc interval prolongation, avoid the concurrent adr ziprasidone and agents that can prolong the QTc interval (Prod Info GEODON(R) oral capsules, IM injection,
7) Probable Mechanism: additive cardiac effects

3.5.1.GA 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 interva recommended therapeutic dose (Prod Info Zomig(R), 2001; Marshall & Forker, 1982l). Even though no forma studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong tl 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 rec
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.GB 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 1999), haloperidol (O'Brien et al, 1999), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001 (Owens, 2001b), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003). Even though no formal drug studies have been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recomm Pamelor(R), 2001; Marshall & Forker, 1982t).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 m proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricu (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 be impairment in psychomotor performance. Almost all studies to date have evaluated the effects of the combina skills, driving behavior and psychomotor skills (Landauer et al, 1969; Patman et al, 1969; Milner & Landauer, al, 1975; Seppala, 1977). There are no studies evaluating respiratory response with the combination.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Encourage abstention from alcohol during at least the first few weeks of tricyclic adı allow patient accommodation to potential CNS depressant effects of the tricyclic.
7) Probable Mechanism: additive CNS depressant activity; impaired hepatic metabolism of the tricyclic antide
8) Literature Reports
a) The studies available indicate that the interaction between amitriptyline (and other antidepressants) ir ethanol is unpredictable. They indicate that antidepressants may enhance, prevent, or not affect the CNS actions of ethanol. The most significant effect reported is enhanced CNS depression. However, there are tricyclic antidepressants may actually antagonize the sedative effects of ethanol (Milner & Landauer, 197
b) The propensity for interaction may be related to the inherent CNS depressant action of the tricyclic ar listed in one series in descending order as amitriptyline, doxepin, imipramine, nortriptyline, desipramine, (Marco & Randels, 1981).
c) Imipramine and amitriptyline are the best documented examples of disruptions of metabolism. Cleara 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 combina amitriptyline or imipramine (Hudson, 1981), and reversible extrapyramidal effects (parkinsonian effects, a amoxapine (Shen, 1984).

3.5.4 Drug-Tobacco Combinations

3.5.4.A Tobacco

1) Interaction Effect: decreased imipramine concentrations

2) Summary: The administration of oral imipramine 3.5 mg/kg to tobacco smokers (15 cigarettes daily) result lower mean plasma levels of combined imipramine and desmethylimipramine (160 ng/mL) when compared to ng/mL) (Perel et al, 1975). Tobacco smoking may alter the response to antidepressants (Linnoila et al, 1981;

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Patients who smoke may require larger doses of imipramine than non-smokers. Mo receiving imipramine for antidepressant efficacy.

7) Probable Mechanism: increased hepatic metabolism

3.5.5 Intravenous Admixtures

3.5.5.1 Drugs

Doxapram

Haloperidol

3.5.5.1.A Doxapram

1) Compatible

a) Doxapram (400 mg/20 mL with imipramine 12.5 mg/1 mL physically compatible and no loss of dc imipramine stability not described) (Trissel, 1990)

b) Imipramine (12.5 mg/1 mL with doxapram 400 mg/20 mL physically compatible in syringe with nc decomposition in 24 hours; temperature not specified) (Trissel, 1990a)

3.5.5.1.B Haloperidol

1) Conflicting Data

a) Incompatible

1) Haloperidol in a 1:1 or 1:2 mixture with imipramine, compatibility is questionable because the no visual changes in 1 hour, was slightly cloudy and viscous in 2 hours, was clear and very visc room temperature, but no haloperidol decomposition was observed in a 4 hour study period; dru not specified (Pers Comm, 1990)

b) Compatible

1) Haloperidol in a 1:1 or 1:2 mixture with imipramine, compatibility is questionable because the no visual changes in 1 hour, was slightly cloudy and viscous in 2 hours, was clear and very visc room temperature, but no haloperidol decomposition was observed in a 4 hour study period; dru not specified (Pers Comm, 1990)

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) Imipramine Hydrochloride

1) Therapeutic

a) Laboratory Parameters

1) MHPG Urinary Concentration
a) Patients with urinary levels of 3-methoxy-4-hydroxy-phenyl glycol (MHPG) less than 1950 mcg/d antidepressant (TCA) therapy, respond to imipramine, and other TCAs, more predictably than patier urinary levels greater than 1950 mcg/day (Rosenbaum et al, 1980); (Beckmann & Goodwin, 1975)(M
b) Newer data (Maas et al, 1982) confirm some of the earlier data and hypotheses while failing to c fact that a low cerebrospinal fluid (CSF) 5-HIAA (5-hydroxyindoleacetic acid) or low urinary MHPG v pretreatment period is associated with a favorable response to amitriptyline therapy was not confirm study showed no significant relationships between pre-treatment urinary MHPG, CSF MHPG, 5-HIA (homovanillic acid) values and subsequent amitriptyline efficacy.
c) Low urinary NE and MHPG values are associated with a greater incidence of response to amitrip imipramine therapy in bipolar affective disorder patients, but not in unipolar patients (Maas et al, 198
2) Dexamethasone Suppression Test (DST)
a) The DST has been reported to be a useful tool in predicting whether or not a patient would respo antidepressant therapy (Brown et al, 1979, Brown et al, 1980). Eighty percent of patients with a posi responded to therapy versus a 37% response rate in patients with a negative DST (Brown et al, 197 of DST results as an indicator of tricyclic antidepressant therapy efficacy in the treatment of depress confirmed in one study (Peselow et al, 1983a).
b) Depressed patients with abnormal DST may respond better to imipramine or desipramine therap or clomipramine therapy (Brown et al, 1980). The result of this study must be considered with cautio investigator made a single evaluation of efficacy after 2 weeks of therapy. These results were not re imipramine and amitriptyline therapy (Greden et al, 1981). Therefore, DST results may not be a usef selection of a particular antidepressant.
3) Platelet Monoamine Oxidase Activity
a) Measurements of platelet MAO activity with serotonin reveals that unmedicated depressed patier significantly higher degree of activity compared to controls. This degree of activity decreases progre imipramine therapy and falls within normal limits at the time the patient is classified as recovered (Q Whether platelet MAO activity is useful as a monitoring parameter remains to be determined.
4) Platelet Binding
a) Imipramine has been shown to have specific high-affinity binding sites on human platelet membr McChesney, 1985). These binding sites appear to be similar to those found in the human brain. Rec indicates that platelet membrane binding may be decreased in some depressed patients (Lewis & M Pecknold et al, 1987; De Leo et al, 1991); (Ambrusini et al, 1992). The exact value of this finding is s however, it may be of value in predicting which depressed patients are more likely to respond to ant therapy.
b) The ability of the platelet to bind imipramine decreases with age. Whether this decrease in platel related to decreases in the density or number of receptors or an alteration in membrane microenviro Even though the decrease in platelet binding is significant, whether the changes effects the efficacy unknown (Marazziti et al, 1987).
c) Significant reductions in platelet imipramine binding have been observed in depressed patients. I diagnosed with panic disorders or panic disorders concurrent with depression and patients with a pr depression have normal platelet imipramine binding compared to controls. The reason for this differ but may indicate that the 2 syndromes differ neurochemically (Pecknold et al, 1987).
5) Serum Concentrations
a) Indications for determination of serum imipramine concentration (Hollister, 1982):
1) Utilization of adequate doses without experience clinical effect;
2) Side effects uncertainly related to imipramine therapy;
3) Monitoring high dose imipramine therapy;
4) Assess the influence of intercurrent illness on imipramine serum concentrations;
5) Evaluating a patient suspected of intentional or unintentional overdose of imipramine.

b) Physical Findings
1) Depression
a) Clinical improvement of the signs and symptoms of depression.
2) Enuresis
a) Decreased frequency of nocturnal wetting episodes.
3) Attention Deficit Hyperactivity Disorder (ADHD)
a) Improvement in mental and behavioral symptoms, including inappropriate inattention, impulsivity cognitive performance.

2) Toxic
a) Laboratory Parameters
1) Obtain WBC and differential cells in patients with fever, sore throat, or other signs of infection (Prod I oral tablets, 2007).

b) Physical Findings
1) Obtain baseline ECG in patients with cardiac disease, elderly, or if initiating larger-than-usual doses. during therapy if clinically warranted (Prod Info imipramine hcl oral tablets, 2007).
a) Depression
1) Monitor patients receiving antidepressants for worsening of depression, suicidality, or unusu behavior, especially at the initiation of therapy or when the dose increases or decreases. Such include at least weekly face-to-face contact with patients or their family members or caregivers

weeks of treatment, then visits every other week for the next 4 weeks, then at 12 weeks, and th indicated beyond 12 weeks. Families and caregivers should be advised of the need for close ob observation) of patients and communication with the prescriber (Anon, 2004).

2) Patients who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, impulsivity, akathisia, hypomania, or mania may be at an increased risk for worsening depressi these symptoms are observed, therapy should be reevaluated and it may be necessary to disco medications when symptoms are severe, sudden in onset, or were not part of the patient's initia 2004).

b) Attention Deficit Hyperactivity Disorder (ADHD)

1) The American Academy of Pediatrics (AAP) does not recommend the routine use of electroc (ECGS) or routine subspecialty cardiology evaluations (which were previously recommended by Heart Association (AHA) scientific statement to detect cardiac conditions that might place the ch sudden cardiac death) before initiating stimulant therapy to treat attention-deficit/hyperactivity d most children. The APA cited specific reasons for changing the recommendation including: lack establishing a relationship between stimulant drugs used to treat ADHD and sudden cardiac de frequency of sudden unexpected deaths among patients taking stimulant drugs is not higher tha general population of children, and lack of cost-effective analysis to support ECG screening or s by pediatric cardiologist (Perrin et al, 2008).

2) Based on the American Academy of Pediatrics (AAP) and the American Heart Association (A statements, the following cardiac monitoring recommendations have been established to assist evaluation of children treated with stimulant drugs, including imipramine, for ADHD (Perrin et al, 2008):

- Conduct a thorough examination prior to initiating imipramine therapy for a diagnosis of A attention should be given to symptoms indicative of a cardiac condition, including palpitatio or syncope.
- Obtain a complete family and patient history for conditions associated with SCD, and dete of any other prescription or over-the-counter medications.
- Conduct a complete physical evaluation of the patient for hypertension, cardiac murmurs, associated with Marfan syndrome, and signs of irregular cardiac rhythms. Prolongation of C tachycardia, and rarely sudden death have all been reported with imipramine use.
- Perform further evaluation if family history, patient history or physical exam is suggestive 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
- Blood pressure and heart rate should be evaluated at baseline, at dose increases, during within 1 to 3 months, and at follow up visits every 6 to 12 months.

B) Imipramine Pamoate

1) Therapeutic

a) Laboratory Parameters

1) Dexamethasone Suppression Test (DST)

a) The DST has been reported to be a useful tool in predicting whether or not a patient would respo antidepressant therapy (Brown et al, 1979, Brown et al, 1980). Eighty percent of patients with a posi responded to therapy versus a 37% response rate in patients with a negative DST (Brown et al, 197 of DST results as an indicator of tricyclic antidepressant therapy efficacy in the treatment of depress confirmed in one study (Peselow et al, 1983a).

b) Depressed patients with abnormal DST may respond better to imipramine or desipramine therap or clomipramine therapy (Brown et al, 1980). The result of this study must be considered with cautio investigator made a single evaluation of efficacy after 2 weeks of therapy. These results were not re imipramine and amitriptyline therapy (Greden et al, 1981). Therefore, DST results may not be a usef selection of a particular antidepressant.

2) Platelet Monoamine Oxidase Activity

a) Measurements of platelet MAO activity with serotonin reveals that unmedicated depressed patie significantly higher degree of activity compared to controls. This degree of activity decreases progre imipramine therapy and falls within normal limits at the time the patient is classified as recovered (Q Whether platelet MAO activity is useful as a monitoring parameter remains to be determined.

3) Serum Concentrations

a) Indications for determination of serum imipramine concentration (Hollister, 1982):

1) Utilization of adequate doses without experience clinical effect;
2) Side effects uncertainly related to imipramine therapy;
3) Monitoring high-dose imipramine therapy;
4) Assess the influence of intercurrent illness on imipramine serum concentrations;
5) Evaluating a patient suspected of intentional or unintentional overdose of imipramine.

4) Platelet Binding

a) Imipramine has been shown to have specific high-affinity binding sites on human platelet membr McChesney, 1985). These binding sites appear to be similar to those found in the human brain. Rec indicates that platelet membrane binding may be decreased in some depressed patients (Lewis & M Pecknold et al, 1987; De Leo et al, 1991); (Ambrusini et al, 1992). The exact value of this finding is s however, it may be of value in predicting which depressed patients are more likely to respond to ant therapy.

b) The ability of the platelet to bind imipramine decreases with age. Whether this decrease in platel related to decreases in the density or number of receptors or an alteration in membrane microenviro Even though the decrease in platelet binding is significant, whether the changes effects the efficacy unknown (Marazziti et al, 1987).

c) Significant reductions in platelet imipramine binding have been observed in depressed patients. I diagnosed with panic disorders or panic disorders concurrent with depression and patients with a pr depression have normal platelet imipramine binding compared to controls. The reason for this differ but may indicate that the 2 syndromes differ neurochemically (Pecknold et al, 1987).

b) Physical Findings

1) Depression

a) Clinical improvement of the signs and symptoms of depression.

2) Attention Deficit Hyperactivity Disorder (ADHD)

a) Improvement in mental and behavioral symptoms, including inappropriate inattention, impulsivity cognitive performance.

2) Toxic

a) Laboratory Parameters

1) Obtain WBC and differential cells in patients with fever, sore throat, or other signs of infection (Prod I (R) oral capsules, 2007).

b) Physical Findings

1) Obtain baseline ECG in patients with cardiac disease, elderly, or if initiating larger-than-usual doses. during therapy if clinically warranted (Prod Info TOFRANIL-PM(R) oral capsules, 2007).

2) Monitor patients receiving antidepressants for worsening of depression, suicidality, or unusual chang especially at the initiation of therapy or when the dose increases or decreases. Such monitoring should i weekly face-to-face contact with patients or their family members or caregivers during the initial 4 weeks visits every other week for the next 4 weeks, then at 12 weeks, and then as clinically indicated beyond 1 and caregivers should be advised of the need for close observation (ie, daily observation) of patients and with the prescriber (Anon, 2004).

3) Patients who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, akathisia, hypomania, or mania may be at an increased risk for worsening depression or suicidality. If the observed, therapy should be reevaluated and it may be necessary to discontinue medications when sym sudden in onset, or were not part of the patient's initial symptoms (Anon, 2004).

a) Attention Deficit Hyperactivity Disorder (ADHD)

1) The American Academy of Pediatrics (AAP) does not recommend the routine use of electroc (ECGS) or routine subspecialty cardiology evaluations (which were previously recommended by Heart Association (AHA) scientific statement to detect cardiac conditions that might place the ch sudden cardiac death) before initiating stimulant therapy to treat attention-deficit/hyperactivity d most children. The APA cited specific reasons for changing the recommendation including: lack establishing a relationship between stimulant drugs used to treat ADHD and sudden cardiac de frequency of sudden unexpected deaths among patients taking stimulant drugs is not higher tha general population of children, and lack of cost-effective analysis to support ECG screening or s by pediatric cardiologist (Perrin et al, 2008).

2) Based on the American Academy of Pediatrics (AAP) and the American Heart Association (statements, the following cardiac monitoring recommendations have been established to assist evaluation of children treated with stimulant drugs, including imipramine pamoate, for ADHD (P Vetter et al, 2008):

- Conduct a thorough examination prior to initiating imipramine pamoate therapy for a diagn Special attention should be given to symptoms indicative of a cardiac condition, including p syncope, or syncope.
- Obtain a complete family and patient history for conditions associated with SCD, and dete of any other prescription or over-the-counter medications.
- Conduct a complete physical evaluation of the patient for hypertension, cardiac murmurs, associated with Marfan syndrome, and signs of irregular cardiac rhythms. Prolongation of Q tachycardia, and rarely sudden death have all been reported with imipramine pamoate use
- Perform further evaluation if family history, patient history or physical exam is suggestive 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
- Blood pressure and heart rate should be evaluated at baseline, at dose increases, during within 1 to 3 months, and at follow up visits every 6 to 12 months.

4.2 Patient Instructions

A) Imipramine (By mouth)

Imipramine

Treats depression. May also be used to treat bedwetting in children. This medicine is a tricyclic antidepressant.

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to imipramine or to related medicines such a (Elavil®), carbamazepine (Tegretol®), maprotiline (Ludiomil®), or nortriptyline (Aventyl®). You should not use this

have had a recent heart attack or have taken an MAO inhibitor such as isocarboxazid (Marplan®), phenelzine (Na
(Eldepryl®), or tranylcypromine (Parnate®) in the past 14 days.

How to Use This Medicine:
Capsule, Tablet

Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed
order to find out what works best for you. Do not use more medicine or use it more often than your doctor tell
You may take this medicine with or without food.
Do not crush or chew the capsules. You may open the capsules and mix the medicine beads with soft food (p
applesauce). Swallow the mixture without chewing.
If you are taking this drug for depression, it may take 2 to 3 weeks before you start to feel better.
This medicine should come with a Medication Guide. Read and follow these instructions carefully. Ask your d
pharmacist if you have any questions. Ask your pharmacist for the Medication Guide if you do not have one.
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 d
then to use the medicine and skip the missed dose. Do not use extra medicine to make up for a missed dose
If you take one dose a day at bedtime, you should not use the missed dose the next morning. Wait until your
bedtime 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
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, a
products.

Make sure your doctor knows if you are using atropine, benztropine (Cogentin®), cimetidine (Tagamet®), gua
(Ismelin®), methylphenidate (Ritalin®), scopolamine, medicine for high blood pressure (such as clonidine or
certain medicine for heart rhythm problems (such as quinidine, flecainide, propafenone, Quinaglute®, Tambo
Rythmol®), medicine to treat seizures (such as phenobarbital, phenytoin, or Dilantin®), a phenothiazine med
chlorpromazine, perphenazine, prochlorperazine, promethazine, thioridazine, Compazine®, Mellaril®, Phene
Thorazine®, or Trilafon®), or other medicines to treat depression (such as fluoxetine, paroxetine, sertraline, P
Zoloft®).
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and a
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, planning to become pregnant, or breastfeeding. Tell your d
glaucoma, trouble urinating, mental problems, stomach problems, seizures, heart disease, liver disease, kidn
thyroid disease.
For some children, teenagers, and young adults, this medicine can increase thoughts of suicide. Tell your do
doctor right away if you or your child start to feel more depressed and have thoughts about hurting yourselves
unusual thoughts or behaviors that trouble you or your child, especially if they are new or are getting worse q
the doctor knows if you or your child have trouble sleeping, get upset easily, have a big increase in energy, o
reckless. Also tell the doctor if you or your child have sudden or strong feelings, such as feeling nervous, ang
violent, or scared. Let the doctor know if you, your child, or anyone in your family has bipolar disorder (manic-
tried to commit suicide.
Do not give this medicine to a child unless directed to do so by the child's doctor.
This medicine may raise or lower your blood sugar, or it may cover up symptoms of very low blood sugar (hyp
Make sure any doctor or dentist who treats you knows that you are using this medicine. You may need to sto
medicine several days before having surgery or medical tests.
Do not stop using this medicine suddenly without asking your doctor. You may need to slowly decrease your
stopping it completely.
This medicine may make your skin more sensitive to sunlight. Use a sunscreen when you are outdoors. Avoi
tanning beds.
This medicine may cause dizziness and vision changes. Avoid driving, using machines, or doing anything els
dangerous if you are not alert or able to see well.
Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to ke
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, d

trouble breathing.
Anxiety, restlessness, nervousness, or mood or mental changes.
Change in how much or how often you urinate, or problems with urination.
Changes in behavior, or thoughts of hurting yourself or others.
Chest pain, shortness of breath, cold sweats, and bluish-colored skin.
Fast, pounding, or irregular heartbeat.
Lightheadedness or fainting when getting up suddenly from a lying or sitting position.
Numbness or tingling in the hands and feet.
Numbness or weakness in your arm or leg, or on one side of your body.
Seizures or tremors.
Sudden or severe headache, problems with vision, speech, balance, or walking.
Swelling in your hands, ankles, or feet.
Trouble sleeping.
Twitching or muscle movements you cannot control.
Unexplained fever or sore throat.
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:
Breast swelling or discharge.
Changes in vision.
Changes in weight.
Dizziness or drowsiness.
Dry mouth.
Nausea, vomiting, diarrhea, constipation, or upset stomach.
Problems having sex.
Ringing in the ears.
Skin rash or itching.
Swelling of the breast or testicles in men.

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 this disease's treatment regimens are diverse. The two mc diagnostic syndromes among affective disorders are major depression and bipolar disorders. The tricyclic antidepress the monoamine oxidase inhibitors (MAOIs) are considered the most effective agents for treating major depression. Fo disorders, lithium is considered the standard of therapy over TCAs, MAOIs and other agents such as carbamazepine

B) Imipramine and amitriptyline, along with the selective sorotonin reuptake inhibitors (SSRI) antidepressants, are cor standard of therapy for endogenous or typical depression. In addition, imipramine may be employed for treating agora has also been used adjunctively for pediatric enuresis, adult urinary incontinence associated with neurogenic bladder, incontinence, and geriatric spontaneous unstable detrusor contractions. Some studies indicate that chronic pain and d neuropathies may also be alleviated with imipramine. Although TCAs reportedly lower seizure threshold, imipramine h demonstrated to reduce the frequency of absence and myoclonic seizures. When an epileptic patient is refractory to o antidepressants and a TCA is deemed necessary for treatment, imipramine should be considered.

C) Imipramine and amitriptyline still have a place in therapy as the standards for the treatment of major depression al antidepressants. Newer classes of antidepressants are not more effective than imipramine for typical depression, but alternatives for treating patients intolerant of TCAs or exhibiting atypical depression. Being versatile, imipramine may b therapy of other disorders besides depression and should be included on hospital formularies. Institutions that commo depression should consider a diverse formulary with agents from each antidepressant class.

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) DEPRESSION

a) The antidepressant mechanism of action of imipramine has not been completely determined but appears interaction with biogenic amines. Imipramine, like other tricyclic antidepressants, blocks the re-uptake of nore hydroxy-tryptamine at nerve terminals preventing their degradation and increasing their availability. This resu turnover of these amines in selective neurons but the relation of this effect to anti-depressant activity has not demonstrated (Gilman et al, 1990). Effects on the D1 dopamine receptor may also be important in the mediat antidepressant activity (Gambarana et al, 1995).

2) ENURESIS

a) Why imipramine works in the treatment of enuresis is not well understood. It beneficial effects do not appe changes in sleep architecture, anticholinergic properties, antiadrenergic properties, or effects on thyroid relea induced urinary urgency. In patients with nocturnal polyuria, imipramine had a vasopressin-independent antic attributed primarily to increased tubular reabsorption of urea and to a lesser extent to decreased sodium and excretion (Hunsballe et al, 1997). The drug improves functional bladder capacity during chronic administratio 1992; Prod Info Tofranil(R), 1995a).

B) REVIEW ARTICLES

1) A Consensus Statement on Panic Disorder is available from the International Consensus Group on Depressio
(Ballenger et al, 1998). Also an excellent review is available on the treatment of panic disorder (Bennett et al, 199
2) Drug-interactions of antidepressants are reviewed in German language (Zapotoczky & Simhandl, 1995).

4.5 Therapeutic Uses

Imipramine

Imipramine Hydrochloride

Imipramine Pamoate

4.5.A Imipramine

Anorexia nervosa

Cataplexy - Narcolepsy

Ophthalmoplegic migraine

Severe major depression with psychotic features

4.5.A.1 Anorexia nervosa
See Drug Consult reference: ANOREXIA NERVOSA - DRUG THERAPY

4.5.A.2 Cataplexy - Narcolepsy
See Drug Consult reference: NARCOLEPSY AND CATAPLEXY - DRUG THERAPY

4.5.A.3 Ophthalmoplegic migraine
See Drug Consult reference: THERAPY OF HEADACHE IN CHILDREN

4.5.A.4 Severe major depression with psychotic features
See Drug Consult reference: PSYCHOTIC DEPRESSION - DRUG THERAPY

4.5.B Imipramine Hydrochloride

Agoraphobia

Anorexia nervosa

Attention deficit hyperactivity disorder, predominantly inattentive type

Binging

Bulimia nervosa

Cardiac dysrhythmia

Depression

Diabetic neuropathy

Disorder of ejaculation

Drug dependence

Gardner-Diamond syndrome

Globus hystericus

Mood swings

Nocturnal enuresis

Obsessive-compulsive disorder

Pain

Panic disorder

Posttraumatic stress disorder

Schizophrenia; Adjunct

Separation anxiety disorder of childhood

Sexual disorder

Sleep disorder

Social phobia

Trichotillomania

Urinary incontinence

4.5.B.1 Agoraphobia

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:

Effective in the treatment of agoraphobia (Deltito et al, 1991)
Efficacy appears to be dose-related and usually requires doses of 150 milligrams or greater per day

c) Adult:

1) Imipramine and placebo were equally effective in the treatment of agoraphobia in a double-blind clinic drug therapy with brief psychological treatment (Cohen et al, 1984a). The drugs were started 2 weeks pr of the psychological therapy. At week 6 the mean dose of IMIPRAMINE was 124 milligrams and at week mg/day. During week 2 to week 12 each treatment group received 6 fortnightly sessions of therapist-aide addition each patient was given a leaflet describing the nature of agoraphobia and ways to cope with it. A requested to complete systematic self-exposure homework and record these activities in a diary. Drug th gradually withdrawn over weeks 26 to 28 of therapy. At the 2-year follow-up only 40 subjects were availa had dropped out of the study (2 refused follow-up, 1 died, 1 moved out of the country, and 1 was untrace of the patients remained improved with regards to their phobias. There was no significant difference betv patients treated with imipramine or placebo therapy. Nor was there a superior effect of therapist-aided ex therapist-aided relaxation.

2) The plasma IMIPRAMINE levels, but not DESIPRAMINE, correlated with the improvement in agoraph (Mavissakalian et al, 1984), which may indicate that the antiphobic effects of IMIPRAMINE therapy are m post-synaptic serotonergic neurotransmitter system and not the noradrenergic system.

3) IMIPRAMINE therapy plus programmed in vivo exposure practice was superior to IMIPRAMINE thera (Mavissakalian & Michelson, 1986; Mavissakalian et al, 1983).

4.5.B.2 Anorexia nervosa

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 resulted in some improvement in patients with anorexia nervosa

c) Adult:
1) Imipramine treatment resulted in some improvement in 7 patients with anorexia nervosa treated seria antidepressants (tricyclics, MAOIs, and triazolopyridines) including imipramine. Three of the patients rec imipramine; the treatment trials ranged from 6 to 14 weeks. Four of the patients had some improvement symptoms, 2 experienced some weight gain, and 3 of 3 who had bulimic symptoms reported improveme anorexic symptoms (3 to 6 weeks) was slower than the improvement observed in depression and anxiet following tricyclic therapy (Hudson et al, 1985). Significant weight gain generally began after 2 to 3 montl with IMIPRAMINE tended to tolerate the drug poorly and appeared to have an extraordinary sensitivity to anticholinergic side effects when compared to patients treated with trazodone or MAOIs (Hudson et al, 1 extraordinary sensitivity to the drug's side effects may be associated with their low body weight.

4.5.B.3 Attention deficit hyperactivity disorder, predominantly inattentive type

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

b) Summary:
Stimulants (eg, amphetamine, methylphenidate) are the drugs of choice in the treatment of attention defi

c) Pediatric:
1) Imipramine therapy should be considered an alternative or adjunctive agent when these agents fail o unable to tolerate them (Hilton et al, 1991; Rancurello, 1985a). The dose used ranges from 25 to 100 mi tends to be lower than those needed to treat depression. Children tend to respond within 24 hours after i The monitoring of serum imipramine and desipramine levels may be useful. The serum levels associate responses have been 10 to 54 ng/ml of imipramine and 10 to 65 ng/ml of desipramine (Linnoila et al, 197
2) A 6-year-old retarded child with Fragile X syndrome and attention deficit disorder responded to IMIPR (Hilton et al, 1991). IMIPRAMINE improved the boy's insomnia, enuresis, and attention deficit disorder, w therapy with METHYLPHENIDATE had caused a deterioration in behavior.
3) A 12-year-old boy with a history of severe attention deficit disorder and stimulant-induced Tourette's s responded well to IMIPRAMINE therapy (50 milligrams/d). During the course of IMIPRAMINE therapy th disorder substantially improved and the Tourette's symptomatology was not affected (Dillon et al, 1985).
4) Ten hyperactive children were treated with IMIPRAMINE 75 to 150 milligrams/day and no response w of the patients (Winsberg et al, 1980).
5) Fifty-two children, 3 to 14 years of age, were enrolled in an open clinical study to evaluate the efficac in the treatment of CHILDHOOD HYPERACTIVITY (Huessy & Wright, 1970). Thirty-five of the 52 childre marked improvement in behavior. The average daily dose of IMIPRAMINE was 50 mg (25 to 125 mg). S (11/17) of the children failing to respond to IMIPRAMINE therapy subsequently responded to METHYLPI therapy.

4.5.B.4 Binging

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

b) Summary:
May be beneficial for weight loss when added to diet counseling and psychological support in obese bing

c) Adult:
1) A short course of low dose imipramine added to diet counseling and psychological support helped ob to lose weight and maintain their weight loss. In a double-blind study, binge eaters (as defined by DSM-I body mass index of greater than 27.5-kilograms (kg)/square meter randomly received imipramine 25 mil daily (n=15) or placebo (n=16) for 8 weeks. Diet counseling and psychological support were provided du phase and continued for 6 months thereafter. Imipramine- treated patients experienced a weight loss of placebo group remained stable (p=0.0002). The occurrence of depression was low for both groups; how on the Hamilton Depression scale declined in the imipramine group (p less than 0.001) but not in the pla eating episodes declined from 7.1 episodes/week to 2.8 episodes for the imipramine group (p less than episodes to 5.4 episodes in the placebo group (p not significant). After the active treatment phase, imipra continued their weight loss by a mean of 1.9 kg (p less than 0.001) while placebo- treated patients regai significant) (Laederach-Hofmann et al, 1999).

4.5.B.5 Bulimia nervosa

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:

Approximately 75% of patients show at least a moderate response (reduction of binge eating by 50% antidepressant therapy
Monoamine oxidase inhibitors also appear effective in bulimia, and may be superior to tricyclic antid et al, 1983)

c) Adult:

1) Twenty bulimic subjects were followed for a period of up to 2 years to assess the long term efficacy o therapy (Pope et al, 1985). At the end of the follow-up period, 95% had at least partial improvement and experienced a complete remission. Over the course of the study period 85% had either maintained or im quality of their initial response. The one patient that failed to respond discontinued her medication and pr her original frequency of binge eating.

2) A retrospective study of 22 patients with bulimia treated with antidepressants (AMITRIPTYLINE, IMIP DESIPRAMINE, DOXEPIN, TRAZODONE, TRANYLCYPROMINE, or PHENELZINE) showed a decreas bingeing and/or an improvement in depression (Brotman et al, 1984). During a 3-month follow-up period relapsed despite continuation of their antidepressant therapy, while others continued to benefit from drug

4.5.B.6 Cardiac dysrhythmia

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Some patients with ventricular tachycardia or premature ventricular contractions may benefit from imipra

c) Adult:

1) IMIPRAMINE was included in a double-blinded crossover pilot study to evaluate the efficacy of ventri complex (VPC) suppression after acute myocardial infarction as a means to improve survival (Anon, 198 was assigned to ENCAINIDE, FLECAINIDE, IMIPRAMINE, MORICIZINE, or placebo. The dose of the m adjusted to achieve 70% or greater reduction of VPC and greater than 90% reduction in unsustained ver tachycardia. If the patient failed to achieve an adequate response or was unable to tolerate the drug, the discontinued and they were crossed over to a different antiarrhythmic class (class 1C to class 1A or clas ENCAINIDE (79%) and FLECAINIDE (83%) were superior to IMIPRAMINE (52%), MORICIZINE (66%), as first line-drugs. In patients failing IMIPRAMINE or MORICIZINE therapy, ENCAINIDE was 68% and F effective. It would appear that IMIPRAMINE is not the drug of choice for the prevention of VPC following myocardial infarction. In addition, changes in therapy secondary to the development or worsening of con failure occurred in 26% of the treatment groups compared to 18% in the placebo group (Greene et al, 19

2) IMIPRAMINE in doses of 50 to 400 milligrams/day (mean = 210 +/- 103 mg/day) and NORTRIPTYLIN to 150 mg/day (mean = 100 +/- 29 mg/day) were effective in the reduction of PVCs (Giardina et al, 1985a percent of the patients had a greater than 80% suppression of their PVCs. Neither drug significantly cha ejection fraction or peak systolic pressure end-systolic volume ratio. Both drugs produced a reduction in blood pressure.

3) Twenty-two patients with 30 or more ventricular premature complexes (PVCs) per hour were treated IMIPRAMINE 1 milligrams/kilogram/day (in two divided doses), increasing by 1 mg/kg/day every other da suppressed by at least 80% (or until adverse effects were observed or a daily dose of 5 mg/kg/day was a Eighteen patients (82%) exhibited antiarrhythmic effects from IMIPRAMINE therapy. All patients treated psychological depression. The elimination half-life was approximately 8 hours, however, duration of actio much longer and antiarrhythmic effects were observed over at least a 12 hour period, which suggests tha IMIPRAMINE may contribute to the duration of antiarrhythmic efficacy (Giardina & Bigger, 1982).

4) In patients with premature ventricular contractions, IMIPRAMINE was noted to suppress arrhythmias 90% in 10 of 11 patients. IMIPRAMINE shortens action potential duration and decreases conduction velo velocity and therefore is classified as a class 1 antiarrhythmic drug. Since the half-life of IMIPRAMINE is to 18 hours) it may be dosed on a twice daily regimen. Antiarrhythmic doses appear to be similar to antic (3.5 mg/kg/day). The antiarrhythmic activity of IMIPRAMINE is partially attributed to its metabolites, desm and 2-hydroxyimipramine. Due to complications, IMIPRAMINE should not be used in patients with pre-ex defects (Thase & Perel, 1982).

4.5.B.7 Depression

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective; Pediatric, Evidence is inconclusive
Recommendation: Adult, Class IIb; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Indicated for the relief of symptoms of depression (Prod Info TOFRANIL(R) tablets, 2005)
Endogenous depression may be more likely to respond to imipramine therapy than other depressive
TOFRANIL(R) tablets, 2005)

c) Adult:
1) Various depressive illnesses have responded to treatment with IMIPRAMINE in daily doses of 75 to 2
(Prod Info Tofranil(R), 1995b; Kocsis et al, 1989; Kocsis et al, 1988; Battistini et al, 1980a; Eilenberg, 19
1979a); (Lindberg et al, 1979)(Amin et al, 1978). Patients suffering from endogenous depression (Fabre
endogenous depression (Lindberg et al, 1979), depression of myotonic dystrophy (Brumback & Carlson,
depression (Finnerty et al, 1978a) alcoholic patients with primary depression (McGrath et al, 1996), and
patients with depressive disorders (Nunes et al, 1998) may benefit from IMIPRAMINE therapy. However
of IMIPRAMINE and a neuroleptic are effective in the treatment of delusional depression (Kaskey et al, 1
2) High dose tricyclic antidepressant therapy (IMIPRAMINE 150 to 200 milligrams/d, DESMETHYLIMIPI
500 mg/d) was effective in only a small portion of elderly patients with delusional depression. The dropou
to side effects was 58% and the overall success rate was only 25% (Brown et al, 1984).

d) Pediatric:
1) IMIPRAMINE is efficacious in the treatment of depression in children (Rancurello, 1985a; Petti & Con
general overview of the treatment of childhood behavioral and emotional disorders has been published (
1985a).
2) IMIPRAMINE therapy in adolescents with major depressive illness was less effective than in adults in
of 35 patients (Strober et al, 1990). Twenty-four females and 11 male depressed patients between 13 an
with a Hamilton Rating Scale for Depression scores of 16 or greater were enrolled in the study. Followinç
period, patients received IMIPRAMINE 5 milligrams/kilogram/day (up to a maximum of 300 mg) for 6 wee
adolescents completed the trial. The average daily dose was 222 mg/day. Overall efficacy was low, with
with delusional subtypes responding more poorly than the nondelusional patients. Eight of the 24 nondel
displayed delayed onset of response, followed by sustained improvement. Only one delusional patient d
clinical improvement. Steady state plasma levels did not vary between responders and nonresponders. T
study suggest that imipramine may be less efficacious in the treatment of major depression in adolescen
as has previously been suggested for other tricyclic antidepressants, and raises questions about age diff
neurotransmitter and neuroregulatory system responses to specific antidepressant agents.
3) Twenty-one children (ages 5.8 to 10.25 years) with various types of depression were treated with IMI
67% of the children showing some improvement (Conners & Petti, 1983). The dose of IMIPRAMINE was
at bedtime and slowly increased over a period of 7 to 14 days to a maximum dosage of 5 milligrams/kilog
mg/day (one older child was treated with 225 mg/d (4.9 mg/kg/day). Seven (33%) of the children experie
worsening or no significant change in any of the areas monitored. In fact, 2 children showed a significant
and hostility during the IMIPRAMINE therapy.
4) Imipramine was efficacious in the treatment of 20 prepubertal children hospitalized for major depressi
III) with imipramine (Preskorn et al, 1982). IMIPRAMINE therapy consisted of 75 milligrams/day, adminis
for the first 3 weeks and increased to a maximum of 5 milligrams/kilogram if no response. Serum IMIPRA
DESIPRAMINE levels were drawn during each phase of the study. During phase I, none of the 15 childre
tricyclic antidepressant (TCA) plasma concentration outside the 125 to 225 ng/mL range showed a remis
improvement in their condition. Eighty percent of those children with serum levels between 125 to 225 ng
a remission. During phase II, 12 of the 16 children achieved steady-state total TCA plasma concentration
ng/mL and 11 (92%) of them had experienced a remission by the end of the treatment period. Based on
be concluded that IMIPRAMINE is effective in the treatment of depression in prepubertal children and its
concentration-dependent.

4.5.B.8 Diabetic neuropathy

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 for diabetic neuropathy in selected patients

c) Adult:
1) In most patients, an imipramine plasma drug concentration of 400 to 500 nmol/L was sufficient to ach
in the treatment of diabetic neuropathy (Sindrup et al, 1990a). All patients were diabetic and had one or
(pain, paresthesia, dysesthesia, and hypesthesia) and signs (reduction of sensibility, strength, or tendon
peripheral neuropathy. One patient demonstrated no significant improvement even with IMIPRAMINE plu
levels below 400 nmol/L. In the other eleven patients doses of 125 to 350 milligrams/day were required t
levels to about 400 mmol/L. One patient required a blood level of 730 mmol/L to achieve maximal relief.
2) A double-blind, cross-over comparison of IMIPRAMINE with placebo was conducted in nine patients
peripheral diabetic neuropathy (Sindrup et al, 1989). The dose of IMIPRAMINE was adjusted to achieve
IMIPRAMINE plus DESIPRAMINE level of 300 to 750 nmol (125 to 225 milligrams/day) during the first w

treatment period was three weeks and no washout phase was used between treatment periods. Efficacy
the end of each treatment period based on symptoms and measurement of peripheral and autonomic ne
IMIPRAMINE provided significant beneficial symptomatic improvement in all patients, but not beneficial c
peripheral or autonomic nerve function.
3) IMIPRAMINE in doses of 50 milligrams (mg) daily for one week, then 100 mg daily for 4 weeks, was e
producing improvement in 7 of 12 patients with severe diabetic neuropathy of the lower extremities in a c
over study (Kvinesdal et al, 1984). IMIPRAMINE had beneficial effects on pain, paresthesia, dysesthesia
nocturnal aggravation.

4.5.B.9 Disorder of ejaculation

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

In case reports, imipramine has been effective in treating ejaculatory disorders

c) Adult:

1) IMIPRAMINE 25 milligrams three times/day corrected RETROGRADE EJACULATION of 18 months
duration in 2 adult diabetics. One patient had normal gonadotropin levels; the other had low plasma testo
testosterone therapy did not correct retrograde ejaculation (Brooks et al, 1980).
2) A 29-year-old male with ASPERMIA of 4 years duration secondary to lymphadenectomy noted ejacul
volume and consistency 1 day after beginning IMIPRAMINE 50 milligrams daily for depression. Motile sp
seen on microscopic examination and sperm count was 115,600,000/mm(3). Aspermia returned within 2
discontinuing IMIPRAMINE therapy. These results recurred on 3 separate occasions (Kelly & Needle, 19

4.5.B.10 Drug 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:

Has little effect in the treatment of drug addiction
Does improve mood in drug-addicted patients with depressive disorders

c) Adult:

1) Treatment of depressed METHADONE-MAINTENANCE OPIATE ADDICTS with IMIPRAMINE or a p
similar subjective results in one study (Kleber et al, 1983). At the end of 8 weeks of therapy both groups
reduction in depressive symptoms. However, a 12-week, double-blind trial that excluded initial placebo r
pre-randomization period found significantly improved depression rating scores after treatment with imipr
compared to placebo (n=42) (p less than 0.001). Imipramine doses were titrated based on response to a
of 268 milligrams daily (Nunes et al, 1998).
2) Imipramine had little effect in the treatment of COCAINE DEPENDENCE and METHAMPHETAMINE
patients (151 cocaine dependent and 32 methamphetamine dependent) seen at the Haight-Ashbury Fre
et al, 1994). Patients were randomly assigned to treatment with imipramine 10 or 150 milligrams/day for
this double-blind study. In addition, all subjects were given intensive drug abuse counseling during the co
treatment. Efficacy was based on negative urine samples, self reporting of abstinence, craving, and Bec
inventory. The longest retention in the program occurred with the group receiving the higher imipramine
retention 34 days vs 17 days). No differences in craving or depressive symptoms were observed and the
scores in both groups decreased after the start of therapy. Positive urine analyses were less in the high
group (5% vs 14%) at 14 days, but were no different at 28 or 90 days. Based on these results it appears
of limited value in the treatment of cocaine or methamphetamine dependent patients who do not have a
disorder.

4.5.B.11 Gardner-Diamond 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:

Effective only for short-term therapy of autoerythrocyte sensitization

c) Adult:

1) A 20-year-old female with autoerythrocyte sensitization and depression was treated with IMIPRAMIN
1983). One week later the bleeding resolved and after 2 weeks the depression began to resolve. In 3 to

symptoms had resolved. Six weeks later, while still receiving therapeutic doses of IMIPRAMINE, the dep
recurred and 10 days later bleeding restarted. Compared to previous episodes the severity of depressior
less severe. The bleeding resolved in 10 days and the depressive symptoms were gone within 6 weeks.
subsequent relapse in therapy the IMIPRAMINE was discontinued and AMITRIPTYLINE therapy (300 m
Since the start of AMITRIPTYLINE therapy the patient has been free of depression and bleeding for 10 r

4.5.B.12 Globus hystericus

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:

Efficacy demonstrated in case reports only

c) Adult:

1) Globus hystericus syndrome is a condition in which the individual develops a fear that he/she is interr
and unable to breathe. If the condition is left untreated the patient may become profoundly disabled or m
threatening weight loss. Case reports of three patients have shown that psychoactive drugs may be effe
this condition. IMIPRAMINE therapy was effective in the treatment of one case, PHENELZINE in anothe
TRANYLCYPROMINE in the other case (Brown et al, 1986). Two additional cases of successful imipram
globus hystericus syndrome were reported (Kaplan, 1987; Rosenthal, 1987).

4.5.B.13 Mood swings

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:

Possibly effective for PATHOLOGICAL CRYING/LAUGHING

c) Adult:

1) Heightened tendency for crying or laughing in frequency and inappropriate circumstances (pathologic
laughing) and emotional lability unrelated to depression can occur in individuals with brain damage (eg, s
Small doses of IMIPRAMINE (30 to 60 milligrams) may partially or completely control the emotionalism v
(Allman, 1992).

4.5.B.14 Nocturnal enuresis

FDA Labeled Indication

a) Overview

FDA Approval: Adult, no; Pediatric, yes (6 years and older)
Efficacy: Pediatric, Effective
Recommendation: Pediatric, Class IIa
Strength of Evidence: Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indicated as temporary adjunctive therapy for the reduction of enuresis in children 6 years and older
TOFRANIL(R) tablets, 2005)

c) Pediatric:

1) Numerous double-blind, crossover, placebo-controlled studies have demonstrated IMIPRAMINE's eff
adjunct treatment of enuresis in pediatric patients. Most studies report the use of doses ranging from 10
administered at bedtime although doses as high as 100 mg have been utilized. The application of pharm
Bayesian methods) may improve the individualization of IMIPRAMINE dosing in the treatment of enuresi
1994a; Tamayo et al, 1992; Fernandez de Gatta et al, 1989). Most studies report only minor side effects
mouth, constipation, irritability, anorexia, and sleep disturbances (Prod Info Tofranil(R), 1995b; Fernande
1990; Fournier et al, 1987; Wagner et al, 1982; Jorgenson et al, 1980; Rapoport et al, 1980b; Lake et al,
et al, 1974; Maxwell & Seldrup, 1971; Alderton, 1970).

2) Follow-up of 29 young adults, 10 years after IMIPRAMINE therapy for enuresis, suggests that no psy
results from this therapy; these patients showed no psychological decompensation, inhibition of learning
to drug abuse (Bindelglas & Dee, 1978).

4.5.B.15 Obsessive-compulsive disorder

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Questionable efficacy in the treatment of obsessive-compulsive disorder

c) Adult:

1) Imipramine was ineffective in treating obsessive- compulsive disorder (OCD) in a double-blind, placel study that evaluated the efficacy of IMIPRAMINE in the treatment of depression and obsessive-compulsi patients (Foa et al, 1987). Nineteen (10 women and 9 men) were treated with IMIPRAMINE and 18 (9 w were treated with a placebo. Each placebo patient received 10 tablets per day. The IMIPRAMINE group increased by 25 mg every other day until clinical response, side effects, or a maximum daily dose of 250 daily IMIPRAMINE dose was 233 mg (150 to 250 mg). At the end of 6 weeks the IMIPRAMINE was effec symptoms associated with depression, but had little to no effect on their obsessive-compulsive symptom

2) Four patients with obsessive-compulsive bowel obsessions were treated with IMIPRAMINE (3) or DO patients were free of their bowel obsession within 30 days (10, 14, 14, 30) of starting drug therapy (Jenik

4.5.B.16 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:

Pain has occasionally resolved with imipramine therapy

c) Adult:

1) Patients with chest pain, but normal coronary angiograms, may respond to imipramine therapy (Cann The dose of medications used in the study were imipramine 50 milligrams at night and placebo in the mo 0.1 milligrams twice daily, and placebo twice daily. The incidence of chest pain was decreased by 52 +/- with 1 +/- 86% with placebo and 39 +/- 51% with clonidine therapy (data is presented as means +/- SD). associated with imipramine use was statistically significant (p=0.03). A follow-up evaluation of these pati average of 21 months, indicated that none of the patients had been seen in an emergency room or had b because of chest pain. Seventeen patients have had the imipramine therapy discontinued and 16 asked imipramine therapy because of recurrent chest pain symptoms (Cannon, 1994b). The mechanism of this unknown, but may be a result of a visceral analgesic effect and not dependent on cardiac, esophageal, c characteristics or gender. Another possible mechanism for this effect may be an increased pain threshol reduction in psychological depression (Hare, 1994).

2) A survey of Italian oncology centers revealed that 43% of their patients were given antidepressants. T frequently utilized drugs were AMITRIPTYLINE, CLOMIPRAMINE, IMIPRAMINE, and TRAZODONE. Mo that the antidepressants were useful in controlling pain and were most efficacious in depressed patients 1987).

3) A case report of a 26-year-old graduate student being treated with IMIPRAMINE for suicidal thoughts esteem noted an improvement in her chronic pelvic pain (induced by endometriosis four years earlier) wl IMIPRAMINE therapy (Beresin, 1986).

4.5.B.17 Panic disorder

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Similar in efficacy to alprazolam

c) Adult:

1) GENERAL INFORMATION

a) The clinical response to IMIPRAMINE in the treatment of panic disorder is independent of the pre depression or dysphoria (Deltito et al, 1991). Patients with high baseline depression scores have ter poorest outcomes (Rosenberg et al, 1991aa; Rosenberg et al, 1991c; Zitrin, 1983; Nurnberg & Cocc Maintenance with half-dose IMIPRAMINE therapy may be useful in providing patients with a protecti relapses (Mavissakalian & Perel, 1992a; Mavissakalian & Perel, 1992b). The use of IMIPRAMINE in panic disorder may not be as safe as other anxiolytics in patients with cardiovascular disease (Roth

2) Combination imipramine and cognitive-behavioral therapy (CBT) was of limited value initially but prov during maintenance therapy in patients with panic disorder. Patients with panic disorder randomly receiv (n=77), imipramine alone (n=83), placebo alone (n=24), CBT with imipramine (n=65), or CBT alone (n=6 acute treatment phase. Thereafter, responders entered a 6-month maintenance phase. Patient response following the 12- week acute treatment phase, the 6-month maintenance phase, and 6-months after ther discontinuation; assessment tools included the Panic Disorder Severity Scale (PDSS) and the Clinical G Scale (CGI). Initial imipramine doses were 10 milligrams (mg)/day slowly increased over 5 weeks to 200 increased to 300 mg if symptoms continued. Following acute treatment, responses for the PDSS were 4

alone, 45.8% for imipramine alone, 21.7% for placebo alone, 60.3% for CBT with imipramine, and 57.1% placebo. Both CBT alone and imipramine alone were significantly better than placebo (p=0.03 and p=0.0 however, combination therapy provided no greater response rate over each treatment alone (p not signif during the acute phase, none of the therapies were significantly better than the others. Following mainter responses on the PDSS were 39.5% for CBT alone, 37.8% for imipramine alone, 13% for placebo alone, with imipramine, and 46.8% for CBT plus placebo. Responses on both the PDSS and the CGI were sign imipramine versus placebo (p=0.02 for both) and CBT versus placebo (p=0.02, p=0.01, respectively). Us combination therapy was significantly better than either CBT alone (p=0.04) and better than imipramine a the CGI, combination therapy was only significantly better than imipramine alone (p=0.03) and not better not significant). Following treatment discontinuation after the 6-month maintenance phase, the only statis was the PDSS scores in the CBT group compared to the placebo group (p=0.05) (Barlow et al, 2000).

3) Maintenance treatment with imipramine had a significant protective effect against relapse in patients and agoraphobia. Patients who had shown an initial good and stable response to imipramine therapy ov randomly received same-dose imipramine continuation (n=29) or placebo discontinuation (n=27). Patient initial imipramine at a target dose of 2.25 milligrams/kilogram or discontinued their imipramine by decrea 25% each week (substituted with placebo). During this study, no patient received behavioral or cognitive a crisis-type intervention was needed. During the study, if relapse was confirmed the patient exited the s defined as a worsening of their condition (measured as a 33% decline in the End- State Function scale s accompanied by insistent requests for therapeutic action. After 12 months, the study population consiste the imipramine group and 10 patients in the placebo group. This resulted in a 92.5% lower hazard rate o imipramine as compared to placebo (Mavissakalian & Perel, 1999).

4) In a double-blind study, an 8-month therapy period for panic disorder with either alprazolam or imipra (Rickels & Schweizer, 1998). Patients received alprazolam (n=37), imipramine (n=34), or placebo (n=35) period of short-term treatment, a 6-month maintenance period, and then a 15-month follow-up period. Pa alprazolam began at 1 milligram (mg) daily and were titrated up to 10 mg. Those receiving imipramine be were increased to 250 mg. Alprazolam patients had notable reductions in panic attacks during the first 2 while imipramine patients showed improvement over placebo patients after 3 to 4 weeks. Drop-out rates were 11% in the alprazolam group, 41% in the imipramine group, and 57% in the placebo group (p less t alprazolam versus the other groups). In the remaining patients it was noted that tolerance developed to a during the maintenance phase. After the 6-month maintenance phase, doses were titrated off over 3 wee 62% of the alprazolam and 26% of the imipramine groups were panic-free (p less than 0.01). During the patients could be treated with non-study medications. Regardless of medication, patients who completed treatment were more likely to be panic-free than those who had dropped out, even if they received non-s (85% versus 55%, p less than 0.01). Remission rates were higher in younger patients, those with a histo or intense panic attacks, those with a lower initial phobia score, and those with an initial lower score of in self-confidence, and passivity (Minnesota Multiphasic Personality Inventory Dependency Scale).

5) A comparison of cognitive therapy, applied relaxation, and imipramine found that at 3 months cognitiv superior to both applied relaxation and imipramine therapy (Clark et al, 1994). At 6 months the cognitive imipramine treatment produced similar results and were better than applied relaxation. However, betwee months of therapy, several of the imipramine patients relapsed while the patients treated with cognitive th to do better than with imipramine and relaxation therapy.

4.5.B.18 Posttraumatic stress disorder

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Resulted in improvement in positive symptoms of post-traumatic stress disorder

c) Adult:

1) Imipramine treatment resulted in improvement in positive symptoms of post-traumatic stress disorder patients (Burstein, 1984). Therapy was initiated at a low dose and increased over the following 7 days to tolerable dose (mean 260 milligrams/day; range 50 to 350 mg/d). After 2 to 3 weeks of therapy, there wa decrease in the severity of forced recollection, sleep and dream disturbances, and a cessation or reducti Most avoidance items, eg, staying away from reminders of the event, trying not to talk about the event, a remove it from their memory, did not decrease significantly in severity. Based on these results it would a IMIPRAMINE, in combination with psychotherapy, may be an effective treatment for patients.

2) Treatment of 3 patients with acute post-traumatic stress disorder (PTSD) with either DOXEPIN or IMI in an improvement in PTSD symptoms (Blake, 1986). Whether or not tricyclic antidepressant therapy is s equivalent, or inferior to psychotherapy or other means of treatment remains to be determined.

4.5.B.19 Schizophrenia; Adjunct

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive; Pediatric, Evidence is inconclusive
Recommendation: Adult, Class IIb; Pediatric, Class III

Strength of Evidence: Adult, Category B; Pediatric, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
May be effective as adjunct therapy in depressed schizophrenic patients
Ineffective for schizophrenia itself

c) Adult:
1) Schizophrenic or schizoaffective patients with POSTPSYCHOTIC DEPRESSION may benefit from th IMIPRAMINE to their neuroleptic therapy. Favorable results were observed in 27 patients previously trea FLUPHENAZINE DECANOATE and BENZTROPINE after the addition of IMIPRAMINE to their drug regi beneficial effects continued in those patients with postpsychotic depression that initially responded to the IMIPRAMINE to their regimen and were monitored for an additional six months on the triple drug regimer patients that did not complete the six-month observation period were discontinued for administrative reas a relapse in either psychosis or depression (Siris et al, 1992). A one-year follow-up study documented th maintaining imipramine therapy in the treatment of postpsychotic depression (Siris et al, 1994).
2) A preliminary study indicates that imipramine may be an effective adjunctive agent in the acute treatn abusing dysphoric schizophrenic or schizoaffective patients (Siris et al, 1993). The importance of these r proven.

d) Pediatric:
1) A pilot study in 10 autistic and schizophrenic children age 2 to 6 years found IMIPRAMINE therapy to (Campbell et al, 1971). The drug did decrease affective blunting, anergy, and withdrawal and stimulated in several children, but increased psychotic speech, behavioral disorganization, and excitation in other cl

4.5.B.20 Separation anxiety disorder of childhood

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

b) Summary:
Routine use of tricyclic antidepressants is not recommended for separation anxiety in children
Behavioral therapy may be just as effective as imipramine

c) Pediatric:
1) The combination of imipramine and nonpharmacologic therapies (eg, parent management training, be and family therapy) may improve subjective comfort, reduce anxiety and somatic symptoms in 70% of th experiencing separation-anxiety disorder (Rancurello, 1985a). This disorder is associated with a high rat recovery, therefore the routine use of tricyclic antidepressants is not recommended (Rancurello, 1985a).
2) Both IMIPRAMINE and placebo therapy were equally effective for separation anxiety. A small, double placebo-controlled study was conducted with 21 children with separation anxiety disorder (Klein et al, 19 children were first given a month of vigorous behavioral treatment, then randomly assigned to IMIPRAMI therapy for six weeks. Both treatments were approximately 50% effective.

4.5.B.21 Sexual 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:
Effective in case reports only

c) Adult:
1) IMIPRAMINE may be useful, alone or in combination with LITHIUM, in the treatment of men with PAF NONPARAPHILIC SEXUAL ADDICTIONS (Kafka, 1991). Two patients with sexual disorders improved f IMIPRAMINE therapy. Whether IMIPRAMINE and other antidepressants are useful in the treatment of al paraphilias or nonparaphilic sexual addictions or just specific types remains to be determined.

4.5.B.22 Sleep disorder

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

b) Summary:
Used successfully in the treatment of NIGHT TERRORS, SOMNABULISM, NARCOLEPSY, and CATAP

c) Adult:
1) IMIPRAMINE therapy (50 to 100 milligrams at bedtime) resulted in a dramatic reduction in frequency

night terrors in 2 patients unresponsive to DIAZEPAM therapy (Cooper, 1987).
2) IMIPRAMINE therapy resulted in a significant reduction (242 +/- 156 to 142.8 +/- 120.1) in the total nu episodes in 41.9% of the patients tested (Rubin et al, 1986). Based on these results it appears that IMIP may be an alternative form of therapy for some nonoverweight patients with negative ear, nose and throa and for some patients who had not responded to weight reduction or ENT surgery.
3) A 62-year-old female had suppression of night terrors with IMIPRAMINE 50 milligrams at bedtime; 75 completely suppressed night terrors but caused daytime drowsiness (Beitman & Carlin, 1979).

4.5.B.23 Social phobia

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:

No studies currently support the use of imipramine for social phobia

c) Adult:

1) Imipramine was not useful in the treatment of social phobia in an 8-week, open-trial of 15 patients (Si 1998). Imipramine was started at 50 milligrams (mg) for 3 nights and increased at weekly intervals to a m 300 mg by the fourth week. Only 9 patients were able to complete the study as the others dropped out d effects. Only 2 patients responded to imipramine therapy as determined by the Liebowitz Social Anxiety Liebowitz Social Phobia Disorders Scale-Overall Severity. They were also unable to continue further ther developed urinary hesitancy and the other became hypomanic.

4.5.B.24 Trichotillomania

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Used successfully in a case of trichotillomania and depression in a pediatric patient (Weller et al, 1989).

4.5.B.25 Urinary incontinence

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Used alone or in combination with other anticholinergic medications, can improve urinary continence
May not be better than bladder training in some patients
May help to achieve continence in children with myelodysplasia alone or in combination with oxybut

c) Adult:

1) Imipramine was useful for genuine stress continence. In a prospective study, women with genuine str received imipramine 25 milligrams 3 times daily for 3 months. A urodynamic assessment was done with test to determine the amount of urine leakage. A cure was defined as a pad weight that resulted in 0 gra After 3 months, 35% of women were cured, 25% showed an improved pad weight result of 50% or bette therapy. The women that were cured or improved had a higher urethral closure pressure than those that 0.001). The authors note that a high pre-treatment urethral closure pressure may serve as a predictor fo success (Lin et al, 1999).
2) IMIPRAMINE 75 milligrams orally daily for four weeks was reported effective in the treatment of fema INCONTINENCE in 21 of 30 women (71%). The drug was reported to extend the functional urethral leng independent of stress factors in women who are continent after therapy. These data support that a short result in urinary incontinence and lengthening of the urethra by IMIPRAMINE treatment or vesicopexy wi dysfunction (Gilja et al, 1984).
3) Bladder drill is more effective than drug therapy in the treatment of incontinence due to idiopathic det women. Fifty women with urinary incontinence due to DETRUSOR INSTABILITY were randomly assigne patient bladder drill training or out-patient drug therapy (FLAVOXATE HYDROCHLORIDE 200 mg three IMIPRAMINE 25 milligrams three times/day) for 4 weeks (Jarvis, 1981). At the completion of the study 8 patients treated with bladder drill were continent and 76% were symptom free. Fifty-six percent (14/25) o with medication were continent and 48% were symptom-free. Side effects occurred in 56% of the patient therapy and 5 patients discontinued drug therapy on their own secondary to side effects.
4) Six of 10 elderly patients (x=80 year old, 63 to 88 years) with urinary incontinence associated with sp unstable detrusor contractions were successfully treated with IMIPRAMINE. The dose of IMIPRAMINE w

mg at bedtime and increased every third day by 25 mg, until the patient was continent, experienced side reached 150 mg/day. At the completion of the study 60% of the patients were continent. No correlation b plasma concentrations of desmethylimipramine and clinical or urodynamic effects could be found (Castle

d) Pediatric:

1) Children and adolescents with myelodysplasia and incontinence (i.e. wet between their clean intermit times performed 3 to 5 times daily) benefited from imipramine therapy. Children (n=19, 4- to 12-years-old imipramine 10 milligrams (mg) daily increased to a maximum of 20 mg twice daily. Combination therapy was used in 10 patients. Eight of the children had also failed therapy with oxybutynin, flavoxate, or ephed imipramine, 15 children developed at least partial continence (dry 50% to 80% of the time) with 9 achievi continence (dry at least 80% of the time). The authors suggest low-dose imipramine alone or in combina oxybutynin for children with myelodysplasia to help achieve continence (Hurley et al, 2000).

4.5.C Imipramine Pamoate

Agoraphobia

Anorexia nervosa

Bulimia nervosa

Cardiac dysrhythmia

Depression

Diabetic neuropathy

Gardner-Diamond syndrome

Globus hystericus

Obsessive-compulsive disorder

Pain

Panic disorder

Posttraumatic stress disorder

Separation anxiety disorder of childhood

Sexual disorder

Sleep disorder

Trichotillomania

4.5.C.1 Agoraphobia

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:

Effective in the treatment of agoraphobia (Deltito et al, 1991)
Efficacy appears to be dose-related and usually requires doses of 150 milligrams or greater per day

c) Adult:

1) Imipramine and placebo were equally effective in the treatment of agoraphobia in a double-blind clinic drug therapy with brief psychological treatment (Cohen et al, 1984a). The drugs were started 2 weeks pr

of the psychological therapy. At week 6 the mean dose of IMIPRAMINE was 124 milligrams and at week
mg/day. During week 2 to week 12 each treatment group received 6 fortnightly sessions of therapist-aide
addition each patient was given a leaflet describing the nature of agoraphobia and ways to cope with it. A
requested to complete systematic self-exposure homework and record these activities in a diary. Drug th
gradually withdrawn over weeks 26 to 28 of therapy. At the 2-year follow-up only 40 subjects were availa
had dropped out of the study (2 refused follow-up, 1 died, 1 moved out of the country, and 1 was untrace
of the patients remained improved with regards to their phobias. There was no significant difference betv
patients treated with imipramine or placebo therapy. Nor was there a superior effect of therapist-aided ex
therapist-aided relaxation.
2) The plasma IMIPRAMINE levels, but not DESIPRAMINE, correlated with the improvement in agoraph
(Mavissakalian et al, 1984), which may indicate that the antiphobic effects of IMIPRAMINE therapy are m
post-synaptic serotonergic neurotransmitter system and not the noradrenergic system.
3) IMIPRAMINE therapy plus programmed in vivo exposure practice was superior to IMIPRAMINE thera
(Mavissakalian & Michelson, 1986; Mavissakalian et al, 1983).

4.5.C.2 Anorexia nervosa

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 resulted in some improvement in patients with anorexia nervosa

c) Adult:

1) Imipramine treatment resulted in some improvement in 7 patients with anorexia nervosa treated seria
antidepressants (tricyclics, MAOIs, and triazolopyridines) including imipramine. Three of the patients rec
imipramine; the treatment trials ranged from 6 to 14 weeks. Four of the patients had some improvement
symptoms, 2 experienced some weight gain, and 3 of 3 who had bulimic symptoms reported improveme
anorexic symptoms (3 to 6 weeks) was slower than the improvement observed in depression and anxiety
following tricyclic therapy (Hudson et al, 1985). Significant weight gain generally began after 2 to 3 montl
with IMIPRAMINE tended to tolerate the drug poorly and appeared to have an extraordinary sensitivity to
anticholinergic side effects when compared to patients treated with trazodone or MAOIs (Hudson et al, 1
extraordinary sensitivity to the drug's side effects may be associated with their low body weight.

4.5.C.3 Bulimia nervosa

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:

Approximately 75% of patients show at least a moderate response (reduction of binge eating by 50%
antidepressant therapy
Monoamine oxidase inhibitors also appear effective in bulimia, and may be superior to tricyclic antid
et al, 1983)

c) Adult:

1) Twenty bulimic subjects were followed for a period of up to 2 years to assess the long term efficacy o
therapy (Pope et al, 1985). At the end of the follow-up period, 95% had at least partial improvement and
experienced a complete remission. Over the course of the study period 85% had either maintained or im
quality of their initial response. The one patient that failed to respond discontinued her medication and pr
her original frequency of binge eating.
2) A retrospective study of 22 patients with bulimia treated with antidepressants (AMITRIPTYLINE, IMIP
DESIPRAMINE, DOXEPIN, TRAZODONE, TRANYLCYPROMINE, or PHENELZINE) showed a decreas
bingeing and/or an improvement in depression (Brotman et al, 1984). During a 3-month follow-up period
relapsed despite continuation of their antidepressant therapy, while others continued to benefit from drug

4.5.C.4 Cardiac dysrhythmia

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Some patients with ventricular tachycardia or premature ventricular contractions may benefit from imipra

c) Adult:

1) IMIPRAMINE was included in a double-blinded crossover pilot study to evaluate the efficacy of ventri complex (VPC) suppression after acute myocardial infarction as a means to improve survival (Anon, 198 was assigned to ENCAINIDE, FLECAINIDE, IMIPRAMINE, MORICIZINE, or placebo. The dose of the m adjusted to achieve 70% or greater reduction of VPC and greater than 90% reduction in unsustained ver tachycardia. If the patient failed to achieve an adequate response or was unable to tolerate the drug, the discontinued and they were crossed over to a different antiarrhythmic class (class 1C to class 1A or clas ENCAINIDE (79%) and FLECAINIDE (83%) were superior to IMIPRAMINE (52%), MORICIZINE (66%), as first line-drugs. In patients failing IMIPRAMINE or MORICIZINE therapy, ENCAINIDE was 68% and F effective. It would appear that IMIPRAMINE is not the drug of choice for the prevention of VPC following myocardial infarction. In addition, changes in therapy secondary to the development or worsening of con failure occurred in 26% of the treatment groups compared to 18% in the placebo group (Greene et al, 19

2) IMIPRAMINE in doses of 50 to 400 milligrams/day (mean = 210 +/- 103 mg/day) and NORTRIPTYLIN to 150 mg/day (mean = 100 +/- 29 mg/day) were effective in the reduction of PVCs (Giardina et al, 1985a percent of the patients had a greater than 80% suppression of their PVCs. Neither drug significantly cha ejection fraction or peak systolic pressure end-systolic volume ratio. Both drugs produced a reduction in blood pressure.

3) Twenty-two patients with 30 or more ventricular premature complexes (PVCs) per hour were treated IMIPRAMINE 1 milligrams/kilogram/day (in two divided doses), increasing by 1 mg/kg/day every other da suppressed by at least 80% (or until adverse effects were observed or a daily dose of 5 mg/kg/day was a Eighteen patients (82%) exhibited antiarrhythmic effects from IMIPRAMINE therapy. All patients treated psychological depression. The elimination half-life was approximately 8 hours, however, duration of actio much longer and antiarrhythmic effects were observed over at least a 12 hour period, which suggests tha IMIPRAMINE may contribute to the duration of antiarrhythmic efficacy (Giardina & Bigger, 1982).

4) In patients with premature ventricular contractions, IMIPRAMINE was noted to suppress arrhythmias 90% in 10 of 11 patients. IMIPRAMINE shortens action potential duration and decreases conduction velo velocity and therefore is classified as a class 1 antiarrhythmic drug. Since the half-life of IMIPRAMINE is to 18 hours) it may be dosed on a twice daily regimen. Antiarrhythmic doses appear to be similar to antio (3.5 mg/kg/day). The antiarrhythmic activity of IMIPRAMINE is partially attributed to its metabolites, desm and 2-hydroxyimipramine. Due to complications, IMIPRAMINE should not be used in patients with pre-ex defects (Thase & Perel, 1982).

4.5.C.5 Depression

FDA Labeled Indication

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indicated for the relief of symptoms of depression (Prod Info TOFRANIL-PM(R) capsules, 2005)
Endogenous depression may be more likely to respond to imipramine therapy than other depressive TOFRANIL-PM(R) capsules, 2005)

c) Adult:

1) Intramuscular S-adenosyl-L-methionine 1,4-butanedisulphonate (SAMe) was found to be as efficacio imipramine (IMI) for the treatment of depression. In a randomized, double-blind, comparative trial, patien of major depressive episode according to DSM-IV criteria received SAMe 400 milligrams (mg) by intramu once daily (n=146) or oral IMI 150 mg per day in 3 divided doses. Blinding was maintained by a double d IMI dose was titrated over the first week to reach the full dose by day 8. Both treatments were given for 4 preestablished criteria (final score on the Hamilton Depression Rating Scale (HAMD), difference betwee HAMD scores, percentage of responders defined as those with a Clinical Global Impression (CGI) endpo less, and percentage of responders defined as those with a drop of at least 50% from baseline in HAMD treatments were equivalent. By the CGI criterion, 68% of patients in the SAMe group and 66% in the IMI responders; by the HAMD criterion, 59% of the SAME group and 50% of the IMI were responders. Drug reactions occurred in significantly fewer subjects of the SAMe group than of the IMI group: 9.5% vs 33% relevant differences were observed in laboratory measures, vital signs, or ECG parameters (Pancheri et

2) Various depressive illnesses have responded to treatment with IMIPRAMINE in daily doses of 75 to 2 (Prod Info Tofranil(R), 1995b; Kocsis et al, 1989; Kocsis et al, 1988; Battistini et al, 1980a; Eilenberg, 19 1979a); (Lindberg et al, 1979)(Amin et al, 1978). Patients suffering from endogenous depression (Fabre endogenous depression (Lindberg et al, 1979), depression of myotonic dystrophy (Brumback & Carlson, depression (Finnerty et al, 1978a) alcoholic patients with primary depression (McGrath et al, 1996), and patients with depressive disorders (Nunes et al, 1998) may benefit from IMIPRAMINE therapy. However, of IMIPRAMINE and a neuroleptic are effective in the treatment of delusional depression (Kaskey et al, 1

3) High dose tricyclic antidepressant therapy (IMIPRAMINE 150 to 200 milligrams/d, DESMETHYLIMIPI 500 mg/d) was effective in only a small portion of elderly patients with delusional depression. The dropou to side effects was 58% and the overall success rate was only 25% (Brown et al, 1984).

d) Pediatric:

1) IMIPRAMINE is efficacious in the treatment of depression in children (Rancurello, 1985a; Petti & Con

general overview of the treatment of childhood behavioral and emotional disorders has been published (
1985a).
2) Twenty-one children (ages 5.8 to 10.25 years) with various types of depression were treated with IMI
67% of the children showing some improvement (Conners & Petti, 1983).
3) Imipramine was efficacious in the treatment of 20 prepubertal children hospitalized for major depressi
III) with imipramine (Preskorn et al, 1982). IMIPRAMINE therapy consisted of 75 milligrams/day, adminis
for the first 3 weeks and increased to a maximum of 5 milligrams/kilogram if no response. Serum IMIPRA
DESIPRAMINE levels were drawn during each phase of the study. During phase I, none of the 15 childre
tricyclic antidepressant (TCA) plasma concentration outside the 125 to 225 ng/mL range showed a remis
improvement in their condition. Eighty percent of those children with serum levels between 125 to 225 ng
a remission. During phase II, 12 of the 16 children achieved steady-state total TCA plasma concentratior
ng/mL and 11 (92%) of them had experienced a remission by the end of the treatment period. Based on
be concluded that IMIPRAMINE is effective in the treatment of depression in prepubertal children and its
concentration-dependent.

4.5.C.6 Diabetic neuropathy

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 for diabetic neuropathy in selected patients

c) Adult:

1) In most patients, an imipramine plasma drug concentration of 400 to 500 nmol/L was sufficient to ach
in the treatment of diabetic neuropathy (Sindrup et al, 1990a). All patients were diabetic and had one or
(pain, paresthesia, dysesthesia, and hypesthesia) and signs (reduction of sensibility, strength, or tendon
peripheral neuropathy. One patient demonstrated no significant improvement even with IMIPRAMINE plu
levels below 400 nmol/L. In the other eleven patients doses of 125 to 350 milligrams/day were required t
levels to about 400 mmol/L. One patient required a blood level of 730 mmol/L to achieve maximal relief.
2) A double-blind, cross-over comparison of IMIPRAMINE with placebo was conducted in nine patients
peripheral diabetic neuropathy (Sindrup et al, 1989). The dose of IMIPRAMINE was adjusted to achieve
IMIPRAMINE plus DESIPRAMINE level of 300 to 750 nmol (125 to 225 milligrams/day) during the first w
treatment period was three weeks and no washout phase was used between treatment periods. Efficacy
the end of each treatment period based on symptoms and measurement of peripheral and autonomic ne
IMIPRAMINE provided significant beneficial symptomatic improvement in all patients, but not beneficial c
peripheral or autonomic nerve function.
3) IMIPRAMINE in doses of 50 milligrams (mg) daily for one week, then 100 mg daily for 4 weeks, was e
producing improvement in 7 of 12 patients with severe diabetic neuropathy of the lower extremities in a c
over study (Kvinesdal et al, 1984). IMIPRAMINE had beneficial effects on pain, paresthesia, dysesthesia
nocturnal aggravation.

4.5.C.7 Gardner-Diamond 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:

Effective only for short-term therapy of autoerythrocyte sensitization

c) Adult:

1) A 20-year-old female with autoerythrocyte sensitization and depression was treated with IMIPRAMIN
1983). One week later the bleeding resolved and after 2 weeks the depression began to resolve. In 3 to
symptoms had resolved. Six weeks later, while still receiving therapeutic doses of IMIPRAMINE, the dep
recurred and 10 days later bleeding restarted. Compared to previous episodes the severity of depressior
less severe. The bleeding resolved in 10 days and the depressive symptoms were gone within 6 weeks.
subsequent relapse in therapy the IMIPRAMINE was discontinued and AMITRIPTYLINE therapy (300 m
Since the start of AMITRIPTYLINE therapy the patient has been free of depression and bleeding for 10 r

4.5.C.8 Globus hystericus

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:
Efficacy demonstrated in case reports only

c) Adult:

1) Globus hystericus syndrome is a condition in which the individual develops a fear that he/she is interr and unable to breathe. If the condition is left untreated the patient may become profoundly disabled or m threatening weight loss. Case reports of three patients have shown that psychoactive drugs may be effec this condition. IMIPRAMINE therapy was effective in the treatment of one case, PHENELZINE in anothe TRANYLCYPROMINE in the other case (Brown et al, 1986). Two additional cases of successful imipram globus hystericus syndrome were reported (Kaplan, 1987; Rosenthal, 1987).

4.5.C.9 Obsessive-compulsive disorder

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Questionable efficacy in the treatment of obsessive-compulsive disorder

c) Adult:

1) Imipramine was ineffective in treating obsessive- compulsive disorder (OCD) in a double-blind, placel study that evaluated the efficacy of IMIPRAMINE in the treatment of depression and obsessive-compulsi patients (Foa et al, 1987). Nineteen (10 women and 9 men) were treated with IMIPRAMINE and 18 (9 w were treated with a placebo. Each placebo patient received 10 tablets per day. The IMIPRAMINE group increased by 25 mg every other day until clinical response, side effects, or a maximum daily dose of 250 daily IMIPRAMINE dose was 233 mg (150 to 250 mg). At the end of 6 weeks the IMIPRAMINE was effec symptoms associated with depression, but had little to no effect on their obsessive-compulsive symptom

2) Four patients with obsessive-compulsive bowel obsessions were treated with IMIPRAMINE (3) or DO patients were free of their bowel obsession within 30 days (10, 14, 14, 30) of starting drug therapy (Jenik

4.5.C.10 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:
Pain has occasionally resolved with imipramine therapy

c) Adult:

1) Patients with chest pain, but normal coronary angiograms, may respond to imipramine therapy (Cann The dose of medications used in the study were imipramine 50 milligrams at night and placebo in the mo 0.1 milligrams twice daily, and placebo twice daily. The incidence of chest pain was decreased by 52 +/- with 1 +/- 86% with placebo and 39 +/- 51% with clonidine therapy (data is presented as means +/- SD). associated with imipramine use was statistically significant (p=0.03). A follow-up evaluation of these pati average of 21 months, indicated that none of the patients had been seen in an emergency room or had b because of chest pain. Seventeen patients have had the imipramine therapy discontinued and 16 asked imipramine therapy because of recurrent chest pain symptoms (Cannon, 1994b). The mechanism of this unknown, but may be a result of a visceral analgesic effect and not dependent on cardiac, esophageal, c characteristics or gender. Another possible mechanism for this effect may be an increased pain threshol reduction in psychological depression (Hare, 1994).

2) A survey of Italian oncology centers revealed that 43% of their patients were given antidepressants. T frequently utilized drugs were AMITRIPTYLINE, CLOMIPRAMINE, IMIPRAMINE, and TRAZODONE. Mo that the antidepressants were useful in controlling pain and were most efficacious in depressed patients 1987).

3) A case report of a 26-year-old graduate student being treated with IMIPRAMINE for suicidal thoughts esteem noted an improvement in her chronic pelvic pain (induced by endometriosis four years earlier) wh IMIPRAMINE therapy (Beresin, 1986).

4.5.C.11 Panic disorder

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Similar in efficacy to alprazolam

c) Adult:

1) GENERAL INFORMATION

a) The clinical response to IMIPRAMINE in the treatment of panic disorder is independent of the pre depression or dysphoria (Deltito et al, 1991). Patients with high baseline depression scores have ter poorest outcomes (Rosenberg et al, 1991aa; Rosenberg et al, 1991c; Zitrin, 1983; Nurnberg & Cocc use of IMIPRAMINE in the treatment of panic disorder may not be as safe as other anxiolytics in pat cardiovascular disease (Roth et al, 1992a).

2) Combination imipramine and cognitive-behavioral therapy (CBT) was of limited value initially but prov during maintenance therapy in patients with panic disorder. Patients with panic disorder randomly receiv (n=77), imipramine alone (n=83), placebo alone (n=24), CBT with imipramine (n=65), or CBT alone (n=6 acute treatment phase. Thereafter, responders entered a 6-month maintenance phase. Patient response following the 12- week acute treatment phase, the 6-month maintenance phase, and 6-months after ther discontinuation; assessment tools included the Panic Disorder Severity Scale (PDSS) and the Clinical G Scale (CGI). Initial imipramine doses were 10 milligrams (mg)/day slowly increased over 5 weeks to 200 increased to 300 mg if symptoms continued. Following acute treatment, responses for the PDSS were 48 alone, 45.8% for imipramine alone, 21.7% for placebo alone, 60.3% for CBT with imipramine, and 57.1% placebo. Both CBT alone and imipramine alone were significantly better than placebo (p=0.03 and p=0.0 however, combination therapy provided no greater response rate over each treatment alone (p not signif during the acute phase, none of the therapies were significantly better than the others. Following mainter responses on the PDSS were 39.5% for CBT alone, 37.8% for imipramine alone, 13% for placebo alone, with imipramine, and 46.8% for CBT plus placebo. Responses on both the PDSS and the CGI were sign imipramine versus placebo (p=0.02 for both) and CBT versus placebo (p=0.02, p=0.01, respectively). Us combination therapy was significantly better than either CBT alone (p=0.04) and better than imipramine a the CGI, combination therapy was only significantly better than imipramine alone (p=0.03) and not better not significant). Following treatment discontinuation after the 6-month maintenance phase, the only statis was the PDSS scores in the CBT group compared to the placebo group (p=0.05) (Barlow et al, 2000).

3) Maintenance treatment with imipramine had a significant protective effect against relapse in patients and agoraphobia. Patients who had shown an initial good and stable response to imipramine therapy ov randomly received same-dose imipramine continuation (n=29) or placebo discontinuation (n=27). Patient initial imipramine at a target dose of 2.25 milligrams/kilogram or discontinued their imipramine by decrea 25% each week (substituted with placebo). During this study, no patient received behavioral or cognitive a crisis-type intervention was needed. During the study, if relapse was confirmed the patient exited the s defined as a worsening of their condition (measured as a 33% decline in the End- State Function scale s accompanied by insistent requests for therapeutic action. After 12 months, the study population consiste the imipramine group and 10 patients in the placebo group. This resulted in a 92.5% lower hazard rate o imipramine as compared to placebo (Mavissakalian & Perel, 1999).

4) In a double-blind study, an 8-month therapy period for panic disorder with either alprazolam or imipra (Rickels & Schweizer, 1998). Patients received alprazolam (n=37), imipramine (n=34), or placebo (n=35) period of short-term treatment, a 6-month maintenance period, and then a 15-month follow-up period. Pa alprazolam began at 1 milligram (mg) daily and were titrated up to 10 mg. Those receiving imipramine be were increased to 250 mg. Alprazolam patients had notable reductions in panic attacks during the first 2 while imipramine patients showed improvement over placebo patients after 3 to 4 weeks. Drop-out rates were 11% in the alprazolam group, 41% in the imipramine group, and 57% in the placebo group (p less t alprazolam versus the other groups). In the remaining patients it was noted that tolerance developed to a during the maintenance phase. After the 6-month maintenance phase, doses were titrated off over 3 wee 62% of the alprazolam and 26% of the imipramine groups were panic-free (p less than 0.01). During the patients could be treated with non-study medications. Regardless of medication, patients who completed treatment were more likely to be panic-free than those who had dropped out, even if they received non-s (85% versus 55%, p less than 0.01). Remission rates were higher in younger patients, those with a histo or intense panic attacks, those with a lower initial phobia score, and those with an initial lower score of in self-confidence, and passivity (Minnesota Multiphasic Personality Inventory Dependency Scale).

5) A comparison of cognitive therapy, applied relaxation, and imipramine found that at 3 months cognitiv superior to both applied relaxation and imipramine therapy (Clark et al, 1994). At 6 months the cognitive imipramine treatment produced similar results and were better than applied relaxation. However, betwee months of therapy, several of the imipramine patients relapsed while the patients treated with cognitive th to do better than with imipramine and relaxation therapy.

4.5.C.12 Posttraumatic stress disorder

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Resulted in improvement in positive symptoms of post-traumatic stress disorder

c) Adult:

1) Imipramine treatment resulted in improvement in positive symptoms of post-traumatic stress disorder

patients (Burstein, 1984). Therapy was initiated at a low dose and increased over the following 7 days to tolerable dose (mean 260 milligrams/day; range 50 to 350 mg/d). After 2 to 3 weeks of therapy, there wa decrease in the severity of forced recollection, sleep and dream disturbances, and a cessation or reducti Most avoidance items, eg, staying away from reminders of the event, trying not to talk about the event, a remove it from their memory, did not decrease significantly in severity. Based on these results it would a IMIPRAMINE, in combination with psychotherapy, may be an effective treatment for patients.

2) Treatment of 3 patients with acute post-traumatic stress disorder (PTSD) with either DOXEPIN or IMI in an improvement in PTSD symptoms (Blake, 1986). Whether or not tricyclic antidepressant therapy is s equivalent, or inferior to psychotherapy or other means of treatment remains to be determined.

4.5.C.13 Separation anxiety disorder of childhood

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Routine use of tricyclic antidepressants is not recommended for separation anxiety in children
Behavioral therapy may be just as effective as imipramine

c) Pediatric:

1) The combination of imipramine and nonpharmacologic therapies (eg, parent management training, be and family therapy) may improve subjective comfort, reduce anxiety and somatic symptoms in 70% of th experiencing separation-anxiety disorder (Rancurello, 1985a). This disorder is associated with a high rat recovery, therefore the routine use of tricyclic antidepressants is not recommended (Rancurello, 1985a).

2) Both IMIPRAMINE and placebo therapy were equally effective for separation anxiety. A small, double placebo-controlled study was conducted with 21 children with separation anxiety disorder (Klein et al, 19 children were first given a month of vigorous behavioral treatment, then randomly assigned to IMIPRAMI therapy for six weeks. Both treatments were approximately 50% effective.

4.5.C.14 Sexual 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:

Effective in case reports only

c) Adult:

1) IMIPRAMINE may be useful, alone or in combination with LITHIUM, in the treatment of men with PAR NONPARAPHILIC SEXUAL ADDICTIONS (Kafka, 1991). Two patients with sexual disorders improved f IMIPRAMINE therapy. Whether IMIPRAMINE and other antidepressants are useful in the treatment of al paraphilias or nonparaphilic sexual addictions or just specific types remains to be determined.

4.5.C.15 Sleep disorder

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Used successfully in the treatment of NIGHT TERRORS, SOMNABULISM, NARCOLEPSY, and CATAP

c) Adult:

1) IMIPRAMINE therapy (50 to 100 milligrams at bedtime) resulted in a dramatic reduction in frequency night terrors in 2 patients unresponsive to DIAZEPAM therapy (Cooper, 1987).

2) IMIPRAMINE therapy resulted in a significant reduction (242 +/- 156 to 142.8 +/- 120.1) in the total nu episodes in 41.9% of the patients tested (Rubin et al, 1986). Based on these results it appears that IMIP may be an alternative form of therapy for some nonoverweight patients with negative ear, nose and throa and for some patients who had not responded to weight reduction or ENT surgery.

3) A 62-year-old female had suppression of night terrors with IMIPRAMINE 50 milligrams at bedtime; 75 completely suppressed night terrors but caused daytime drowsiness (Beitman & Carlin, 1979).

4.5.C.16 Trichotillomania

a) Overview

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

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

b) Summary:
Used successfully in a case of trichotillomania and depression in a pediatric patient (Weller et al, 1989).

4.6 Comparative Efficacy / Evaluation With Other Therapies

Adinazolam

Alprazolam

Amineptine

Amisulpride

Amitriptyline

Amoxapine

Binedaline

Brofaromine

Bromocriptine

Bupropion

Buspirone

Butylscopolamine

Chlordiazepoxide

Chlorprothixene

Citalopram

Clomipramine

Clonazepam

Delorazepam

Desipramine

Desmopressin

Diazepam

Dibenzepin

Diclofenac

Dothiepin

Doxepin

Electroconvulsive therapy

Encainide

Flecainide

Fluoxetine

Fluvoxamine

Gepirone

Haloperidol

Lithium

Lofepramine

Maprotiline

Melitracen

Methscopolamine

Mianserin

Milnacipran

Moclobemide

Moricizine

Nefazodone

Nomifensine

Nortriptyline

Paroxetine

Phenelzine

Reboxetine

Ritanserin

Rolipram

Sertraline

Sotalol

Tranylcypromine

Trazodone

Trimipramine

Tryptophan

Venlafaxine

Viloxazine

Zimeldine

4.6.A Adinazolam

4.6.A.1 Depression

a) SUMMARY: In several small controlled studies, adinazolam has been as effective as imipramine in depres including patients with melancholic depression.

b) Several controlled studies have reported the similar efficacy of adinazolam and imipramine in the treatme depressive disorder in outpatients (Amsterdam et al, 1986; Feighner, 1986). Equivalent efficacy has also bee patients with more severe melancholic depression (Amsterdam et al, 1986). However, all studies have emplo numbers of patients, lending themselves to a type II error. Larger studies of adequate duration, incorporating needed to adequately compare these two agents. In addition, compliance is always a problem in outpatient s involving depressed patients. Either a well-controlled inpatient study or the use of serum drug levels in future required.

c) Adinazolam and imipramine had similar efficacy in the treatment of major depressive disorder, with or with symptoms, in a double-blind study involving 43 outpatients (Amsterdam et al, 1986). Following a 1-week, sing period, patients were randomized to receive either adinazolam 10 milligrams (mg) three times daily initially, ir mg by day 14 of treatment if needed, or imipramine 25 mg three times day initially, increasing up to 225 mg b of therapy, if required. Hamilton Depression Rating (HDR) scores and clinical global impression scale scores similar efficacy of both agents; there was trend toward lower HDR scores in the imipramine group at week 12 improvement in the adinazolam group by week 1. Further analysis revealed the comparable efficacy of the 2 with the more severe, melancholic, subtype of depression. Anticholinergic adverse effects of dry mouth, cons blurred vision occurred more frequently in the imipramine group, as did lightheadedness, agitation and nervo sedation or drowsiness was more prevalent in adinazolam patients. Mood swings into hypomania and worse were more frequent in the adinazolam group, with total episodes during study being 4 versus 1 and 3 versus Other adverse effects occurred to a similar degree in each group.

4.6.B Alprazolam

Anxiety

Depression

Panic disorder

4.6.B.1 Anxiety

a) A six-week, double-blind, parallel study was conducted in 60 patients with generalized anxiety disorder to efficacy of alprazolam and imipramine (Hoehn-Saric et al, 1988). After a three-week washout period, patients divided and randomly assigned to alprazolam 0.5 milligram or imipramine 25 milligrams three times daily for s the first week the dose of the medication could be increased by one capsule daily up to a maximum of 12 cap the end of the study the average dose was for the alprazolam-treated group was 2.2 mg/day (0.5 to 6 mg/day imipramine group 91 mg/day (25 to 200 mg/day). During the first two weeks, alprazolam was superior to imip weeks both drugs were effective based on psychic and somatic parameters, but imipramine predominantly af symptoms (eg, negative anticipatory thinking and dysphoria) as alprazolam was superior in attenuating soma

b) Alprazolam and imipramine might be useful in the treatment of school refusal (school phobia); however, fu need to be conducted to document their usefulness (Bernstein et al, 1991).

4.6.B.2 Depression

a) Alprazolam was as effective as imipramine in the treatment of primary depression (Fabre & McLendon, 19 effective doses of alprazolam in the study were 2.6 milligrams daily in divided doses, as compared with 128.4 for imipramine. The onset of action with alprazolam was more rapid than that observed with imipramine; antic were more evident with alprazolam during the first week of therapy. A similar incidence of side effects occurre medication, with the main side effects being drowsiness, insomnia, nervousness, constipation and lightheade alprazolam was reported to have less anticholinergic side effects (confusion, tachycardia, palpitations, dry mo

retention). Imipramine was reported to cause fewer headaches than alprazolam. However, a detailed descrip in these patients was not provided in this study. In addition, specific data regarding the onset of effects of eac also not provided satisfactorily. More importantly, the patient population ("primary" depression) is unclear in t difficult to evaluate which types of depression were being treated.

b) Alprazolam was compared with imipramine in a 6-week, double-blind study on 723 outpatients (Feighner, were selected with moderate to severe symptoms of a unipolar major depressive disorder of at least one mor Patients were given imipramine 25 milligrams two or three times daily or alprazolam 0.5 milligram two to thre initially, followed by increases in doses at one-week intervals to a maximum of 4.5 mg alprazolam and 225 m Both drugs were more effective than placebo in alleviating depression, with alprazolam being at least as effec imipramine. Alprazolam was reported more effective in relieving somatic symptoms and the data suggested a effect in some evaluated parameters, but the significance of this is questionable. Toxicity, primarily anticholin was reported in patients receiving imipramine; drowsiness was the main side effect reported with alprazolam. suggests benefits of alprazolam in the treatment of unipolar depression as defined by the Feighner Diagnosti primary depression (similar to the DMS-III Criteria for major depression). However, this study was performed basis, and even the best blinding techniques are useless if patients are taking other medications. The author other psychotropic medications were not to be used except for "emergencies". Evaluation of drug response ir difficult at best, especially on an outpatient basis with several investigators doing the evaluation. Alprazolam antidepressant effects.

c) Alprazolam, imipramine, and a placebo were compared in a 6-week, double-blind study of 175 patients wi depressive disorder (DSM-III) (Rickels et al, 1982a). Patients were randomly assigned to alprazolam (N=58), or placebo (N=57) therapy. Dosage increases were allowed during the course of treatment and the mean dos and imipramine during the last 2 weeks of treatment were 3 milligrams/day and 150 milligrams/day, respectiv indicate that alprazolam was more effective than imipramine and placebo therapy. However it should be note placebo response rate was observed at 2 weeks (53% compared to 75% for alprazolam and 64% for imipram placebo response rate may be attributed to the fact that a high percentage of the patient were of the anxious depression subtypes. (Note: The data supplied in the figure comparing clinical improvement over time on the drug therapy is for 171 different patients, which is interesting since only 153 patients completed at least 4 we No information is supplied regarding the study dropouts other than the fact that the dropout rates were not sig between the 3 treatment groups.) Imipramine therapy was associated with a higher incidence of drowsiness a alprazolam or placebo therapy.

d) The efficacy of alprazolam and imipramine were evaluated in the inpatient treatment of depressive illness 1984). Patients were randomly assigned to either alprazolam or imipramine therapy. Dosage was individualiz response. Patients receiving alprazolam therapy improved over the first 10 days of therapy and then reached whereas the patients treated with imipramine continued to improve in vegetative and cognitive symptomology examination of the HAM-D scale indicated that the initial improvements seen with alprazolam is predominantl vegetative features of the illness.

e) Both drugs administered once daily were efficacious in the treatment of outpatients with major depressive (Mendels & Schless, 1986). Fifty percent of the alprazolam treatment group had a greater than 50% improver D scores, compared to the 38% success rate observed in the imipramine treatment group and 18% in the pla groups.

f) Patients who can be classified as DSM-III - major depressive episode but fail to satisfy more restrictive crit depression disorder appear to respond better to alprazolam therapy than imipramine therapy. Patients satisfy criteria for primary depression also appear to tolerate and respond better to alprazolam therapy initially. How appeared to be more efficacious during long term therapy. In addition, patients with biologic depression (eg, r positive DST, and shortened REM latency) tended to respond better to imipramine therapy (Overall et al, 198

g) An 8-week, double-blind, controlled study compared the efficacy of alprazolam (58 patients), diazepam (5 imipramine (63 patients), and placebo (61 patients) in 241 outpatients with a DSM-III diagnosis of major depr was a washout period with all patients receiving placebo. Week 2 through 7, the patients received their assig and during week 8 the dose of the medication was reduced by half for 3 days and discontinued for the remair end of the study the mean daily doses were 143 milligrams imipramine, 3.1 milligrams alprazolam, 24 milligra 6.8 capsules of placebo. Attrition rates were significant, 23% by week 4 of treatment and 39% by week 6. By the study, 41% of the imipramine group had withdrawn, 23% of the alprazolam group, 44% of the diazepam g the placebo group. The main reason given for attrition was side effects with the active compounds and ineffe placebo. Alprazolam and imipramine were both significantly better than placebo in treating depression, but di effective. The clinical effects of imipramine and alprazolam were equivalent, and overall the frequency of side similar. Imipramine produced less drowsiness and more anticholinergic effects than both alprazolam and diaz al, 1987a).

4.6.B.3 Panic disorder

a) Summary: Alprazolam and imipramine appear to be equally efficacious in the treatment of panic disorder i The onset of action is faster with alprazolam, but by the end of four weeks their effectiveness is similar (Ricke 1998)(Taylor et al, 1990; Rosenberg et al, 1991; Rosenberg et al, 1991a; Anon, 1992; Roth et al, 1992; Schw Pollack et al, 1994). The decision to use imipramine over alprazolam should be based on patient-related cha concurrent depression, anxiety disorders, cardiovascular disease), potential drug interactions, and side effect

b) In a double-blind study, an 8-month therapy period for panic disorder with either alprazolam or imipramine (Rickels & Schweizer, 1998). Patients received alprazolam (n=37), imipramine (n=34), or placebo (n=35) duri period of short-term treatment, a 6- month maintenance period, and then a 15-month follow-up period. Patien alprazolam began at 1 milligram (mg) daily and were titrated up to 10 mg. Those receiving imipramine began

were increased to 250 mg. Alprazolam patients had notable reductions in panic attacks during the first 2 wee
imipramine patients showed improvement over placebo patients after 3 to 4 weeks. Drop-out rates during this
the alprazolam group, 41% in the imipramine group, and 57% in the placebo group (p less than 0.001 for alpr
other groups). In the remaining patients it was noted that tolerance developed to adverse effects during the m
After the 6-month maintenance phase, doses were titrated off over 3 weeks. At this point, 62% of the alprazo
the imipramine groups were panic-free (p less than 0.01). During the follow-up period, patients could be treat
medications. Regardless of medication, patients who completed 8 months of treatment were more likely to be
those who had dropped out, even if they received non-study medications (85% versus 55%, p less than 0.01)
were higher in younger patients, those with a history of more frequent or intense panic attacks, those with a l
score, and those with an initial lower score of inadequacy, low self-confidence, and passivity (Minnesota Mult
Inventory Dependency Scale).

c) Seventy-nine patients were enrolled in a placebo controlled, double-blind trial comparing the efficacy and
effects of imipramine, alprazolam, and placebo in patients with panic disorders (Taylor et al, 1990). Doses ra
alprazolam 1 to 8 milligrams/day and imipramine 30 to 270 milligrams/day. In terms of global improvement, th
with alprazolam or imipramine experienced significantly greater improvement than the placebo patients. Alpra
rapid onset of effect, but after four weeks of therapy no significant differences in efficacy were apparent betw
and imipramine treated patients. Imipramine did have a number of significant effects on the cardiovascular sy
the heart rate was significantly increased at resting and standing, and the systolic and diastolic blood pressur

d) Cerebrospinal fluid levels of homovanillic acid, 5-hydroxyindoleacetic acid, 3-methoxy-4-hydroxyphenylgly
somatostatin and beta-endorphin were measured in 12 patients with panic disorders who had been treated w
imipramine for seven months. Seven patients treated with alprazolam (mean dose 4.7 mg, range 2 to 6 mg) a
therapy. Four of the five imipramine-treated patients (mean dose 135 mg, range 100 to 150 mg) benefited. C
levels of the monoamine metabolites and neuropeptides remained unchanged during therapy in both treatme
were similar to levels measured in a control group, suggesting the antipanic activities of alprazolam and imipr
involve the monoamine or neuropeptide systems as was previously believed (Lepola et al, 1989).

e) A double-blind, placebo-controlled trial comparing the effects of imipramine and alprazolam in patients wit
revealed both agents were significantly more effective than placebo, however the patients treated with alpraz
fear than the patients in the imipramine and placebo groups after eight weeks of therapy (Taylor et al, 1990).

f) The Cross-National Collaborative Panic Study compared alprazolam, imipramine, and placebo in the treat
disorder (Anon, 1992). The study used in this evaluation was a double-blind, placebo-controlled, multicenter s
1168 patients with a diagnosis of panic disorder based on DSM-III criteria. Prior to the start of drug treatment
drugs were discontinued during a one- to two-week washout period. Patients were then randomly assigned to
alprazolam 1 milligram, imipramine 25 milligrams, or placebo (1 tablet). The initial starting dose was increase
alprazolam, 150 mg imipramine, and 6 placebo tablets by day 19. Subsequently the dosage could be adjuste
response. Formal psychotherapy and behavioral treatment sessions were to be avoided during the eight wee
Efficacy was assessed by using global improvement scores, a panic attach scale, phobia scale, frequency of
anxiety, 14-item Hamilton Rating Scale for Anxiety, 21-item Hamilton Rating scale for Depression, and Hopki
self-rating scale. The treatment-cohort (anyone completing three weeks of therapy) consisted of 1010 patient
completed the entire eight-week study. Reasons for dropping-out were side effects (alprazolam 3.4%, imipra
placebo 3.1%), lack of efficacy (alprazolam 3.1%, imipramine 2.6%, and placebo 12.8%), treatment refusal (1
reasons (alprazolam 7%, imipramine 7.7%, and placebo 11.8%); percentage are expressed as the number o
divided by number of patients enrolled in that treatment group. Onset of therapeutic benefits was noted by we
alprazolam and week 4 with imipramine. By week 8 there was no difference between the alprazolam and imip
and both groups were statistically superior to placebo.

g) Alprazolam was more effective than imipramine and placebo on anticipatory anxiety and phobic symptom
Scandinavian multicenter study in 41 patients with panic disorder (Andersch et al, 1991). Alprazolam had a m
action than imipramine on all symptoms. Patients receiving alprazolam had more drowsiness and those recei
had more anticholinergic effects.

h) In a study of 123 Scandinavian patients with panic disorder, alprazolam had an early effect on variables re
attacks, such as severity of spontaneous attacks and avoidance, whereas imipramine showed a more delaye
measures (Mellergard et al, 1991).

i) Patients with mild-to-moderate depression and panic disorder will respond equally to either alprazolam (av
milligrams/day) or imipramine (avg dose = 159 milligrams/day) therapy. Both drugs are more effective than pl
treatment of patients with mild-to-moderate depression and panic disorder (Keller et al, 1993).

4.6.C Amineptine

4.6.C.1 Depression

a) A controlled, double-blind study compared the efficacy and safety of amineptine (100 to 200 milligrams (m
imipramine (50 to 100 mg/day) for two months in 33 patients who fulfilled the Diagnostic and Statistical Manu
(DSM-III) criteria for major depressive disorders. Amineptine produced steady improvement of the symptoms
during treatment, according to the Hamilton (p = 0.001) and Montgomery and Asberg (p = 0.002) Depression
Clinical Global Impression Scale (p = 0.002). Imipramine produced a significant improvement in the overall sc
less than 0.001). No statistical differences were found between the two drugs; depressive symptoms improve
of treatment for both amineptine and imipramine. The incidence of anticholinergic adverse effects with amine
lower than with imipramine (Mendis et al, 1989).

4.6.D Amisulpride

4.6.D.1 Dysthymia

a) A double-blind, parallel group study compared the efficacy of amisulpride 50 milligrams (mg) daily versus mg daily and placebo in the treatment of dysthymia. No significant difference was found between the two dru whereas amisulpride showed a tendency to generate fewer adverse effects (Lecrubier et al, 1992).

b) A double-blind study, six months in duration, compared the therapeutic effects of amisulpride (50 milligran imipramine (200 mg daily) and placebo (Boyer & Lecrubier, 1996). The active drugs differed significantly from according to the Clinical Global Impression scale (CGI), Montgomery and Asberg Depressive Rating Scale (M Scale for the Assessment of Negative Symptoms (SANS) global score. Difference in efficacy between the act minimal.

4.6.E Amitriptyline

4.6.E.1 Depression

a) Of 11 studies in which amitriptyline and imipramine were directly compared, 5 reported amitriptyline super imipramine superior and 4 reported no difference between the 2 drugs in efficacy (Hutchinson & Smedberg, 1 1966; Snow & Rickels, 1964; Sandifer et al, 1965; Richmond & Roberts, 1964; Hordern, 1963; Burt, 1962).

b) In another study, imipramine (mean 157 milligrams/day) was compared with amitriptyline (mean 186 millig post-psychotic depressed patients who were also receiving one of several neuroleptics (mean chlorpromazin 795 milligrams/day). Thirteen of 14 patients on imipramine improved, while 8 of 11 on amitriptyline improved

4.6.F Amoxapine

4.6.F.1 Depression

a) SUMMARY: Clinical studies have demonstrated that amoxapine is at least as effective as imipramine in th depression (Sathananthan et al, 1973b; Gelenberg et al, 1984; Wilson et al, 1977; Fabre, 1977; Holden et al, Okerson, 1979; Bagadia et al, 1979; Takahashi et al, 1979; Dominguez et al, 1981; Rickels et al, 1981). Side are comparable in type, frequency, and intensity to imipramine (Dugas & Weber, 1982; Kinney & Evans, 198

b) Maprotiline (mean, 165 mg daily) and amoxapine (mean, 230 mg daily) showed similar efficacy in the trea moderate-to-severe depression in a 4-week, double-blind study involving 76 outpatients. Amoxapine is report rapid onset of action than maprotiline as evidenced by a greater improvement at days 4 and 7 (Fabre, 1985).

c) Equivalent doses of amoxapine and imipramine were equally effective in depressed outpatients during 5- blind clinical trials (Rickels et al, 1981; Gelenberg et al, 1984). Amoxapine produced improvement in a 6-wee study involving 90 depressed outpatients more rapidly than did imipramine; however, the dose of amoxapine milligrams/day) was double that of imipramine (105 milligrams/day) (Kiev & Okerson, 1979).

d) Imipramine and amoxapine were comparable in the treatment of depression in inpatients in a controlled st mean doses of 165 milligrams daily was reported comparable with imipramine 175 milligrams daily in manage depressive illness; however, the imipramine-treated patients had slightly more cardiovascular side effects. An patients reportedly had slightly more neurological toxicity (Ahlfors, 1981).

e) Amoxapine and imipramine were comparable in 90 adult outpatients with mixed depressive illnesses in a controlled, double-blind study. Patients received amoxapine 145 to 265 milligrams daily (mean 235 mg) or im milligrams daily (mean 122.5 mg). Amoxapine and imipramine were both significantly superior to placebo as the Hamilton Rating Scale for depression, Zung Self- Rating Scale, and Clinical Global Impression Scale sco there were no significant differences between the 2 drugs (Fabre, 1977).

4.6.F.2 Efficacy

a) Continuous Performance Test (CPT), a visual vigilance test, of amoxapine and imipramine show several d performance and brain function (Buchsbaum et al, 1988). Amoxapine enhanced N120 amplitude in midline pa parietal cortex. Both amoxapine and imipramine enhanced the P200 area, with amoxapine's greatest effect b midline parietal locations. The clinical importance of these differences in brain activity remains to be determin

4.6.G Binedaline

4.6.G.1 Depression

a) Binedaline, a bicyclic antidepressant, was evaluated against imipramine therapy in the treatment of 50 hos endogenously depressed patients (Faltus & Geerling, 1984). Patients were either treated with 150 mg/d of im mg/d of binedaline in 3 equally divided doses. There was no psychiatric, clinical or statistical differences betw treatment groups. Binedaline efficacy was slightly higher than imipramine utilizing the clinical global impressio Frequency of side effects was less in the binedaline treatment group.

4.6.H Brofaromine

4.6.H.1 Depression

a) Brofaromine is a selective and reversible monoamine oxidase inhibitor (MAOI). In addition, the drug may b inhibitor. A comparison of brofaromine with imipramine was made in 216 outpatients with depression. Patient assigned to brofaromine and imipramine therapy in a 2:1 ratio. Both medications were started at a daily dose milligrams. The average dose of medication at the end of eight weeks was brofaromine 93.1 mg/day and imip mg/day. This phase of the study lasted eight weeks. Baseline HAMD scores were 29.4 in the brofaromine gro imipramine group. At the end of the study period the HAMD scores were 9.34 and 12.31 (p=0.01), respective

of adverse reactions was 27.8% in the brofaromine group (eg, headache, sleep disturbances, palpitation, nau the imipramine group (eg, dryness of mouth accommodation disturbances, impaired vision, and sweating). Du phases of the study only those patients receiving brofaromine were followed for up to 52 weeks. The lower H continued to be maintained, with the exception of a slight increase between weeks 28 to 36, and the drug wa (Moller & Volz, 1992).

4.6.I Bromocriptine

4.6.I.1 Depression

a) No significant differences were observed in 33 outpatients with endogenous depression treated with eithe imipramine. Sixteen patients received bromocriptine 10 to 60 milligrams (mg)/day (mean, 34 mg/day) and sev received imipramine 75 to 250 mg/day (mean, 143 mg/day) for a period of 6 weeks. Based on the Hamilton ra total score of the bromocriptine-treated patients decreased from 19.9 to 7.8 and the imipramine-treated patie 20.1 to 6.1. Side effects associated with bromocriptine included nausea, dizziness and headache and those s imipramine included dryness of mouth, dizziness, and sweating. Although bromocriptine has an antidepressa on anxiety, agitation, and insomnia are less pronounced than that of imipramine (Waehrens & Gerlach, 1981)

b) Bromocriptine (15 milligrams (mg) daily) was as effective as imipramine (75 mg/day daily) in a 10-week, d in patients with endogenous depression. However, only 9 patients were evaluated and more studies are nece definite effects of the drug (Bouras & Bridges, 1982).

4.6.J Bupropion

4.6.J.1 Depression

a) A meta-analysis of published studies between 1980 and 1990 comparing imipramine and bupropion in the major depression indicates that both medications are equally effective (Workman & Short, 1993).

b) Bupropion and imipramine were equally efficacious in a double-blind, 5-week, multicenter trial in 63 elderl patients (Branconnier et al, 1983a). Patients were given either bupropion 150 milligrams/day (18 patients), bu 450 milligrams/day (18 patients), imipramine 150 milligrams/day or less (18 patients), or placebo (9 patients). treatment efficacy utilized depression and anxiety scales. All 3 drug treatment groups were more effective tha 7 to 35.

4.6.J.2 Adverse Effects

a) Bupropion may be safer than imipramine in treating depressed patients with congestive heart failure (Roo The cardiovascular effects of imipramine and bupropion were compared in 10 depressed patients with conge Neither drug had an effect on left ventricular ejection fraction or left ventricular function. Hypotension, severe discontinuation, was a problem in 50% of the imipramine patients but did not occur with bupropion.

4.6.K Buspirone

Depression

Panic disorder

4.6.K.1 Depression

a) Imipramine was more effective than placebo (p less than 0.01) while buspirone trended towards being mo placebo (p less than 0.1) for the treatment of major depression in elderly outpatients. The 8-week, randomize placebo-controlled study involved 177 patients aged 65 years and over. Beginning dosages were imipramine twice daily or buspirone 10 mg twice daily, increased to imipramine 25 mg three times daily and buspirone 10 daily after one week. If tolerated after the second week, imipramine was increased to 100 mg/day and buspir in divided doses. A daily maximum dose of 150 mg of imipramine and 60 mg of buspirone could be reached b response, with the mean optimal dose of 89 mg/day for imipramine and 38 mg/day for buspirone. Following 8 treatment, moderate to marked global improvement occurred in 61% of buspirone patients, 70% of imipramin 42% of placebo patients (Schweizer et al, 1998).

4.6.K.2 Panic disorder

a) A placebo-controlled, double-blind study of outpatients with panic disorder or agoraphobia with panic attac any significant differences in total biweekly numbers of panic attacks, decreases in number of attacks, and ev psychopathology and of global improvement over an eight-week period between patients treated with buspirc placebo. All groups improved. The inconclusive results may have been due to a number of factors, including sizes, the episodic nature of the illness, a possible therapeutic effect of the diagnosis for the subjects (many c diagnosed for the first time during the study), and the limited study duration (Pohl et al, 1989). Somewhat bet seen for both active treatments in a study using higher doses (Robinson et al, 1988).

4.6.L Butylscopolamine

4.6.L.1 Nocturnal enuresis

a) Imipramine was significantly superior to butylscopolamine, which was no better than placebo in 14 childre enuresis (Korczyn & Kish, 1979). Imipramine 10 or 20 milligrams was compared to butylscopolamine 10 or 2(investigators concluded that antimuscarinic activity is not sufficient to inhibit detrusor contraction and that ora is not absorbed to any significant extent.

4.6.M Chlordiazepoxide

4.6.M.1 Depression

a) Imipramine was more effective and better tolerated at assessments made at 4 weeks, 6 weeks, and 8 wee with primary depression who completed a double-blind comparison of imipramine, chlordiazepoxide, and plac 1986). At the end of 2 weeks of therapy the therapeutic advantages associated with imipramine therapy were apparent. By weeks 6 and 8, the imipramine- treated group had a marked superior therapeutic advantage in i symptoms of depression, anxiety, anger-hostility, interpersonal sensitivity, and global improvement. Chlordiaz an advantage in patients with sleep difficulties, but these patients did significantly worse on anger-hostility an sensitivity.

4.6.N Chlorprothixene

4.6.N.1 Depression

a) Imipramine 75 to 225 milligrams/day and chlorprothixene 45 to 135 milligrams/day had comparable efficac double-blind, randomized, crossover study involving 32 patients with depressive disorders. The investigators both drugs were equally efficacious and safe, although the side effect profiles varied (Lodge-Patch et al, 196

4.6.O Citalopram

4.6.O.1 Depression

a) Unpublished studies involving small numbers of patients suggest the comparable efficacy of imipramine a depression, although imipramine has tended to be more effective in improving sleep disturbances (Milne & G well-controlled comparisons of these agents are needed.

4.6.P Clomipramine

Depression

Obsessive-compulsive disorder

4.6.P.1 Depression

a) Clomipramine was as effective as imipramine in treating depression in 24 patients during a 44-day, rando blind study (McClure et al, 1973). The patients were diagnosed with psychotic depression independently by 2 imipramine or oral clomipramine was administered 3 times daily in 50 milligrams doses. Throughout the study assessments using the Hamilton Depression Rating Scale and the Beck Depression Inventory demonstrated reduction in depression from baseline for both drugs; however, a significant difference in antidepressant effec could not be seen. Minor and transient anticholinergic adverse effects were noted in all patients and included mouth, increased sweating, hand tremor, and dizziness. Three patients dropped out of the study, but none of adverse effects.

4.6.P.2 Obsessive-compulsive disorder

a) SUMMARY: Clomipramine is superior to imipramine in the treatment of obsessive-compulsive disorder.

b) Oral clomipramine was slightly superior to oral imipramine in improving symptoms of obsessive-compulsiv (Volavka et al, 1985). A 12-week, double-blind study of 23 patients according to DSM-III with secondary depr was conducted to compare the 2 drugs. Both drugs were started at 50 milligrams/day; this was gradually incr mg/day as tolerated. Seven patients did not complete the study: 4 because of adverse effects (2 from each g of unsatisfactory therapeutic response with imipramine, and 1 for no apparent reason. Both drugs produced i depressive symptoms; however, only clomipramine demonstrated improvement in obsessive symptoms wher baseline. Typical anticholinergic adverse effects were experienced by both treatment groups with no significa between the two. It is difficult to accurately evaluate the clinical response in this study because of the small n and the methods used for statistical analysis.

c) Both oral clomipramine and oral imipramine were effective in improving symptoms in obsessive-compulsiv who met DSM-III criteria (Mavissakalian et al, 1985). The study was a 12-week, double-blind trial that compar clomipramine and imipramine in treating obsessive-compulsive disorders. Both drugs were begun at 25 to 50 this was increased to 300 mg/day as tolerated. At the end of the trial, the mean daily dose of both drugs was clomipramine-treated patients and 2 of 5 imipramine-treated patients were classified as responders. For both improvement in depression was evident at 4 weeks, while maximal improvement in obsessive-compulsive sy seen until 8 weeks. The responders also had higher pretreatment depression scores than did nonresponders corresponded with the results of another study (Marks et al, 1980). Because of the small sample size, differe

efficacy between clomipramine and imipramine could not be determined.
d) The relationship between the antiobsessional and antidepressant effects of tricyclic drugs was studied in p
compulsive disorder. Study 1 consisted of a controlled 12-week trial with clomipramine (n=7) and placebo (n=
analyzed the pooled data from 15 uniformly selected patients who were treated with either clomipramine or in
Although the antiobsessional and antidepressant effects of the drugs covaried, antidepressant action was not
antiobsessional effects. Clomipramine, and probably imipramine, possess specific antiobsessive effects that
partially independent of the antidepressant effects (Mavissakalian et al, 1985).

4.6.Q Clonazepam

4.6.Q.1 Panic disorder
a) Preliminary results from an ongoing double blind study comparing imipramine and clonazepam in the treat
disorders in twelve patients have been reported (Svebak et al, 1990). Six patients received imipramine and si
clonazepam, and all were treated for a total of six months. Clonazepam treated patients required an average
(range 1 to 3 mg/day) to achieve relief of symptoms; imipramine patients required 62.5 mg/day) (range 25 to
During the final four months of the study no patients required more than 2 mg/day of clonazepam or 50 mg/da
Over the course of the first two weeks of treatment a substantial drop in the incidence of panic attacks occurr
Mean scores in global improvement were significantly improved in both groups, as were patients assessed sc
physician assessed scores. These early results demonstrate the efficacy of both imipramine and clonazepam
panic disorders.

4.6.R Delorazepam

4.6.R.1 Anxiety
a) Delorazepam 3 to 6 milligrams (mg) was compared to imipramine 50 to 100 mg/day and paroxetine 20 mg
weeks in 81 patients with generalized anxiety disorders according to DSM-IV criteria. Delorazepam produced
improvement in anxiety ratings during the first two weeks of treatment, but both paroxetine and imipramine w
by the fourth week of treatment. At study end, reduction of at least 50% in the Hamilton Rating Scale for Anxi
reported in 55% of the delorazepam patients, compared with 68% and 72% for paroxetine and imipramine, re
Delorazepam affects predominantly somatic symptoms, whereas paroxetine and imipramine affect psychic sy
al, 1997a).

4.6.S Desipramine

4.6.S.1 Depression
a) Desipramine has been evaluated in comparison with imipramine with most open or double-blind trials indi
drugs are equally effective with similar time of onset and side effects and that no significant differences or ad
apparent with either drug (Rose & Westhead, 1964; Waldron & Bates, 1965; Lafave et al, 1965; St Jean et al
& Maxwell, 1967; Rose & Westhead, 1967). However, other limited data indicates that imipramine may be su
being more active (Edwards, 1965; Heller et al, 1971) or, conversely, that desipramine has the advantage of
and earlier clinical response (Agin et al, 1965).

4.6.T Desmopressin

4.6.T.1 Nocturnal enuresis
a) Patients treated with oral imipramine followed by intranasal desmopressin therapy (n=28) experienced ad
compared to those who received desmopressin followed by imipramine (n=29) in an open label, cross-over st
with nocturnal enuresis (Vertucci et al, 1997). Following a 2 week observation period, patients were randomiz
either desmopressin 30 micrograms per day (mcg/day) (3 puffs per nostril) for 3 weeks followed by oral imipra
milligrams per kilogram (mg/kg) for 3 weeks followed by 2 more weeks of follow up, or imipramine therapy firs
desmopressin. Both patient groups experienced significant reductions in the number of wet nights in the first
compared to the first observation period (p value not specified). Irrespective of which agent was administered
desmopressin therapy significantly increased the number of dry nights per week compared to imipramine (p l
Overall, desmopressin was associated with 20% wet nights while imipramine was associated with 37% wet n
up, patient who received desmopressin last had fewer weekly wet nights than those who received imipramine
suggest the results of this study indicate desmopressin is long acting and is safe for long-term treatment of n
Both agents were well tolerated with few adverse events reported. One imipramine patient experienced pallo
and cold extremities. One desmopressin patient reported inflammation of nasal mucosal.

4.6.U Diazepam

4.6.U.1 Depression
a) An 8-week, double-blind, controlled study compared the efficacy of alprazolam (58 patients), diazepam (5
imipramine (63 patients), and placebo (61 patients) in 241 outpatients with a DSM-III diagnosis of major depr
was a washout period with all patients receiving placebo. Week 2 through 7, the patients received their assig
and during week 8 the dose of the medication was reduced by half for 3 days and discontinued for the remair
end of the study the mean daily doses were 143 mg imipramine, 3.1 mg alprazolam, 24 mg diazepam, and 6.
placebo. Attrition rates were significant, 23% by week 4 of treatment and 39% by week 6. By the completion

of the imipramine group had withdrawn, 23% of the alprazolam group, 44% of the diazepam group, and 40%
group. The main reason given for attrition was side effects with the active compounds and ineffectiveness wit
Alprazolam and imipramine were both significantly better than placebo in treating depression, but diazepam v
The clinical effects of imipramine and alprazolam were equivalent, and overall the frequency of side effects w
Imipramine produced less drowsiness and more anticholinergic effects than both alprazolam and diazepam (
1987).

4.6.V Dibenzepin

4.6.V.1 Depression

a) Dibenzepin and imipramine are both well tolerated and equally effective in the treatment of depression. In
comparative trial, depressed patients (n=22) were administered either dibenzepin (160 milligrams (mg) three
imipramine (50 mg three times daily) for 4 weeks. Both drugs were effective and no significant differences we
patients taking dibenzepin and those taking imipramine (Fielding, 1969).

4.6.W Diclofenac

Cancer pain

Depression

4.6.W.1 Cancer pain

a) In a 1-week study, diclofenac plus placebo was as effective as diclofenac plus imipramine or diclofenac pl
cancer pain. This double-blind study enrolled 180 patients who were randomly assigned to receive diclofenac
(mg) 4 times daily with placebo, diclofenac with imipramine 10 or 25 mg 3 times daily (determined by patient
greater than 65 years), or diclofenac with codeine 40 mg 4 times daily. Efficacy was assessed at baseline an
100 millimeter(mm) visual analogue scale (VAS) (0=no pain; 100=worst possible pain); patients with acceptal
continued treatment for the remainder of the study. Significant differences were NOT detected between the 3
Results of this study are limited by the short duration of treatment which may have been insufficient to detect
of imipramine, lack of dose titration for codeine, concomitant use of morphine in 30 patients, and inclusion of
different cancer pain etiologies. Additional studies which address the limitations of this study are needed (Mir

4.6.W.2 Depression

a) Diclofensine is a isoquinoline derivative, structurally similar to nomifensine, that is a potent inhibitor of 5-hy
dopamine, and norepinephrine reuptake (Capponi et al, 1985). In a double-blind comparison with imipramine
dose = 65 milligrams/day) and high dose (average dose = 97.6 milligrams/day) diclofensine therapy was sho
effective as imipramine therapy (average dose = 102.9 milligrams/day) during the 6-week study period. Durin
weeks of therapy diclofensine therapy was more effective, but by the completion of the 6-week study period t
difference between the treatment groups. Whether or not a difference in onset of action would have been obs
initial doses of imipramine were used is unknown. Diclofensine therapy was better tolerated than the imipram
even if higher doses of imipramine were used it would have resulted in an even higher incidence of side effec

4.6.X Dothiepin

4.6.X.1 Depression

a) Dothiepin and imipramine appear to be equally efficacious in the treatment of depression. In a double-blin
patients with existing depression received either dothiepin or imipramine. Therapy was initiated with 25 milligr
which was increased to a maximum of 250 milligrams/day based on clinical response. Although both dothiepi
groups showed similar improvement, dothiepin was associated with fewer adverse effects, including dry mou
(Eilenberg, 1980). Similar results were seen in another study (Sheth et al, 1979).

4.6.Y Doxepin

4.6.Y.1 Depression

a) Imipramine may be slightly more effective than doxepin in the treatment of depression. Ninety-nine patien
depression received imipramine 100 to 200 milligrams/day or doxepin 100 to 200 milligrams/day for 4 weeks
study. Imipramine was superior in 24 of 27 parameters. Imipramine was shown to be superior to doxepin in ir
symptoms of anxiety/depression; global evaluations showed improvement in 39 of 48 (81%) of imipramine pa
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 indicat
response to imipramine, whereas a higher response rate to doxepin was found in male patients (Finnerty & G

c) Amitriptyline was superior to imipramine and doxepin in relation to their effects on interpersonal learning ir
inpatients (Gillis, 1981). All subjects performed better, according to quantitative indices of learning tasks, thar
received antipsychotic or neuroleptic drugs but no antidepressants. Amitriptyline patients scored significantly
imipramine or doxepin patients.

d) No significant differences in overall efficacy of the 2 drugs was reported in one study (Kimura, 1972), but
mg daily was superior to imipramine 150 mg daily in neurotic depression, whereas imipramine appeared to b
doxepin in endogenous depression (Pinder et al, 1977a).
e) Similar antidepressant effects of doxepin and imipramine were reported; however, imipramine had a more
action. Doxepin appeared to have more sustained effects (Hasan & Akhtar, 1971).

4.6.Y.2 Efficacy

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

4.6.Z Electroconvulsive therapy

4.6.Z.1 Depression

a) A double-blind, randomized, controlled trial compared electroconvulsive therapy (ECT) with imipramine th
patients suffering from depression (Gangadhar et al, 1982). Group I received modified bilateral ECT using thi
250 mg, succinylcholine 20 to 30 mg, and atropine 0.65 mg during the procedure. ECT was administered eve
during the first 2 weeks for a total of 6 treatments and then once a week for the next 2 weeks. Following this
maintenance ECTs were administered in the next 8 weeks. During the course of this treatment the patients re
identical to the imipramine group. Group II received imipramine 75 milligrams/day during week one and 150 r
second through the eleventh week. The dose was reduced to 75 mg/day during the twelfth week. During the
each patient received a simulated course of ECT therapy at the same frequency as the ECT-treated group. T
patients completed the study period (5 patients in the ECT group and 3 patients in the imipramine group were
the study during the first 6 weeks). Both treatments produced equally significant improvement which was mai
6-month follow-up period. The rate of improvement was quicker in those patients receiving ECT therapy. ECT
fewer side effects than imipramine therapy. There was no lasting organic brain dysfunction associated with th
previously thought.

4.6.AA Encainide

4.6.AA.1 Cardiac dysrhythmia - Myocardial infarction with complication, Post

a) Encainide and flecainide were more effective in suppressing ventricular arrhythmias than moricizine, imipr
placebo during the dose titration phase of a 1-year, multicenter, randomized, double-blind, placebo-controllec
patients (Anon, 1988a). Patients were eligible for this study if they had an acute myocardial infarction within 6
entrance to the study, were less than 75 years of age and demonstrated either an average of 10 or more ven
complexes (VPCs) per hour, or 5 or more episodes of unsustained ventricular tachycardia during a 24-hour a
recording. The total daily doses of the study drugs were encainide 105 to 180 milligrams, flecainide 200 to 40
150 to 375 milligrams, and moricizine 600 to 900 mg. Efficacy was defined as 70% or more suppression in VI
more than 90% suppression of runs of VPC when compared with baseline. The efficacy rates were 83% for fl
encainide, 66% for moricizine, 52% for imipramine, and 37% for placebo during the dose titration phase of th
incidence of adverse effects was 49% for encainide, 55% for flecainide, 67% for imipramine, 64% for moricizi
placebo. Imipramine was the drug most associated with patient withdrawal due to adverse effects. This study
VPC suppression efficacy at the 1-year follow-up.

4.6.AB Flecainide

4.6.AB.1 Cardiac dysrhythmia - Myocardial infarction with complication, Post

a) Encainide and flecainide were more effective in suppressing ventricular arrhythmias than moricizine, imipr
placebo during the dose titration phase of a 1-year, multicenter, randomized, double-blind, placebo-controllec
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entrance to the study, were less than 75 years of age and demonstrated either an average of 10 or more ven
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incidence of adverse effects was 49% for encainide, 55% for flecainide, 67% for imipramine, 64% for moricizi
placebo. Imipramine was the drug most associated with patient withdrawal due to adverse effects. This study
VPC suppression efficacy at the 1-year follow-up.

4.6.AC Fluoxetine

4.6.AC.1 Depression

a) SUMMARY: Fluoxetine has been as effective as imipramine in the treatment of depression, while producii
incidence of side effects. Overall cost of therapy, clinical efficacy, and patient quality of life have been shown
after six months of treatment.
b) In a double-blind, randomized, parallel group study, fluoxetine was better tolerated although not more effe
imipramine in the treatment of major depression with atypical features. A total of 154 patients (age 18 to 65 y
DSM-IV criteria for major depression for at least 1 month and also met the Columbia criteria for atypical depre

randomized to receive fluoxetine, imipramine, or placebo for 10 weeks. Fluoxetine was administered as 20 m for 4 weeks, 40 mg daily for week 5, and 60 mg daily for the remaining weeks. Imipramine was administered the first week, increasing by 50 mg/day each week until a maximum of 300 mg daily was reached. Mean daily of the study were 51.4 mg/day for fluoxetine and 204.9 mg/day for imipramine. Fluoxetine and imipramine did one another based on the Clinical Global Impression (CGI) scale improvement scores following 10 weeks of t Fluoxetine and imipramine were significantly more effective than placebo in the intention-to-treat (p less than respectively) and completer groups (p less than 0.03 and 0.001, respectively). Imipramine-treated patients de significantly higher dropout rate than fluoxetine-treated patients (p=0.04). In the intention-to-treat group, depr measures including the 17-item and 28-item Hamilton Depression Rating Scale and Patient Global Improvem no differences between fluoxetine and imipramine and a consistent clinical benefit of both treatment groups c placebo. Adverse effects significantly more common for imipramine than for fluoxetine included dry mouth (8 respectively), somnolence (42% versus 24%, respectively), and dizziness (44% versus 25%, respectively); co pain occurred at a significantly higher incidence in fluoxetine- versus imipramine-treated patients (McGrath et

c) For the initial treatment of depression, imipramine and fluoxetine are equivalent in terms of overall treatme and quality of life. In a randomized, controlled trial, patients with newly diagnosed depression (n=536) were p fluoxetine or a tricyclic antidepressant (imipramine or desipramine) and assessed at 1, 3, and 6 months for bo antidepressant regimen as measured by the Hamilton Depression Rating Scale and the Hopkins Symptom C of life. Drug cost and total health care costs were also measured. Clinical efficacy and quality of life were sim two groups; however, patients treated with fluoxetine had fewer adverse effects, were less likely to require a medication, and had less outpatients visits. Although drug costs were higher, total treatment costs were sligh fluoxetine group; however, this difference was not statistically significant (Simon et al, 1996).

d) Controlled studies have demonstrated that oral fluoxetine in doses of 40 to 80 milligrams daily is as effect 150 to 250 milligrams daily in the treatment of major depression (Cohn & Wilcox, 1985; Stark & Hardison, 198 1987a). Fluoxetine was as effective as imipramine doses of 150 to 300 milligrams/day (Byerly et al, 1988). He report (Bremner, 1984), fluoxetine was reported superior to imipramine in several depression scales in a 5-we study involving 40 depressed outpatients. In all studies, the incidence of side effects (anticholinergic effects, drowsiness, dry mouth, cardiovascular effects) was less with fluoxetine as compared with imipramine; fluoxet associated with a greater incidence of anxiety or nervousness, insomnia, and excessive sweating. In another sweating (as well as nausea) was higher with fluoxetine than imipramine (Stark & Hardison, 1985). Of signific has occurred during fluoxetine therapy, as compared to generally no change in body weight or increases in w imipramine. The onset of antidepressant action of each drug has been similar, generally within one week.

e) Imipramine and fluoxetine had similar efficacy in multicenter, double-blind, placebo-controlled, outpatient s the treatment of major depressive disorder (Stark & Hardison, 1985). Five hundred forty patients were randor receive either fluoxetine 60 to 80 milligrams daily, imipramine 150 to 300 milligrams daily (the majority of pati Patients were treated for up to 6 weeks in double-blind fashion. Imipramine and fluoxetine were both superior measures (Hamilton Psychiatric Rating Scale for Depression total, Raskin Severity of Depression Scale, Clin Impressions Severity of Illness Scale, Global Improvement and secondary symptom measures). Fluoxetine a were similarly effective on all general measures of improvement. Anorexia and nausea occurred to a significa in fluoxetine-treated patients; constipation, dizziness, drowsiness, dry mouth, somatosensory disturbances, a sweating were reported more frequently with imipramine.

f) The efficacy and safety of fluoxetine and imipramine was compared in 40 depressed outpatients in a doub parallel trial (Bremner, 1984). Fluoxetine was given in doses increasing from 20 to 40 milligrams daily, then to daily, during the first week; imipramine doses were increased from 75 to 100 milligrams daily, then to 125 mil During the second and third weeks, the maintenance dose of each drug was determined, with fluoxetine bein up to 80 milligrams daily and imipramine up to 300 milligrams daily. During the fourth and fifth weeks of the st maintenance dose was achieved; the maintenance dose for most fluoxetine patients was 60 milligrams daily, milligrams daily for imipramine. Fluoxetine was reported superior to imipramine in the total Hamilton Psychiat Depression, as well as the HAM-D scales for anxiety/somatization, retardation and sleep disturbance. Fluoxe reported more beneficial than imipramine in the Raskin Severity of Depression Scale and Covi Anxiety Scale. HAM-D total score, and the Raskin and Covi scales, fluoxetine was statistically superior to imipramine only du of the study (week 5). The Clinical Global Impressions demonstrated the superiority of fluoxetine over imipran depression but not global improvement. Weight loss (average, 3.8 pounds) occurred with fluoxetine during tre increase in weight being seen with imipramine (average, 0.7 pounds). Heart rate increased significantly with i compared to slight decreases with fluoxetine. Blood pressure decreased with fluoxetine as compared with inc imipramine, and fluoxetine was associated with a lesser degree of gastrointestinal disturbances, dizziness, an mouth occurred in one of 20 fluoxetine patients and in 9 of 20 imipramine-treated patients, with nervousness fluoxetine-treated patients and in two imipramine-treated patients.

4.6.AD Fluvoxamine

4.6.AD.1 Depression

a) SUMMARY: Fluvoxamine and imipramine appear to be equally efficacious in the treatment of depression 1987; Guelfi et al, 1983; Guy et al, 1984; Itil et al, 1983); (March, 1990)(Lydiard et al, 1989).

b) Fluvoxamine demonstrated a trend toward superiority over imipramine in treating 63 patients with major d 4- to 6-week, randomized, placebo-controlled, double-blind study (Lapierre et al, 1987). All drugs were starte milligrams/day, and were gradually increased to a maximum of 300 mg/day. The mean daily dose of fluvoxam of the study was 207 mg, and 192 mg for imipramine. At the end of the study, the total Hamilton Rating Scale (HAM-D) score had decreased by 75%, 55%, and 6% in the fluvoxamine-, imipramine-, and placebo-treated g

respectively. At the end of the study there were 8, 3, and 1 responders from the fluvoxamine, imipramine, and
respectively. Only 1 patient in each active treatment group withdrew from the study because of adverse effec
c) Fluvoxamine was comparable to imipramine in antidepressant activity during a 4-week, double-blind, mult
151 patients (Guelfi et al, 1983). Drug therapy was administered in twice daily dosing in the range of 100 to 3
for fluvoxamine and 50 to 200 milligrams daily for imipramine. At the end of the study there was a mean impr
Hamilton Rating Scale for Depression (HAM-D) of 67.2% in the fluvoxamine-treated group and a 62.1% impr
imipramine-treated group. A similar improvement was detected with both drugs on the Clinical Global Impress
end of the study, the mean daily dose of fluvoxamine was 221 mg and 112 mg for imipramine. A total of 37 p
from the study prematurely; 19 on fluvoxamine and 18 on imipramine. The reasons for early withdrawal appe
between both drugs.
d) Fluvoxamine and imipramine were comparable in efficacy for the treatment of depression in 36 patients di
unipolar or bipolar depression during a 4- to 6-week, randomized, double-blind study (Guy et al, 1984). Both
administered at bedtime with a maximal dosage range between 150 to 225 milligrams/day. In the unipolar de
fluvoxamine-treated patients, 92% were judged "improved" at the end of the study compared to 81% of the im
However, the imipramine-treated group appeared to have a higher percent of patients rated as "much" or "ve
improved, 75% compared to 54% of the fluvoxamine group.
e) A double-blind comparative study of fluvoxamine and imipramine was carried out in 20 outpatients with de
Patients received randomly-assigned medication over a 4-week period in a dosage range of 50 of 300 mg giv
doses. There was a significant symptom severity reduction in both groups at the end of 4 weeks, and fluvoxa
effective than imipramine in reducing suicidal ideas and anxiety/somatic symptoms. Anticholinergic-type adve
predominated for imipramine and gastrointestinal effects for fluvoxamine (Gonella et al, 1990).
f) In a 6-week, double-blind, placebo-controlled, variable-dose study assessing the comparative antidepressa
fluvoxamine (FLU), imipramine (IMI), and placebo (PBO), 45 patients with major depressive disorder were ev
response and side effects. Dosage ranged between 100 to 300 milligrams/day for active medications. No stat
differences between either the FLU (N=17) and PBO or the FLU and IMI groups were found. Side effects wer
three groups: IMI(N=18): constipation (83%), dry mouth (55%), and sweating, dizziness, and nausea, all 39%
diarrhea, headache, dry mouth, all 41%, nausea (35%), and flatus (29%). PBO(N=18): pruritus (29%, nausea
(18%), asthenia and somnolence, both 12%. This study revealed a high placebo response, with a 50% impro
Thus, it is difficult to show differences from active medication unless the study is carried out for a longer time.
numbers of patients are too small to detect a true difference. Second, patients seemed to either respond or n
while the response to IMI appeared to be more graded. This may reflect a subgroup of depressed patients th
serotonin-deficient type of depression (Lydiard et al, 1989).
g) Other double-blind, placebo-controlled studies comparing imipramine and fluvoxamine have only demons
improvement in depression with either drug when compared with placebo (Dominguez et al, 1985; Norton et

4.6.AD.2 Adverse Effects

a) SUMMARY: Fluvoxamine produces less cardiovascular and anticholinergic adverse effects than imipramin
nausea and vomiting are more common with fluvoxamine therapy (Benfield & Ward, 1986; Roos, 1983; Salet
et al, 1993).
b) Adverse effects data was pooled from the results of 10 double-blind, placebo-controlled trials comparing f
(n=222) with imipramine (n=221) (Benfield & Ward, 1986). Anticholinergic effects such as dry mouth, dizzines
sweating, and abnormal accommodation were much more prevalent in patients receiving imipramine. Nausea
only adverse effect to be much more prevalent in the fluvoxamine-treated patients.
c) The cardiac effects of tricyclic antidepressants were compared with fluvoxamine. The major cardiac adver
observed with tricyclic antidepressants include postural hypotension, heart rate increase, and slight prolongat
intraventricular conduction time and QT interval. The only cardiac effect observed with fluvoxamine was a sta
clinically, significant slowing of heart rate (Roos, 1983).
d) Fluvoxamine produced less psychomotor impairment than imipramine. Fluvoxamine was superior to imipr
milligrams in regards to concentration, reaction time, mood, psychomotor activity, and affectivity. Following th
fluvoxamine 75 milligrams to 10 healthy volunteers, psychometric tests demonstrated a tendency towards an
psychomotor activity, concentration, attention, after-effect, and mood and a significant increase in critical flick
frequency when compared to placebo (Saletu et al, 1980).

4.6.AE Gepirone

4.6.AE.1 Depression

a) Gepirone extended-release 10 to 60 mg daily was only marginally superior to placebo at some time points
and tended to be less effective than imipramine 50 to 300 mg daily in one double-blind study involving patien
depression (Feiger, 1996).

4.6.AF Haloperidol

4.6.AF.1 Schizophrenia

a) Haloperidol was compared with placebo, chlorpromazine, diazepam, and imipramine as prophylactic ager
relapse of schizophrenic patients. At the end of the three-year trial, haloperidol and chlorpromazine significan
remission as compared to the other three treatments. Daily doses of haloperidol were 3 milligrams; chlorprom
75 mg (Nishikawa et al, 1982).

4.6.AG Lithium

4.6.AG.1 Depression

a) Lithium was more effective in the treatment of unipolar and bipolar depression in 63 female in-patients in a controlled study. The patients received either lithium in doses producing serum levels of 0.8 to 1.2 mmole/L o milligrams/day in divided doses. Improvement occurred more quickly with imipramine (between days 1 and 8) (days 8 to 22); however, all patients treated with lithium improved, but not all imipramine-treated patients did 1979).

4.6.AH Lofepramine

4.6.AH.1 Depression

a) A meta-analysis of 7 studies comparing lofepramine (n=372) with imipramine (n=372) concluded that lofep comparable with imipramine in efficacy and superior in tolerance (Kerihuel & Dreyfus, 1991). Overall, there w difference between the number of lofepramine-treated patients (64%) and imipramine-treated patients (58%) during the trials that ranged from 4 to 8 weeks. Significantly fewer patients reported side effects with lofepram imipramine (55% vs 68%; p less than 0.0001). Lofepramine doses ranged from 25 to 225 milligrams/d, and in ranged from 25 to 150 milligrams/d.

b) Lofepramine is a tricyclic antidepressant that is structurally similar to imipramine, but has an improved lipo et al, 1982).

c) Lofepramine and imipramine had similar efficacy in a randomized, double-blind, placebo-controlled clinica al, 1982). Of the 139 patients initially enrolled in the study, 89 completed the full 6 weeks of treatment (34 lofe imipramine, and 21 placebo). Dropout rates for the lofepramine and imipramine group were similar when com treatment failures and side effects. There was a significantly high placebo dropout rate, with the majority of pa out due to a lack of clinical efficacy. Lofepramine and imipramine were both significantly better than placebo i primary depression. There was no significant difference between the imipramine and lofepramine group with Lofepramine therapy was associated with significantly lower incidence of severe and/or moderate side effects with 66.7% observed in the imipramine group), and a lower incidence of side effects in general.

d) Lofepramine and imipramine were compared in a double-blind placebo-controlled study involving 158 dep outpatients. Both drugs were equally efficacious and superior to placebo therapy. Lofepramine therapy produ incidence of sedation and anticholinergic effects than imipramine therapy (Rickels et al, 1982).

4.6.AI Maprotiline

4.6.AI.1 Depression

a) SUMMARY: Maprotiline is considered very similar to imipramine in therapeutic efficacy (VanderVelde, 198 1977; Lehmann et al, 1976; Singh et al, 1976; Levine, 1975; Middleton, 1975; Rieger et al, 1975; Balestrieri e Maprotiline therapy may be associated with a quicker onset of action (VanderVelde, 1981); (Clayhorn, 1977).

b) Maprotiline 50 milligrams orally 3 times/day was administered to a maximum of 300 mg/day or imipramine milligrams orally per day to 341 patients with manic depressive illness. Patients ranged in age from 19 to 64 y treatment for 4 weeks. Improvement was based on Hamilton's and Self-Rating scales. Sixty-seven percent of receiving maprotiline were reported as improved compared with 66% of the patients who received imipramine system effects, dry mouth, tremor, blurred vision, and gastrointestinal effects were reported but were significa maprotiline-treated group (Logue et al, 1979).

c) Maprotiline was superior to imipramine in a double-blind, randomized controlled trial of 25 inpatients with p disorder (Rieger et al, 1975). The dose of maprotiline and imipramine was 50 milligrams three times a day for by a flexible dosing schedule for three weeks. Results of the 16 patients completing the trial showed the Ham Scores for the maprotiline group to be significantly better (p less than 0.05) than those for the imipramine gro the trial. The Zung Depression Scale favored maprotiline (p less than 0.01) on day seven and at the end of th than 0.10). Overall rating of global impression (p less than 0.05) and global improvement at endpoint (p less t indicated maprotiline to be superior to imipramine. Dropouts from the study included five maprotiline patients, hospital against medical advice, one improving so as to warrant discontinuation of therapy, and one due to in response. Two patients from the imipramine group dropped out due to toxicity, one due to deterioration after treatment, and one because of physician intervention. Side effects were prevalent on day three but decrease day 14. Common complaints in both groups were dry mouth, blurred vision, drowsiness, and nasal congestio reported only in the imipramine group.

4.6.AJ Melitracen

4.6.AJ.1 Depression

a) Four-week, double-blind trial; 29 patients with chronic schizophrenic or neurotic depression; melitracen 75 (mg)/day vs imipramine 50 to 150 mg/day. Brief Psychiatric Rating Scale, Hamilton Psychiatric Rating Scale Impression: some improvement in both treatment groups, efficacy of imipramine superior to melitracen (not s significant). Melitracen better tolerated than imipramine: 46 adverse effects (drowsiness, dry mouth, increase tinnitus, agitation) for melitracen vs 69 for imipramine. Quicker average onset of therapeutic effect for melitra 2.2 weeks (Biros et al, 1969).

4.6.AK Methscopolamine

4.6.AK.1 Nocturnal enuresis

a) Methscopolamine is ineffective in the treatment of enuresis. In a study with 40 severely enuretic boys, me bromide was used to determine whether some subgroups of enuretic children might respond to the periphera muscarinic receptors. The effects of treatment with imipramine, desipramine, methscopolamine bromide, and compared; the tricyclic antidepressants were superior to methscopolamine and placebo (Rapoport et al, 198

4.6.AL Mianserin

Depression

Nocturnal enuresis

4.6.AL.1 Depression

a) Studies to date suggest that there is no significant difference in overall efficacy between imipramine and n treatment of depression in both inpatients and outpatients (Pichot et al, 1978; Murphy et al, 1976; Murphy, 19 several deficiencies are apparent in clinical trials to date, and 1 study has indicated that improvements seen imipramine were equivalent to those observed with placebo (Perry et al, 1978). (However, these patients wer weeks, which may have been insufficient time for therapeutic effects from either drug to occur).

b) Mianserin therapy (20 to 60 milligrams/day) in elderly depressed patients (n=50, age 60 to 80 years) is as imipramine therapy (75 to 150 milligrams/day) (Eklund et al, 1985). The incidence of dry mouth, dizziness, fai weakness was greater in the imipramine group than in the mianserin group, however the total number of side by each group was not significantly different. From these results the authors concluded that mianserin may b imipramine in the treatment of depression in elderly patients because of its lower incidence of side effects. H number of mianserin treated patients withdrew from the study due to confusion, worsening of the condition, o Considering this, it is to early to conclude that mianserin is superior to imipramine in the treatment of depress

4.6.AL.2 Nocturnal enuresis

a) Imipramine was superior to mianserin and placebo in achieving dry nights and reducing wetness scores (mianserin was not superior to placebo. This was a multicenter, randomized, double-blind study involving 80 c al, 1996).

4.6.AM Milnacipran

4.6.AM.1 Depression

a) SUMMARY: Milnacipran offers no efficacy advantage over tricyclic antidepressants

b) Milnacipran 50 to 100 mg twice daily has been comparable to or less effective than imipramine 100 to 150 amitriptyline 150 mg daily, and clomipramine 75 to 150 mg daily in the treatment of major depressive disorde endpoints were improvements on the Hamilton and Montgomery-Asberg scales (Tignol et al, 1998; Leinonen Kasper et al, 1996; Anon, 1997a; Von Frenckell et al, 1990; Ansseau et al, 1989). A more rapid onset of actio observed with clomipramine and amitriptyline (Leinonen et al, 1997; Ansseau et al, 1989).

c) Greater improvement of CGI-3 scores (therapeutic index, incorporating efficacy and tolerance) was report milnacipran in a manufacturer-prepared meta analysis of tricyclic antidepressant comparative trials (Anon, 19 1996), and this appears in manufacturer product information. However, statistical significance between treatm demonstrated (Anon, 1997a).

4.6.AN Moclobemide

4.6.AN.1 Depression

a) SUMMARY: Moclobemide and imipramine have been similarly effective in the treatment of depression; ac generally been greater with imipramine.

b) Moclobemide 300 to 600 milligrams orally daily has been as effective as imipramine 100 to 200 milligrams treatment of endogenous and non-endogenous depression in controlled clinical trials (Baumhackl et al, 1989; 1990; Versiani et al, 1989a; Versiani et al, 1989; Versiani et al, 1990a; Stabl et al, 1989; Lecrubier & Guelfi, 1 1990). However, a trend (not statistically significant) toward the superiority of imipramine over moclobemide i or neurotic depression has been observed by some investigators (Biziere & Berger, 1990; Versiani et al, 198 rapid response was reported with moclobemide in 1 study (Udabe et al, 1990).

c) In 1 study, the response rate to imipramine and moclobemide was similar in both males and females. How tended to be less effective in depressed patients over 60 years of age as compared with patients under 60 (E 1990).

d) Moclobemide and imipramine were equally efficacious in a placebo-controlled, 6-week study (Versiani et a the largest trials to date (n=490) involving patients with a major depressive episode (50% with endogenous d reduction in the average Hamilton Rating Scale for Depression (HRSD) was observed with moclobemide 300 daily, as compared with 28% with placebo, during 6 weeks of treatment. Imipramine (100 to 200 milligrams da for comparison in this study, and was as effective as moclobemide, producing a 56% reduction in HRSD scor final assessments of efficacy by the investigators, good to very good responses were reported in 70% of patie

moclobemide, 70% treated with imipramine, and 28% treated with placebo. When subgroups of patients with non-endogenous depression were analyzed, both drugs were similarly effective and superior to placebo in ea Overall tolerability assessments favored moclobemide over imipramine (Versiani et al, 1989).

4.6.AN.2 Adverse Effects

a) Adverse effects have generally been less with moclobemide compared to imipramine, particularly dry mou tremor, sweating, and blurred vision (Stabl et al, 1989).

4.6.AO Moricizine

4.6.AO.1 Cardiac dysrhythmia - Myocardial infarction with complication, Post

a) Encainide and flecainide were more effective in suppressing ventricular arrhythmias than moricizine, imipr placebo during the dose titration phase of a 1-year, multicenter, randomized, double-blind and placebo-contro patients (Anon, 1988b). Patients were eligible for this study if they had an acute myocardial infarction within 6 entrance to the study, were less than 75 years of age and demonstrated either an average of 10 or more ven complexes (VPCs) per hour or 5 or more episodes of unsustained ventricular tachycardia (3 to 9 consecutive of 100/minute or more) during a 24-hour ambulatory ECG recording. The total daily doses of the study drugs to 180 milligrams for encainide, from 200 to 400 milligrams for flecainide, from 150 to 375 milligrams for imipr 600 to 900 milligrams for moricizine. Efficacy was defined as 70% or more suppression in VPC frequency and suppression of runs of VCP when compared to baseline. The efficacy rates were 83% for flecainide, 79% for moricizine, 52% for imipramine, and 37% for placebo during the dose titration phase of the study. The incider effects was 49% for encainide, 55% for flecainide, 67% for imipramine, 64% for moricizine, and 60% for place was the drug most associated with patient withdrawal due to adverse effects. This study did not address VPC efficacy at the 1-year follow-up.

4.6.AP Nefazodone

4.6.AP.1 Depression

a) Nefazodone was comparable overall to imipramine in a 6-week double-blind, placebo-controlled study inv with major depression. Average doses at the end of 6 weeks were 180 and 158 milligrams daily, respectively drugs were not always significantly superior to placebo in improving Hamilton Rating Scale for Depression (H imipramine tended to be superior to nefazodone on the visit-wise (observed case) analysis of HAM-D; in this imipramine was statistically superior to placebo at weeks 4 through 6 of treatment, whereas nefazodone was effective only at week 5. Neither agent proved statistically more effective than placebo on the Clinical Global (clinician's rating). Although adverse effects tended to be less with nefazodone, specific effects induced by ei not presented. This study did not provide a direct statistical comparison of imipramine and nefazodone (Feigh

b) Meta-analysis of 6 placebo-controlled, double blind studies showed that nefazodone and imipramine were treating major depression and the accompanying symptoms of anxiety, and nefazodone was superior to imipr treatment of agitation (Fawcett et al, 1995). Nefazodone (100 to 600 milligrams/day; mean endpoint dose=39 n=184), imipramine (25 to 300 milligrams/day; mean endpoint dose=178 milligrams; n=288), and placebo (n= compared in four 6-week and two 8-week studies. Both agents were significantly better than placebo in treati Anxiety symptoms were significantly improved by both agents compared with placebo; nefazodone resulted i both psychic anxiety and somatic anxiety as measured by the HAM-D scale, whereas imipramine had no effe anxiety. Nefazodone was significantly better than placebo in relieving agitation at weeks 1 and 3 through end showed a significant difference from placebo only at endpoint.

c) In a randomized, double-blind, placebo-controlled trial, nefazodone and imipramine were compared in 180 depression (Fontaine et al, 1994). Nefazodone was comparable in antidepressant efficacy to imipramine; sign improvement was evident in self-report anxiety symptoms as early as week 1 for nefazodone patients in eithe therapeutic dose range of nefazodone was found to be 100 to 500 milligrams/day, with most patients ultimate 500 milligrams/day. In this trial, nefazodone-treated patients experienced significantly fewer adverse events t The dose of imipramine ranged from 50 to 250 milligrams/day with the average dose being 214.4 milligrams/

4.6.AP.2 Adverse Effects

a) With acute phase- or long-term use of therapeutic doses of nefazodone or imipramine for depression, sign imipramine-treated patients than nefazodone-treated patients experienced clinically significant weight gain (g body weight). A retrospective analysis of pooled data from 3 studies comparing nefazodone (n=225) and imip showed that, at some time during the long-term phase of treatment, 9.5% of those taking nefazodone and 24 imipramine had clinically significant weight gain. At study endpoint, 2.9% and 19.7%, respectively (p=0.001) s gain. Percentages of patients with weight gain during acute-phase treatment were 0.9% for nefazodone and 4 imipramine (p=0.02) (Sussman et al, 2001).

4.6.AQ Nomifensine

4.6.AQ.1 Depression

a) SUMMARY: Nomifensine and imipramine appear similarly effective in the treatment of depression in inpat outpatients, including the elderly; comparative doses for each have been 75 to 150 milligrams/day. In genera nomifensine is less than imipramine (Merideth et al, 1984; Bremner et al, 1984; Cohn et al, 1984; Amin et al, 1978b; Forrest et al, 1977).

b) Nomifensine was as effective as imipramine in 20 patients with endogenous over-reactive depression (Am Patients received 147.9 milligrams (mean) nomifensine daily or 158.3 milligrams (mean) imipramine daily in a

controlled, double-blind study. The incidence of anticholinergic side effects was lower with nomifensine than i
Nomifensine and imipramine, each in doses of 75 to 150 mg/day for 6 weeks, were equally effective in the tre
depressed patients. Autonomic side effects with nomifensine occurred less frequently than with imipramine (A
c) Nomifensine was equally efficacious as imipramine in 28 patients who received a daily dose of 150 to 200
period of 20 to 30 days. Side effects associated with nomifensine were lower than those associated with imip
al, 1974).
d) Based on the Hamilton rating scale and the Beck depression inventory, nomifensine and imipramine were
efficacious in the treatment of 30 outpatients with depression. Side effects of nomifensine and imipramine we
(Forrest et al, 1977).
e) Nomifensine in average doses of 150 milligrams orally daily was reported similarly effective as imipramine
the treatment of depression in outpatients in a 4-week controlled study (Bremner et al, 1984). However, toxici
mouth and sedation) was more frequent in imipramine patients.

4.6.AR Nortriptyline

4.6.AR.1 Depression

a) Most studies have indicated that there are no significant differences between nortriptyline and other antide
the tricyclic category such as amitriptyline (Rose et al, 1965; Leahy & Martin, 1967; Mendels, 1968; Martin &
Malitz & Kanzler, 1971), desipramine (Levy, 1966; Arieff, 1966; Stewart & Mitchell, 1968; Haider, 1968), protr
1966), and imipramine (Kessell & Holt, 1970).

4.6.AR.2 Efficacy

a) The effects of imipramine and nortriptyline on left ventricular function and blood pressure were studied du
ranging study of 20 patients with ventricular arrhythmias. Ten consecutive patients with more than 30 ventricu
depolarizations (VPDs) were treated with imipramine starting at 1 milligram/kilogram/day, increased by 1 mg/
second day, to a maximum dose of 5 mg/kg/day. Nortriptyline was administered to 10 similar patients beginni
milligram/kilogram/day, increased by 0.5 mg/kg/day every third day to a maximum of 3.5 mg/kg/day. The 2 gr
in terms of age, sex distribution, etiology of heart disease and NYHA functional class. At a mean effective dos
imipramine suppressed VPDs by 74%; VPDs were suppressed 85% by a maximally effective nortriptyline dos
Ejection fraction was slightly decreased with imipramine (from 33% to 31%) and with nortriptyline (from 43 to
decreases in orthostatic systolic pressure were greater following imipramine (26 mmHg) than after nortriptylin
significant change in supine systolic or diastolic blood pressure was noted after either drug. No significant rel
change in standing systolic blood pressure and daily dose, plasma drug concentration, or NYHA functional cl
demonstrated with either drug. Changes in standing systolic pressure were related to patient age with patient
old experiencing greater reductions in systolic pressure following administration of both drugs. To determine i
exist between imipramine and nortriptyline in terms of antiarrhythmic efficacy, studies in cardiac patients who
crossed-over, and randomized to double-blind treatment are needed (Giardina et al, 1985).

4.6.AS Paroxetine

Anxiety

Bipolar disorder, depressed phase

Depression

4.6.AS.1 Anxiety

a) In an uncontrolled trial, paroxetine and imipramine were as effective as 2- chlordesmethyldiazepam, a ben
treating generalized anxiety disorder (Rocca et al, 1997). Patients (n=81) received paroxetine 20 milligrams(r
imipramine 50 to 100 mg/day, or 2-chlordesmethyldiazepam 3 to 6 mg/day for 8 weeks. Over the first 2 week
with 2-chlordesmethyldiazepam showed greater improvement; however, after 4 weeks for paroxetine and 8 w
imipramine, the anti-depressants were more effective. Adverse effects consisted primarily of anticholinergic e
imipramine, nausea for paroxetine, and drowsiness for 2-chlordesmethyldiazepam. Larger, blinded, controlle
needed to confirm the results of this study.

4.6.AS.2 Bipolar disorder, depressed phase

a) Neither paroxetine nor imipramine was more effective than placebo in treating BIPOLAR DEPRESSION ir
stabilized on lithium if their serum lithium levels were above 0.8 milliequivalents per liter (meq/L). However, pa
serum lithium concentration was less than 0.8 meq/L showed greater improvement with 8 weeks of antidepre
than with placebo treatment (p=0.05 for paroxetine, p=0.04 for imipramine). In a double-blind study, patients
according to serum lithium concentration and then randomized to receive paroxetine (n=35), imipramine (n=3
(n=43) for 10 weeks. Among all completers of the study, therapeutic response (Hamilton depression scale sc
was achieved by 56%, 48%, and 54% of patients receiving paroxetine, imipramine, and placebo, respectively
accounted for study discontinuation in 1 patient in the paroxetine group (3%), 12 in the imipramine group (30
placebo group (12%). No patient in the paroxetine group experienced induction to mania, whereas 3 patients
imipramine and 1 treated with placebo developed treatment-emergent mania (Nemeroff et al, 2001).

4.6.AS.3 Depression

a) SUMMARY: Paroxetine, a selective serotonin reuptake inhibitor, and imipramine appear to be similarly eff treatment of major depression. The decision as to which drug to use should be based on patient-related char anxiety disorders, sleep disturbances, cardiovascular disease), potential drug interactions, and side effects.

b) Paroxetine, imipramine, and placebo were compared in 120 outpatients with moderate-to-severe major de (Feighner & Boyer, 1989). Following a 4- to 14-day single-blind, placebo washout period, patients were assig either paroxetine, imipramine, or placebo for 6 weeks. The dose of paroxetine and imipramine could be incre maximum of 50 milligrams and 275 milligrams daily, respectively. Paroxetine was superior to placebo in 5 of evaluated (HAMD scale, Raskin depression scale, MADRS, CGI scale, Covi anxiety scale); no improvement compared to placebo in the 56-item Symptom Checklist (SCL-56). Imipramine was also statistically superior t HAMD, Raskin, MADRS, and the CGI scale, but not on the Covi anxiety scale or the SCL-56. The only outco improved to a significantly greater degree with paroxetine was the HAMD total score. A high number of patie therapy (approximately 50%), which limits evaluation of efficacy. If only the patients completing the study are imipramine and paroxetine appear to be equally effective. Based upon the number of dropouts due to advers paroxetine appeared to be better tolerated than imipramine: 10% versus 30%. The most common adverse ef paroxetine were sedation and gastrointestinal effects, whereas anticholinergic adverse effects (dry mouth, co symptoms) were the most common with imipramine. However, a detailed incidence of all adverse effects was making it difficult to fully compare these agents.

c) Paroxetine was more effective than placebo in the short-term (6-week) treatment of depression; however, less effective than imipramine. The study was double-blinded and 122 patients with a major depressive disor randomized to receive either paroxetine (dose range 20 to 50 milligrams/day), imipramine (dose range 65 to milligrams/day) or placebo. At the end of the study, the imipramine-treated patients demonstrated consistentl both objective and subjective, on all depression rating scales when compared to paroxetine. Overall there wa rate to imipramine, a 48% response rate to paroxetine, and a 33% response rate to placebo (Peselow et al, 1

d) A multicenter, double-blind, placebo-controlled evaluation of paroxetine and imipramine in the outpatient t depression was conducted (Dunbar et al, 1991). After a 4- to 14-day placebo run-in period, patients were ran treatment groups; 240 to the paroxetine group, 237 to the imipramine group, and 240 to the placebo group. T started at 20 milligrams paroxetine and 80 milligrams imipramine. Dosage adjustment, if necessary, was don intervals over the six-week treatment phase. Drop-out rates were high for all groups; paroxetine 42.5%, imipr placebo 53.6%. Lack of efficacy (10%, 7%, and 33%, respectively) and side effects (23%, 36%, and 9%, resp most common reasons stated for dropping out of the study. Imipramine and paroxetine were equally superior produced similar efficacy results. However, paroxetine therapy was associated with less sedation, cardiovasc anticholinergic side effects.

e) Newer clinical trials have continued to support the previous findings that imipramine and paroxetine are si effectiveness. The major differences between the two compounds are the frequency of side effects, types of frequency of patients withdrawing from the clinical trials secondary to side effects from the study medications paroxetine therapy is better tolerated and associated with lower withdrawal rates (Ohrberg et al, 1992; Feighn (Arminen et al, 1994).

f) A 6-week, double-blind study was continued for 1 year by crossing over all patients who had failed to resp treatment to the other drug (Peselow et al, 1989a). Patients first treated with placebo were crossed over to pa total of 15 patients initially treated with paroxetine switched to imipramine, while 10 imipramine patients were paroxetine. Of the patients who initially failed on paroxetine, 73% responded to imipramine, while 50% of the initially failed on imipramine responded to paroxetine. Similar studies have shown paroxetine to be at least as imipramine with fewer side effects (Fabre, 1992; Cohn & Wilcox, 1992; Shrivastava et al, 1992; Feighner & B

4.6.AT Phenelzine

Depression

Posttraumatic stress disorder

4.6.AT.1 Depression

a) SUMMARY: Phenelzine and imipramine have been found to be equally effective in treating depression an imipramine was more effective in the treatment of hostility and paranoia, whereas phenelzine was more effec panic attacks (Davidson et al, 1981; Davidson et al, 1987; Isberg, 1981). Phenelzine therapy is superior to im treatment of atypical depression (Liebowitz et al, 1984; Stewart et al, 1989; Quitkin et al, 1988; Quitkin et al, 1990; Quitkin et al, 1993; McGrath et al, 1991). In one case report, phenelzine treatment was found to relieve obsessive-compulsive disorder (OCD) when treatment with amitriptyline and imipramine had failed.

b) Imipramine (median, 150 milligrams daily) had comparable efficacy with phenelzine (median, 75 milligram treatment of major depression in a 5-week, controlled, outpatient study. However, phenelzine was reported s imipramine in patients also presenting with panic attacks (Davidson et al, 1987).

c) Phenelzine, imipramine, and placebo were compared in a double-blind study in 74 patients with probable depression (Quitkin et al, 1988). Sixty patients completed the study. Dropout was similar among treatment gr weeks, 28% of the placebo-treated group, 50% of imipramine group, and 71% of the phenelzine group were

responders. Patients with reactive mood and only one associated symptom appeared to get more benefit with
During the next 6 weeks of the study, 41% of the placebo patients, 21% of the imipramine patients, and 7% o
patients experienced a relapse, despite continued drug therapy. Patients with definite atypical depression and
attacks responded well to drug therapy; after 6 weeks, response was observed in 60% of the placebo patient
imipramine patients, and 64% of the phenelzine patients. Patients with definite atypical depression without a
attacks did not respond as well; after 6 weeks, response was observed in 7% of the placebo group, 44% in th
group, and 83% in the phenelzine group.

d) A comparison of the results of one study were contrasted with previously published data from 180 patients
depression (Quitkin et al, 1988; Quitkin et al, 1989). Both imipramine and phenelzine were equally effective in
simple mood reactive depressive patients. Patients with atypical depression tended to respond better to phen
imipramine and 66% that had failed imipramine therapy responded with phenelzine therapy.

e) Replication of a previous study (Quitkin et al, 1988) substantiated the previous finding that phenelzine is s
imipramine and placebo in the treatment of atypical depression (Quitkin et al, 1990). This study used the sam
minor changes in dose schedule as in the 1988 study and included 90 patients with atypical depression which
included in the previous study population. Comparison of both groups found no significant difference between
population.

f) A six-week comparison of imipramine, phenelzine, and placebo was conducted in 194 nonmelancholic dep
with features of atypical depression (Stewart et al, 1989). The overall response rates was 71% with phenelzin
73 milligrams/day), 48% with imipramine (mean dose was 265 milligrams/day), and 26% with placebo (mean
tablets/day). Patients with dysrhythmic disorder tended to respond better than those with major depression. A
relationship was found in the placebo group between response and chronicity of the disorder.

g) Double-blind trials demonstrated that some patients may require chronic treatment with antidepressants to
remission from atypical depression. Patients who improved after 6 months of imipramine therapy were rando
either placebo or their same imipramine dose for a further 6 months in a double-bind fashion. A similar double
done in patients who had been maintained successfully on phenelzine. In the imipramine trial (n=32), the recu
continued imipramine (41%) and placebo (47%) was not significantly different. However, in the phenelzine tri
recurrence rate of 87% in the placebo treated patients was significantly higher (p=0.001) than those continue
(23%). Comparison of the results between imipramine and phenelzine is limited by the absence of blinding be
and baseline differences, with earlier onset and longer history of depressive illness in the phenelzine group p
to the high recurrence in those switched from phenelzine to placebo (Stewart et al, 1997).

4.6.AT.2 Posttraumatic stress disorder

a) A double-blind, placebo-controlled study of 60 male veterans found phenelzine to be better than imipramin
of combat-induced post-traumatic stress disorder (Kosten et al, 1991). Patients were treated with an average
milligrams imipramine and 68 milligrams phenelzine for 8 weeks. Dropout rates were high in all three groups
placebo, 60.9% with imipramine, and 21.1% with placebo, 60.9% with imipramine, and 21.1% with phenelzine
common reason being failure to return for clinic visits (50%, 50%, and 25%, respectively). At the end of 8 wee
and phenelzine produced greater improvement than placebo and phenelzine was demonstrated more effectiv
in improving Impact of Event Scale scores and post-traumatic stress disorder symptoms.

4.6.AU Reboxetine

4.6.AU.1 Depression

a) Reboxetine exhibited similar efficacy to, better tolerability than, and earlier onset of effect than imipramine
of major depression in a short-term study (6 weeks) (Berzewski et al, 1997). Patients (n=256) were randomiz
with reboxetine 4 milligrams (mg) twice daily or imipramine 50 mg twice daily with the evening dose increased
weeks of treatment. According to scores on the Hamilton Depression rating scale (HAM-D), response rates fo
with reboxetine or imipramine were 68.5% and 56.2% (statistically significant difference) respectively, and re
last assessment were 52% and 45.5%, respectively. On the Clinical Global Impression Severity of Illness and
Improvement scales (CGI-SI and CGI-GI), the percentage of reboxetine-treated patients classified as "norma
increased more rapidly than the group treated with imipramine, indicating an earlier onset of response. The M
Asberg Depression Rating Scale (MADRS) demonstrated no difference between the two treatment groups. In
adverse events described as probably or definitely related to treatment were 31.9% and 39% for patients trea
reboxetine or imipramine, respectively.

4.6.AV Ritanserin

4.6.AV.1 Depression

a) Ritanserin, a serotonin-2 antagonist, was compared with imipramine in a double-blind, placebo-controlled
patients with mild chronic depression (dysthymic disorder). At the end of the study imipramine was slightly mo
ritanserin based on the Hamilton Depression Rating Scale and the Zerssen Self-Rating Scale but was associ
frequency of side effects and a greater attrition rate (Bakish et al, 1994).

4.6.AW Rolipram

4.6.AW.1 Depression

a) Imipramine was superior to rolipram in patients with major depressive disorder in one double-blind study (
et al, 1989).

4.6.AX Sertraline

Depression

Dysthymia

Mixed anxiety and depressive disorder

4.6.AX.1 Depression

a) More than 50% of chronically depressed patients who were nonresponders to an antidepressant responde to an antidepressant of another class. Patients who had completed a randomized, 12-week, double-blind trial sertraline or imipramine for treatment of chronic depression and had failed to respond were switched to the a for 12 more weeks of double-blind treatment. Fifty-one patients were switched from imipramine to sertraline a sertraline to imipramine. Mean dosages at study end were 221 milligrams (mg) per day for imipramine and 16 sertraline. Ten percent of those switched to sertraline and 25% of those switched to imipramine dropped out. dropout rate was mainly due to intolerable adverse effects of imipramine. Those who switched to imipramine significant reductions in 3 adverse effects but significant increases in 8 adverse effects, whereas those who s sertraline had significant decreases in 6 adverse effects and significant increases in one:

	SERTRALINE TO IMIPRAMINE	IMIPRAMINE TO SE
DECREASED INCIDENCE		
	Insomnia	Dry mout
	Diarrhea	Somnolen
	Abdominal Pain	Increased sw
		Constipati
		Dizzines
		Urinary comp
INCREASED INCIDENCE		
	Dry mouth	Insomnia
	Increased sweating	
	Constipation	
	Dizziness	
	Tremor	
	Abnormal taste	
	Increased appetite	
	Urinary complaints	

b) The intent-to-treat response rates were 60% for sertraline and 44% for imipramine (p=0.03). Among comp response rates were 63% and 55%, respectively (p=0.16). After averaging across the study weeks and adjus status, depression type, and baseline value, there were no significant differences between groups in outcome improvement over time did not differ for the 2 groups (Thase et al, 2002).
c) In a double-blind study of major depression with or without dysthymia, response to sertraline was highest response with imipramine was highest in men. Patients meeting DSM III-R criteria for chronic major depressi

400 women) were randomized to 12-week treatment with sertraline or imipramine in a 2:1 ratio. Both drugs w milligrams (mg) daily and titrated to a maximum of 300 mg for imipramine and 200 mg for sertraline. Althoug response to sertraline was similar to imipramine, a statistically significant gender and treatment interaction wa highest response rates occurred in women taking sertraline and in men taking imipramine. More women resp (147/260; 57%) than to imipramine (61/133; 46%); and more men responded to imipramine (43/69; 62%) tha (73/161; 45%). Gender differences also occurred in the types of adverse events reported, and more women v imipramine group than from the sertraline group; however, withdrawal rates by men were not significantly diff drugs. A significant interaction was also seen between menopausal status and treatment. Withdrawal from tre highest in premenopausal women taking imipramine and postmenopausal women taking sertraline. The mecl these gender differences is unknown, and may relate to interaction of female sex hormones and serotonin ac al, 2000)

4.6.AX.2 Dysthymia

a) Sertraline and imipramine are equally effective for the treatment of dysthymia; however, sertraline is bette randomized trial, sertraline and imipramine were compared and evaluated in a group of 416 patients with ear dysthymia. Outcome was based on response based on clinical evaluation (Hamilton Rate Scale for Depressi Asberg Depression Rating Scale, Hopkins Symptom Checklist) and patient-rated version of the Inventory of D Symptoms. Improvement of scores of Clinical Global Impressions of 1 or 2 (very much or much improved) de response rates of 59% for sertraline, 64% for imipramine, and 44% for placebo. The mean dose of required f was 89.5 milligrams (mg) for sertraline and 159.7 milligrams for imipramine (Thase et al, 1996).

b) Of the 416 patients described in the study above by Thase et al, 355 had completed the Tridimensional P Questionnaire before and after treatment, and the results revealed that temperament scores improved with in dysthymia. At baseline, temperament in dysthymic patients was abnormal, with higher mean harm avoidance Tridimensional Personality Questionnaire than that reported for a community population. After 12 weeks of tr avoidance scores decreased significantly, with no significant differences between the sertraline, imipramine, Scores decreased for those achieving remission and those who did not; however, decreases were significant the remitters. Thus, improvement in temperament was mainly related to disease improvement regardless of t results revealed some gender and treatment effects, and further studies using multiple measures, rather than measure used in this study, would be needed to determine treatment effects on temperament and personality 2000).

4.6.AX.3 Mixed anxiety and depressive disorder

a) Imipramine and sertraline were equally effective in the treatment of anxiety and depression in patients witl disorder and major depressive disorder. In an randomized, multicenter, double-blind study, patients with full A disorder with concurrent major depressive disorder with a minimum of 4 panic attacks in the 4 weeks prior to baseline Montgomery-Asberg Depression Rating Scale (MADRS) score of at least 20 received either sertralir 100 milligrams (mg), mean dose, 65.4 mg/day) or imipramine (n=69; 100 to 200 mg, mean dose 144.2 mg/da Sertraline was given at an initial dose of 25 mg/day for 1 week, then titrated to 50 mg/day for 4 weeks, at whi could be increased to 100 mg, if needed. The initial dose of imipramine was 25 mg/day, increased at weekly 100 mg, and 150 mg. If needed, the dose could be increased again to 200 mg or reduced to 100 mg. Primary measures were weekly panic attack frequency and MADRS score. Sertraline and imipramine produced simila the mean baseline (28.5 vs 28.7, respectively) to endpoint (11.1 vs 11.2, respectively) total MADRS score an baseline (7.1 vs 7, respectively) to endpoint (2.9 vs 2.3, respectively) weekly panic attack frequency. Howeve treated patients reported significantly fewer adverse effects as compared with imipramine-treated patients (23 respectively; p=0.005) and fewer discontinued treatment (11% vs 22%, respectively; p=0.04). Nausea and dia frequently reported with sertraline treatment, while dizziness, dry mouth, sweating, tremor, and constipation w with imipramine administration (Lepola et al, 2003).

4.6.AY Sotalol

4.6.AY.1 Ventricular arrhythmia

a) Sotalol has been shown to be superior to procainamide, quinidine, mexiletine, propafenone, pirmenol, and ability to prevent death and the recurrence of ventricular arrhythmias in selected patients with ventricular tach Patients with a history of ventricular fibrillation or flutter with inducible, sustained ventricular tachyarrhythmias study drugs in random order until one was predicted effective by either Holter monitor assessment or progran stimulation (PES). Long-term therapy with the first effective drug was followed to one of three primary endpoi recurrence, sudden death, or unmonitored syncope. By PES, sotalol was predicted effective in 35% of a total compared to 16% for all other drugs. Although not significant, Holter assessment predicted sotalol effective fo suppression in 41% versus 45% for all other drugs combined. After two years of follow-up on chronic therapy pooled data for all the other drugs, sotalol had the lowest mortality rate (13% to 22%), lowest VT recurrence r and lowest drug withdrawal rate (38% compared to 75% to 80%). Since there was no control group, it is unkn sotalol improved survival or identified a population with a good prognosis (Prod Info Betapace(R), 1996; Mas 1989b).

4.6.AZ Tranylcypromine

4.6.AZ.1 Depression

a) Tranylcypromine is superior to imipramine in the treatment of patients with anergic bipolar depression (Hir

1991). Fifty-six patients with bipolar depression (with 73% meeting the criteria for anergic depression) were ra
to treatment with tranylcypromine 20 to 80 milligrams or imipramine 100 to 400 milligrams/day in a double-bli
study. The mean dose at the end of six weeks was 36.8 mg of tranylcypromine and 245.5 mg of imipramine.
anergic bipolar depression who did not respond to therapy in the initial phase (n=16) were then enrolled in a
with the same doses of each drug (Thase et al, 1992). Nine of the 12 patients who were switched to tranylcyp
to therapy and only one out of four patients switched to imipramine improved. Hypomania and mania develop
drugs, but occurred earlier (5.8 weeks vs 9.2 weeks) in those receiving imipramine.
b) In a double-blind study of 137 patients with psychotic depression, tranylcypromine 10 milligrams three tim
administered for an average of 22 weeks. Patients were also randomly allocated to receive phenelzine or imi
weeks of therapy, 47% of tranylcypromine patients were improved, and after termination of the study 44% we
Tranylcypromine was slightly less effective than imipramine, but more effective than phenelzine (Haydu et al,

4.6.BA Trazodone

4.6.BA.1 Depression

a) Trazodone is not therapeutically superior to imipramine, but its side effects are less troublesome (Fabre e
Feighner, 1980; Gerner et al, 1980; Escobar et al, 1980; Workman & Short, 1993a; Gershon, 1984). Anticholi
occurred more frequently in patients treated with imipramine than those treated with trazodone in a multi-cent
Newton, 1980).
b) A multicenter trial involving 379 patients treated with trazodone 200 to 600 milligrams (mg) per day imipra
mg/day or placebo for 21 to 24 days demonstrated imipramine and trazodone to be of equal efficacy (Gersho
1980). Another study involving 28 patients with endogenous depression receiving an average trazodone dose
an average imipramine dose of 140 mg/day for 28 days also demonstrated equal effectiveness between the 2
al, 1979). The results of a double-blind study involving 45 patients suggested that trazodone 200 to 600 mg/d
more rapid and prolonged improvement than did imipramine 100 to 300 mg/day (Feighner, 1980). In a double
study of 40 patients with endogenous depression, imipramine (maximum daily dose 300 mg) produced more
Hamilton depression scale scores on days 14 and 28 than trazodone (maximum daily dose 600 mg) (Escoba
c) Seventy-four patients were enrolled in a nonrandomized study with placebo baseline treatment to evaluate
imipramine, alprazolam, and trazodone in the treatment of agoraphobia (Charney et al, 1986). Twenty-nine p
assigned to imipramine, 28 to trazodone, and 26 to alprazolam treatment. All patients were treated with place
and then blindly switched to active treatment for clinical response and side effects. Both imipramine and alpra
effective in controlling the agoraphobia, however, alprazolam had a faster onset of action. Clinical responses
within one week with alprazolam therapy and were generally not observed in imipramine treated patients unti
week of therapy. Trazodone therapy was considered not effective in the treatment of agoraphobia.
d) In a double-blind controlled study, imipramine and placebo were compared with trazodone in the treatmer
patients with primary depression. The mean doses received during this study were 6.26 capsules/day of 50 m
trazodone, 6.37 capsules/day of imipramine 25 mg or 10.67 capsules/day of placebo. Three of 17 patients in
groups experienced a 50% reduction in the Hamilton total score on or before day 7 of therapy. On day 14, 8 p
trazodone group achieved this level of improvement. Of the imipramine- treated patients, no one in the group
improvement at day 7. However, by day 14, eight patients in the group had also experienced at least a 50% r
Hamilton differences in the subjects tested through the structured clinical interview. Clinical global impression
significant difference between trazodone and placebo in the proportion of improved patients at the end of 28
Global ward behavior indicated that trazodone was significantly (p less than 0.01) better than placebo for tens
inwardly distressed behavior and difficulty in sleeping. It was significantly (p less than 0.05) better for tired, w
energy behavior and anxious, worried, afraid behavior and concern for bodily health. Trazodone was slightly
0.10) for irritable, annoyed, impatient or angry behavior. Drowsiness was the most frequent side effect experi
trazodone treated patients. Anticholinergic effects were the most common effects in the imipramine group (Fe
e) Ten institutions participated in a multi-center, double-blind, placebo-controlled evaluation of either trazodo
in 263 in-patients. Inclusion criteria included primary depression of the endogenous type, minimum score of 1
Rating Scale for depression (HAM-D) and at least 7 of 21 symptoms in 3 of 5 categories of the symptom prof
Initial doses were 200 mg and 100 mg daily for trazodone or imipramine. At the end of 28 days, 113 patients
lack of efficacy or side effects. Drop out rates were 37% each for imipramine and trazodone and 58% for plac
were statistically superior to placebo in improvement of HAM- D and clinical global interview. There was no si
difference between trazodone and imipramine. Both trazodone and placebo caused statistically significantly f
anticholinergic side effects, 19% and 14% compared WITH imipramine 52% (Gershon, 1981).

4.6.BB Trimipramine

4.6.BB.1 Depression

a) One study showed trimipramine to be slightly superior to imipramine. Thirty-nine inpatients with endogeno
received either imipramine or trimipramine increased over 14 days to a maximum of 300 milligrams at bedtim
another 2 weeks. There were fewer adverse reactions (tremor, drowsiness, insomnia and dry mouth) than wi
however, nasal congestion occurred more frequently during trimipramine therapy (Rifkin et al, 1980).
b) Imipramine was compared with trimipramine in 44 patients with psychotic depression (average duration o
year) (Burns, 1965). Trimipramine was administered in doses of 25 mg three times daily for 1 week followed
times daily for 2 more weeks. Overall recovery was reported in 18 patients receiving trimipramine (in 8.7 days
10 patients receiving imipramine (8.9 days). In addition, anxiety and insomnia responded much better in patie
trimipramine. Similar results have been reported by others (Salzmann, 1965).

4.6.BC Tryptophan

4.6.BC.1 Depression

a) L-tryptophan 6 grams and imipramine 150 milligrams/day were effective in relieving endogenous and non-
depression in 59 patients. Imipramine improved agitation, while L-tryptophan improved work and activities in
endogenous depression. Imipramine therapy improved suicidal feelings in patients with non-endogenous dep
et al, 1979).

4.6.BD Venlafaxine

4.6.BD.1 Depression

a) Venlafaxine and imipramine resulted in similar improvement in depression with melancholia in hospitalize
weeks; however, venlafaxine produced an earlier response than imipramine on 1 test (Benkert et al, 1996). C
dose of venlafaxine was rapidly increased from 75 to 375 milligrams(mg)/day; this dose was continued until d
then decreased to 150 mg/day. The dose of imipramine was increased from 50 to 200 mg/day over 5 days ar
at this dose for the remainder of the study. The time to a 50% response rate was similar for the Montgomery-
Depression Rating Scale (MADRS), but for the 21-item Hamilton Rating Scale for Depression (HAM-D), the ti
was 1 week earlier with venlafaxine than imipramine (p=0.036). Adverse effects were reported in 69% and 76
treated with venlafaxine and imipramine, respectively. Statistically significant differences in dry mouth and tre
for imipramine (p less than 0.05) and nausea for venlafaxine (p=0.011). While this study enrolled 167 patients
than planned, and only 115 patients completed the 6-week study. Additional studies are needed to provide co
for a more rapid onset of effect with venlafaxine.

b) Venlafaxine was found to have antidepressant efficacy comparable to imipramine in outpatients with mod
depression. Venlafaxine was compared to imipramine in a 6 week, double-blind placebo controlled study in 2
depression of moderate to marked severity. Baseline and weekly efficacy measurements were obtained utiliz
Hamilton Rating Scale for Depression (HAM-D), the Montgomery-Asberg Depression Rating Scale (MADRS)
Global Impression severity and improvement scales (CGI). The mean maximal total daily dose of venlafaxine
48 milligrams and the mean maximal total daily dose of imipramine was 176 milligrams and +/- 56 mg. All stu
were administered in a three times a day schedule after meals. Venlafaxine showed a significant clinical adva
imipramine at the week 6 endpoint on the Ham-D total score. It was noted that this effect was probably due to
attrition rate for imipramine as compared to venlafaxine. Attrition rates due to adverse effects were 25% and
imipramine and venlafaxine respectively. Nausea, sedation, dry mouth, and dizziness were the most promine
adverse effects for venlafazine (Schweizer et al, 1994).

4.6.BE Viloxazine

Depression

Nocturnal enuresis

4.6.BE.1 Depression

a) SUMMARY: Several controlled studies have reported the equivalent efficacy of viloxazine 150 to 450 milli
imipramine 75 to 225 milligrams daily in the treatment of depression in inpatients and outpatients (Santonasta
Davies et al, 1977; McEvoy et al, 1982; Battistini et al, 1980; Nair & Schwartz, 1982; Floru et al, 1976; Bayliss
Side effects in some of these reports, primarily anticholinergic, were less with viloxazine; however, others hav
similar incidence as imipramine (McEvoy et al, 1982).

b) At least 2 studies have reported a similar clinical response to placebo as with viloxazine and imipramine ir
neurosis (Petrie et al, 1980; Guy et al, 1982). These data do not necessarily indicate the inefficacy of viloxazi
in this patient group, but rather reflect the methodological problems of placebo responsiveness in neurotic po
effects may also explain the reported early onset of effects with viloxazine in some clinical studies, both neur
endogenous depression.

c) Better scores were reported on the Hamilton Depression Scale in patients treated with viloxazine 50 millig
times/day compared to those treated with imipramine 25 milligrams three times/day (Elwin, 1980). The double
involved 59 depressed patients. However, this data was not reproduced in 40 depressed patients treated with
mg/day or imipramine 150 mg/day (Battistini et al, 1980), nor in 28 depressed patients (Santonastaso et al, 1

d) Viloxazine was compared with imipramine in the treatment of endogenous depression in a double-blind st
patients (McEvoy et al, 1982). Patients were randomly assigned to viloxazine 150 to 450 milligrams (mg) dail
to 225 milligrams daily (10 patients in each group). Flurazepam or chloral hydrate were given for sleep as nee
global impressions indicated that 7 viloxazine patients (70%) and 7 imipramine patients (70%) improved durir
patients receiving viloxazine and 3 receiving imipramine remained unchanged and 1 patient receiving viloxaz
Hamilton Psychiatric Rating Scale for Depression indicated improvement with both drugs with no differences
Imipramine had a faster onset of action for depression (1 week versus 2 weeks). The Hamilton Psychiatric Ra
Anxiety also showed similar degrees of improvement, however, viloxazine had a more rapid onset (1 week ve
Viloxazine had no effect on improving sleep disturbances as determined by the Hamilton Depression Scale, a

compared with other reports. Side effects were similar for both drugs with 1 patient in each group developing treatment (both patients had abnormal EKGs at initiation of treatment).

e) Viloxazine and imipramine has similar efficacy in a 5-week study involving 49 patients with endogenous d Schwartz, 1982). Viloxazine was initiated in oral doses of 50 milligrams (mg) three times a day with meals, wi being given at 5 p.m. Imipramine was given initially in doses of 25 milligrams orally three times a day in a sim dose was increased starting in the second week of the study to a maximum of viloxazine 400 mg daily and im daily by the fourth and fifth weeks. The mean daily dosage by the fifth week of the study was 380 mg daily fo 192 mg daily for imipramine. Both drugs resulted in improvement based upon Clinical Global Impressions, the Scale for Depression, the Hamilton Rating Scale for Anxiety, and the Brief Psychiatric Rating Scale. Based u Impressions, 12 of 24 viloxazine patients were very much improved, with 5 much improved; 13 of 25 imipram very much improved, with 7 being much improved. Side effects occurred more frequently in imipramine patie side effects of dry mouth, constipation, blurred vision, sweating, and sedation occurred more frequently in the However, nausea and vomiting occurred only in viloxazine patients.

4.6.BE.2 Nocturnal enuresis

a) Viloxazine was evaluated in the treatment of nocturnal enuresis in a controlled study with imipramine and children (Attenburrow et al, 1984). The drugs were randomly assigned for a 7-week period. Viloxazine 100 m bedtime was administered to children between 5 and 10 years of age. Imipramine was given in doses of 50 a respectively. At week 7, significantly more dry nights occurred with both viloxazine and imipramine as compa with no statistically significant difference between the two active agents. Toxicity was greater in the imipramin consisting of, primarily anticholinergic effects. These data suggest the efficacy of viloxazine in enuretic childre prove to be a useful alternative to imipramine in children who develop side effects during imipramine therapy.

4.6.BE.3 Adverse Effects

a) The most frequent side effects associated with viloxazine therapy are nausea and vomiting (Elwan, 1980; 1980), and the incidence of anticholinergic side effects is much lower than with imipramine.

b) Viloxazine appears to cause less impairment of psychomotor performance than imipramine. The driving o was tested after multiple doses of viloxazine 50 milligrams three times/day, imipramine 25 milligrams three tir or nothing. The group treated with imipramine demonstrated significantly worse performance in the gap acce subsidiary task responses. There was no effect on driving skills noted 2 hours after the first dose of each drug 1977).

4.6.BF Zimeldine

Agoraphobia

Depression

4.6.BF.1 Agoraphobia

a) A double-blind comparison of zimeldine, imipramine, and placebo in the treatment of 44 patients with agor attacks revealed that zimeldine was better, (not statistically significant), than imipramine and placebo therapy 1986). In fact, the imipramine therapy was not considered to be superior to placebo. Previous positive results (Mavissakalian & Perel, 1985; Cohen et al, 1984) would indicate that the dose of imipramine used in this stud mmilligrams/day) or the group of patients studied is not indicative of all patients with agoraphobia and panic a further studies are conducted the utilization of zimeldine in the treatment of agoraphobia should be limited to

4.6.BF.2 Depression

a) Zimeldine 100 milligrams orally twice a day was compared with oral imipramine 50 milligrams three times treatment of primary major depressive disorders (endogenous) in 95 patients in a controlled study (Hiramatsu During the 4-week study, zimeldine produced similar antidepressant activity as imipramine as evaluated on th Depression Scale. Zimeldine was reported more effective in patients over the age of 40, patients whose initia over 40 years, patients with mild-to-moderate depression and patients who had previously failed to show an a response to other antidepressants. Zimeldine was less toxic than imipramine, primarily with regard to anticho

b) Zimeldine demonstrated significantly lower Hamilton Depression scale total scores compared with imipran forty depressed patients were administered zimeldine, imipramine, and matching placebo in doses of 50 milli Fewer adverse effects were reported in the zimeldine group (Merideth & Feighner, 1983).

4.6.BF.3 Adverse Effects

a) Zimeldine did not differ in psychomotor or cognitive function tests in 18 healthy volunteers. In a double-bli fashion, each subject received zimeldine 100 milligrams, imipramine 50 milligrams, or matching placebo. A ba not exhibit a significant difference between active drugs (Ferris et al, 1980).

b) Zimeldine in therapeutic doses (200 milligrams/day) produces more pronounced anticholinergic effects, as accommodation width and salivary secretion rate, than imipramine in therapeutic doses (75 milligrams/day) (V 1981).

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