DRUGDEX® Evaluations

ARIPIPRAZOLE

0.0 Overview

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

2) Dosing Information
- **a)** Adult
  - **1)** oral solution may be substituted for the tablet dosages on a mg-per-mg basis for up to a 25 mg dose; patients oral solution (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM injection, 2008)
    - **a)** Bipolar disorder - Psychomotor agitation
      - **1)** initial, 9.75 mg IM (dose range 5.25 mg to 15 mg); cumulative doses up to a total of 30 mg/day may b dose required, wait at least 2 h after initial dose; for ongoing therapy, oral aripiprazole in a range of 10 m injection as soon as possible (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM
    - **b)** Bipolar I disorder, Adjunctive therapy with lithium or valproate for acute manic or mixed episodes
      - **1)** initial and target dose, 15 mg ORALLY once a day; may increase to MAX dose of 30 mg ORALLY on solution, orally disintegrating tablets, IM injection, 2008)
    - **c)** Bipolar I disorder, Monotherapy, manic or mixed episodes
      - **1)** initial and target dose, 15 mg ORALLY once a day; may increase up to MAX dose of 30 mg ORALLY solution, orally disintegrating tablets, IM injection, 2008)
    - **d)** Major depressive disorder, Adjunctive treatment in patients also receiving antidepressants
      - **1)** initial, 2 mg to 5 mg ORALLY once daily; dose adjust in up to 5 mg/day increments at intervals of 1 w (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM injection, 2008)
    - **e)** Psychomotor agitation - Schizophrenia
      - **1)** initial, 9.75 mg IM (dose range 5.25 mg to 15 mg); cumulative doses up to a total of 30 mg/day may b dose required, wait at least 2 hr after initial dose; for ongoing therapy, oral aripiprazole in a range of 10 n injection as soon as possible (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM
    - **f)** Schizophrenia
      - **1)** initial, 10 to 15 mg ORALLY once daily (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrati
      - **2)** maintenance, MAX daily dosage is 30 mg/day ORALLY; increase dose only after 2 weeks at each do greater with doses higher than 10 to 15 mg/day (Prod Info ABILIFY(R) oral tablets, solution, orally disinte
- **b)** Pediatric
  - **1)** safety and efficacy not established in pediatric patients with major depressive disorder or agitation associated less than 13 years of age with schizophrenia, or patients less than age 10 years with bipolar I disorder (Prod Info disintegrating tablets, IM injection, 2008)
  - **2)** oral solution may be substituted for the tablet dosages on a mg-per-mg basis for up to a 25 mg dose; patients oral solution (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM injection, 2008)
    - **a)** Bipolar I disorder, Monotherapy, manic or mixed episodes
      - **1)** 10 yr and older, oral tablets, initial, 2 mg ORALLY once a day for 2 days, then 5 mg ORALLY once a ORALLY once a day; MAX dose 30 mg ORALLY once a day, titrated in 5 mg per day increments (Prod I disintegrating tablets, IM injection, 2008)
    - **b)** Schizophrenia
      - **1)** initial, oral tablets, 2 mg ORALLY once daily; increase to 5 mg after 2 days and to 10 mg (target dose mg; efficacy not greater at 30 mg/day compared to 10 mg/day (Prod Info ABILIFY(R) oral tablets, solutio 2008)

3) Contraindications
- **a)** hypersensitivity to aripiprazole or any component of the product (Prod Info ABILIFY(R) oral tablets, oral solution, IM disintegrating tablets, 2008)

4) Serious Adverse Effects
- **a)** At risk for suicide
- **b)** Cerebrovascular accident
- **c)** Death
- **d)** Diabetic ketoacidosis
- **e)** Immune hypersensitivity reaction
- **f)** Leukopenia
- **g)** Neuroleptic malignant syndrome
- **h)** Prolonged QT interval
- **i)** Seizure
- **j)** Suicidal behavior
- **k)** Tardive dyskinesia
- **l)** Transient ischemic attack

5) Clinical Applications
- **a)** FDA Approved Indications

1) Bipolar disorder - Psychomotor agitation
2) Bipolar I disorder, Adjunctive therapy with lithium or valproate for acute manic or mixed episodes
3) Bipolar I disorder, Monotherapy, manic or mixed episodes
4) Major depressive disorder, Adjunctive treatment in patients also receiving antidepressants
5) Psychomotor agitation - Schizophrenia
6) Schizophrenia

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
Aripiprazole
C) Physicochemical Properties
1) Molecular Weight
a) 448.38 (Prod Info Abilify™, 2002)

1.2 Storage and Stability

A) Preparation
1) Intramuscular route
a) Aripiprazole should not be injected by intravenous or subcutaneous injection. It should only be used intran
muscle mass. The required volumes of solution for a dose of 5.25 milligrams (mg), 9.75 mg, and 15 mg are 0
respectively. Discard any unused portion of the injection (Prod Info ABILIFY(R) oral tablets, solution, orally di
2) Oral route
a) Aripiprazole may be taken without regard to meals (Prod Info ABILIFY(R) oral tablets, solution, orally disin
B) Oral route
1) Solution
a) Aripiprazole oral solution should be stored at 25 degrees Celsius (77 degrees Fahrenheit) with excursions
Celsius (59 and 86 degrees Fahrenheit). The oral solution should be used within 6 months after opening, but
(Prod Info ABILIFY(R) oral tablets, disintegrating tablets, solution, 2006).
2) Tablet/Tablet, Disintegrating
a) Aripiprazole tablets should be stored at 25 degrees Celsius (77 degrees Fahrenheit) with excursions perm
to 86 degrees Fahrenheit) (Prod Info ABILIFY(R) oral tablets, disintegrating tablets, solution, 2006).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Geriatric Patients

1.3.1 Normal Dosage

Intramuscular route

Oral route

1.3.1.A Intramuscular route

Bipolar disorder - Psychomotor agitation

Psychomotor agitation - Schizophrenia

1.3.1.A.1 Bipolar disorder - Psychomotor agitation

a) The recommended dose to control agitation in patients with schizophrenia or bipolar mania is 9.75 mi
5.25 mg to 15 mg). No additional benefit was observed after a 15 mg dose compared to a 9.75 mg dose.
day may be administered if a second dose is required. However, the efficacy of repeated doses in agitat
evaluated in clinical trials. Additionally, the safety of total daily doses greater than 30 mg or injections ad
have not been adequately evaluated. For ongoing therapy, oral aripiprazole in a range of 10 mg to 30 m
as soon as possible (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM injection

b) Concomitant CYP3A4 Inhibitors

1) The dosage of aripiprazole should be reduced to one-half the usual dose when administered con
as ketoconazole or clarithromycin. When the CYP3A4 inhibitor is discontinued, the aripiprazole dose
oral tablets, solution, orally disintegrating tablets, IM injection, 2008).

c) Concomitant CYP3A4 Inducers

1) The dosage of aripiprazole should be doubled when administered concurrently with a potential C
dose may be further increased if needed based on clinical evaluation. When the CYP3A4 inducer is
reduced to 10 to 15 mg (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM i

d) Concomitant CYP2D6 Inhibitors

1) The dosage of aripiprazole should be reduced to at least one-half the usual dose when administe
inhibitors, such as quinidine, fluoxetine, or paroxetine. When the CYP2D6 inhibitor is discontinued fr
dose should be increased (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, Il

1.3.1.A.2 Psychomotor agitation - Schizophrenia

a) The recommended dose to control agitation in patients with schizophrenia is 9.75 milligrams (mg) intr
No additional benefit was observed after a 15 mg dose compared to a 9.75 mg dose. Cumulative doses
administered if a second dose is required. However, the efficacy of repeated doses in agitated patients h
clinical trials. Additionally, the safety of total daily doses greater than 30 mg or injections administered m
been adequately evaluated. For ongoing therapy, oral aripiprazole in a range of 10 mg to 30 mg/day sho
possible (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM injection, 2008).

b) Concomitant CYP3A4 Inhibitors

1) The dosage of aripiprazole should be reduced to one-half the usual dose when administered con
as ketoconazole or clarithromycin. When the CYP3A4 inhibitor is discontinued, the aripiprazole dose
oral tablets, solution, orally disintegrating tablets, IM injection, 2008).

c) Concomitant CYP3A4 Inducers

1) The dosage of aripiprazole should be doubled when administered concurrently with a potential C
dose may be further increased if needed based on clinical evaluation. When the CYP3A4 inducer is
reduced to 10 to 15 mg (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM i

d) Concomitant CYP2D6 Inhibitors

1) The dosage of aripiprazole should be reduced to at least one-half the usual dose when administe
inhibitors, such as quinidine, fluoxetine, or paroxetine. When the CYP2D6 inhibitor is discontinued fr
dose should be increased (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, Il

1.3.1.B Oral route

Bipolar I disorder, Adjunctive therapy with lithium or valproate for acute manic or mixed episodes

Bipolar I disorder, Monotherapy, manic or mixed episodes

Major depressive disorder, Adjunctive treatment in patients also receiving antidepressants

Schizophrenia

1.3.1.B.1 Bipolar I disorder, Adjunctive therapy with lithium or valproate for acute manic or mixed ep

a) As adjunctive therapy with lithium or valproate, the recommended initial and target dose is aripiprazol
Depending on clinical response, the dose may be increased to 30 mg orally once a day. There have bee
safety of daily doses greater than 30 mg (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating

b) Concomitant CYP3A4 Inhibitors

1) The dosage of aripiprazole should be reduced to one-half the usual dose when administered con
as ketoconazole or clarithromycin. When the CYP3A4 inhibitor is discontinued, the aripiprazole dose
oral tablets, solution, orally disintegrating tablets, IM injection, 2008).

c) Concomitant CYP3A4 Inducers

1) The dosage of aripiprazole should be doubled when administered concurrently with a potential C dose may be further increased if needed based on clinical evaluation. When the CYP3A4 inducer is reduced to 10 to 15 mg (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM i

d) Concomitant CYP2D6 Inhibitors

1) The dosage of aripiprazole should be reduced to at least one-half the usual dose when administe inhibitors, such as quinidine, fluoxetine, or paroxetine. When the CYP2D6 inhibitor is discontinued fr dose should be increased (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM

1.3.1.B.2 Bipolar I disorder, Monotherapy, manic or mixed episodes

a) The recommended starting and target dose is aripiprazole 15 milligrams (mg) orally once a day. Depe increased to 30 mg orally once a day. There have been no clinical trials performed evaluating the safety ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM injection, 2008).

b) Maintenance Therapy

1) Aripiprazole has been effective for stabilizing and maintaining patients with a recent manic or mi 2006). However, it is unclear how long a patient should remain on aripiprazole therapy. Patients wh aripiprazole monotherapy for at least 6 weeks demonstrated a benefit from maintenance treatment. beyond 6 weeks should be reassessed at regular intervals to determine the need for ongoing treatm solution, orally disintegrating tablets, IM injection, 2008).

c) Concomitant CYP3A4 Inhibitors

1) The dosage of aripiprazole should be reduced to one-half the usual dose when administered con as ketoconazole or clarithromycin. When the CYP3A4 inhibitor is discontinued, the aripiprazole dose oral tablets, solution, orally disintegrating tablets, IM injection, 2008).

d) Concomitant CYP3A4 Inducers

1) The dosage of aripiprazole should be doubled when administered concurrently with a potential C dose may be further increased if needed based on clinical evaluation. When the CYP3A4 inducer is reduced to 10 to 15 mg (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM i

e) Concomitant CYP2D6 Inhibitors

1) The dosage of aripiprazole should be reduced to at least one-half the usual dose when administe inhibitors, such as quinidine, fluoxetine, or paroxetine. When the CYP2D6 inhibitor is discontinued fr dose should be increased (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM

1.3.1.B.3 Major depressive disorder, Adjunctive treatment in patients also receiving antidepressants

a) The recommended initial dose of aripiprazole as adjunctive treatment in patients with major depressi 2 to 5 milligrams (mg) orally once daily. The aripiprazole dose may be gradually adjusted by 5 mg/day in patient tolerability and efficacy. In two 6-week, placebo-controlled trials, the aripiprazole dose ranged fro CYP2D6 inhibitors (eg, fluoxetine, paroxetine) and 2 to 20 mg/day in patients not on potential CYP2D6 i established; reassess periodically to evaluate the need for maintenance therapy (Prod Info ABILIFY(R) o tablets, IM injection, 2008).

1.3.1.B.4 Schizophrenia

a) The recommended initial and target oral dose of aripiprazole for the treatment of schizophrenia is 10 daily, with or without meals (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM i daily have been effective in patients with acutely relapsed schizophrenia or schizoaffective disorder (Kan Petrie et al, 1998a). However, in clinical trials efficacy has not been significantly greater with doses highe not should be made before 2 weeks at each dose strength (Prod Info ABILIFY(R) oral tablets, solution, o

b) Doses of 30 mg daily could be administered without dose titration in one study (Petrie et al, 1998a).

c) Maintenance Therapy

1) It is unclear how long a patient should remain on aripiprazole therapy; however, patients who ha antipsychotic mediations for at least 3 months and were discontinued from those medication and giv weeks did demonstrate a benefit from maintenance treatment. Patients should be reassessed at reg ongoing treatment (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM inject

d) Switching from Other Antipsychotics

1) Data are not available to recommend guidelines for switching from other antipsychotics to aripipr other antipsychotics. The previous antipsychotic treatment may be immediately discontinued or mor individual patient. However, in all cases, duration of antipsychotic administration overlap should kep tablets, solution, orally disintegrating tablets, IM injection, 2008).

e) Concomitant CYP3A4 Inhibitors

1) The dosage of aripiprazole should be reduced to one-half the usual dose when administered con as ketoconazole or clarithromycin. When the CYP3A4 inhibitor is discontinued, the aripiprazole dose oral tablets, solution, orally disintegrating tablets, IM injection, 2008).

f) Concomitant CYP3A4 Inducers

1) The dosage of aripiprazole should be doubled when administered concurrently with a potential C dose may be further increased if needed based on clinical evaluation. When the CYP3A4 inducer is reduced to 10 to 15 mg (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM i

g) Concomitant CYP2D6 Inhibitors

1) The dosage of aripiprazole should be reduced to at least one-half the usual dose when administe inhibitors, such as quinidine, fluoxetine, or paroxetine. When the CYP2D6 inhibitor is discontinued fr dose should be increased (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM

1.3.1.B.5 Oral Solution

a) Doses of the aripiprazole oral solution may be substituted for the tablet dosages on a milligram (mg)-
receiving 30 mg tablets should receive 25 mg of the oral solution (Prod Info ABILIFY(R) oral tablets, solu
2008).

b) Patients using the oral solution should be advised that every milliliter of aripiprazole oral solution con
200 mg (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM injection, 2008).

1.3.1.B.6 Orally Disintegrating Tablet

a) Dosing with orally disintegrating tablets is the same as for the oral tablets (Prod Info ABILIFY(R) oral
IM injection, 2008)

b) Abilify Discmelt(R) 10 milligram (mg) orally disintegrating tablets contain 1.12 mg of phenylalanine, a
phenylalanine (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM injection, 2008

1.3.2 Dosage in Renal Failure

A) Dosage adjustment is not necessary in patients with renal impairment (Prod Info ABILIFY(R) oral tablets, solu
2008).

1.3.3 Dosage in Hepatic Insufficiency

A) Dosage adjustment is not necessary in patients with hepatic impairment (Prod Info ABILIFY(R) oral tablets, so
injection, 2008).

1.3.4 Dosage in Geriatric Patients

A) Dosage adjustment is not necessary for elderly patients (Prod Info ABILIFY(R) oral tablets, solution, orally disi

1.4 Pediatric Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

1.4.1 Normal Dosage

1.4.1.A Oral route

Bipolar I disorder, Adjunctive therapy with lithium or valproate for acute manic or mixed episodes

Bipolar I disorder, Monotherapy, manic or mixed episodes

Schizophrenia

1.4.1.A.1 Bipolar I disorder, Adjunctive therapy with lithium or valproate for acute manic or mixed ep

a) As adjunctive therapy with lithium or valproate, the recommended starting dose of oral tablets in pedi
aripiprazole 2 milligrams (mg) orally once a day for 2 days, then titrated to 5 mg orally once a day for 2 d
orally once a day. Depending on clinical response, the dose may be increased in 5 mg per day increme
performed evaluating the safety of daily doses greater than 30 mg (Prod Info ABILIFY(R) oral tablets, so
2008).

b) Maintenance Therapy

1) The efficacy of aripiprazole for the maintenance treatment of bipolar I disorder in pediatric patien
maintenance therapy can be extrapolated from adult data. It is recommended that responding pedia
acute response, but at the lowest dose needed to maintain remission with periodic reassessments p
solution, orally disintegrating tablets, IM injection, 2008).

c) Concomitant CYP3A4 Inhibitors

1) The dosage of aripiprazole should be reduced to one-half the usual dose when administered con
as ketoconazole or clarithromycin. When the CYP3A4 inhibitor is discontinued, the aripiprazole dose
oral tablets, solution, orally disintegrating tablets, IM injection, 2008).

d) Concomitant CYP3A4 Inducers

1) The dosage of aripiprazole should be doubled when administered concurrently with a potential C
dose may be further increased if needed based on clinical evaluation. When the CYP3A4 inducer is
reduced to 10 to 15 mg (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM i

e) Concomitant CYP2D6 Inhibitors

1) The dosage of aripiprazole should be reduced to at least one-half the usual dose when administe

inhibitors, such as quinidine, fluoxetine, or paroxetine. When the CYP2D6 inhibitor is discontinued fr
dose should be increased (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, II

1.4.1.A.2 Bipolar I disorder, Monotherapy, manic or mixed episodes

a) The recommended starting dose of oral tablets in pediatric patients age 10 years and older is aripipra
days, then titrated to 5 mg orally once a day for 2 days, and titrated to the target dose of 10 mg orally on
dose may be titrated in 5 mg per day increments. There have been no clinical trials performed evaluating
(Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM injection, 2008).

b) Maintenance Therapy

1) The efficacy of aripiprazole for the maintenance treatment of Bipolar I Disorder in pediatric patier
maintenance can be extrapolated from adult data. It is recommended that responding pediatric patie
response, but at the lowest dose needed to maintain remission with periodic reassessments perform
solution, orally disintegrating tablets, IM injection, 2008).

c) Concomitant CYP3A4 Inhibitors

1) The dosage of aripiprazole should be reduced to one-half the usual dose when administered con
as ketoconazole or clarithromycin. When the CYP3A4 inhibitor is discontinued, the aripiprazole dose
oral tablets, solution, orally disintegrating tablets, IM injection, 2008).

d) Concomitant CYP3A4 Inducers

1) The dosage of aripiprazole should be doubled when administered concurrently with a potential C
dose may be further increased if needed based on clinical evaluation. When the CYP3A4 inducer is
reduced to 10 to 15 mg (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM i

e) Concomitant CYP2D6 Inhibitors

1) The dosage of aripiprazole should be reduced to at least one-half the usual dose when administe
inhibitors, such as quinidine, fluoxetine, or paroxetine. When the CYP2D6 inhibitor is discontinued fr
dose should be increased (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, II

1.4.1.A.3 Schizophrenia

a) The recommended target dose for the treatment of schizophrenia in adolescents aged 13 to 17 years
tablets at 2 mg/day and increase the dose to 5 mg after 2 days and then to 10 mg after an additional 2 d
should be done in 5-mg increments. However, no additional benefit has been seen with the 30 mg dose
orally disintegrating tablets, IM injection, 2008).

b) Maintenance Therapy

1) The efficacy of aripiprazole for the maintenance treatment of schizophrenia in pediatric patients h
of maintenance can be extrapolated from adult data. It is recommended that responding pediatric pa
response, but at the lowest dose needed to maintain remission with periodic reassessments perform
solution, orally disintegrating tablets, IM injection, 2008).

c) Switching from Other Antipsychotics

1) Data are not available to recommend guidelines for switching from other antipsychotics to aripipr
other antipsychotics. The previous antipsychotic treatment may be immediately discontinued or mor
individual patient. However, in all cases, duration of antipsychotic administration overlap should kep
tablets, solution, orally disintegrating tablets, IM injection, 2008)

d) Concomitant CYP3A4 Inhibitors

1) The dosage of aripiprazole should be reduced to one-half the usual dose when administered con
as ketoconazole or clarithromycin. When the CYP3A4 inhibitor is discontinued, the aripiprazole dose
oral tablets, solution, orally disintegrating tablets, IM injection, 2008).

e) Concomitant CYP3A4 Inducers

1) The dosage of aripiprazole should be doubled when administered concurrently with a potential C
dose may be further increased if needed based on clinical evaluation. When the CYP3A4 inducer is
reduced to 10 to 15 mg (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM i

f) Concomitant CYP2D6 Inhibitors

1) The dosage of aripiprazole should be reduced to at least one-half the usual dose when administe
inhibitors, such as quinidine, fluoxetine, or paroxetine. When the CYP2D6 inhibitor is discontinued fr
dose should be increased (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, II

4) The safety and efficacy of aripiprazole have not been established in pediatric patients with major depressi
schizophrenia or bipolar mania, patients less than 13 years of age with schizophrenia, or patients less than a
ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM injection, 2008).

1.4.1.A.5 Oral Solution

a) Doses of the aripiprazole oral solution may be substituted for the tablet dosages on a milligram (mg)-
receiving 30 mg tablets should receive 25 mg of the oral solution (Prod Info ABILIFY(R) oral tablets, solu
2008).

b) Patients using the oral solution should be advised that every milliliter of aripiprazole oral solution con
200 mg (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM injection, 2008).

1.4.1.A.6 Orally Disintegrating Tablets

a) Dosing with orally disintegrating tablets is the same as for the oral tablets (Prod Info ABILIFY(R) oral
IM injection, 2008)

b) Abilify Discmelt(R) 10 milligram (mg) orally disintegrating tablets contains 1.12 mg of phenylalanine a
phenylalanine (Prod Info ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM injection, 2008

1.4.2 Dosage in Renal Failure

A) Dosage adjustment is not necessary in patients with renal impairment (Prod Info ABILIFY(R) oral tablets, solu 2008).

1.4.3 Dosage in Hepatic Insufficiency

A) Dosage adjustment is not necessary in patients with hepatic impairment (Prod Info ABILIFY(R) oral tablets, sc injection, 2008).

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset

1) Initial Response

a) SCHIZOPHRENIA, ORAL: 1 week (10 to 30 mg daily) (Petrie et al, 1998b; Anon, 2000b).

1) In phase II studies involving hospitalized schizophrenic patients, significant improvement (including n of therapy with aripiprazole 30 mg daily. With lower doses (2 or 10 mg daily), symptom improvement was less substantial (Petrie et al, 1998b).

2.2 Drug Concentration Levels

A) Therapeutic Drug Concentration

1) Not established.

B) Peak Concentration

1) Following an intramuscular dose, the geometric mean maximum concentration (Cmax) was on average 19% h administration (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006).

C) Time to Peak Concentration

1) Oral: 3 to 5 hours (Anon, 2000b; Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, I

2) Intramuscular: 1 to 3 hours (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM inj

a) In healthy subjects receiving once-daily doses of 5 and 20 mg, mean peak plasma levels on day 14 were in 3 to 5 hours (Anon, 2000b).

b) With a titrated dosing schedule of 10 mg daily for 2 days, then 20 mg daily for 2 days, and finally 30 mg da concentration on day 14 was 452 ng/mL (3 hours) (Anon, 2000b).

c) In 2 studies of healthy subjects, the median times to peak plasma concentrations following intramuscular a hours (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006).

D) Area Under the Curve

1) The aripiprazole area under the curve (AUC) in the first 2 hours after an intramuscular injection was 90% great tablet; however, both routes had similar systemic exposure over 24 hours. When intramuscular aripiprazole doses schizophrenia or schizoaffective disorder, the pharmacokinetics of aripiprazole were linear over a dose range of 1 orally-disintegrating tablets, oral solution, IM injection, 2006).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption

A) Bioavailability

1) Oral: tablet, 87%; solution, well-absorbed (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets,

2) Intramuscular: 100% after a 5-mg intramuscular injection (Prod Info ABILIFY(R) oral tablets, orally-disinte

2006).

a) A comparative bioavailability study which compared the pharmacokinetics of a 30 milligram aripiprazo found that plasma concentrations of aripiprazole were higher with the solution than with the tablet. In hea concentration and area under the curve values were 22% and 14% higher with the solution as compared (R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006).

b) Pharmacokinetic studies with the orally disintegrating aripiprazole tablet indicate that they are bioequ ABILIFY(R) DISCMELT(TM) orally disintegrating tablets, 2006).

B) Effects of Food

1) Absorption unaffected (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM inje

a) Peak serum levels and AUC of aripiprazole and dehydroaripiprazole are not significantly affected whe peak serum levels is delayed (by 3 hours for aripiprazole and by 12 hours for dehydroaripiprazole) (Prod disintegrating tablets, oral solution, IM injection, 2006).

2.3.2 Distribution

A) Distribution Sites

1) Protein Binding

a) greater than 99% (aripiprazole and dehydroaripiprazole) (Prod Info ABILIFY(R) oral tablets, orally-dis 2006).

B) Distribution Kinetics

1) Volume of Distribution

a) 404 L or 4.9 L/kg (intravenous) (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral so

2.3.3 Metabolism

A) Metabolism Sites and Kinetics

1) Liver, extent unknown (Lawler et al, 1999).

a) Metabolic pathways include dehydrogenation and hydroxylation (via cytochrome P450 (CYP)-3A4 an CYP-3A4 . Aripiprazole is the primary compound in plasma. Aripiprazole does not inhibit or induce the C tablets, orally-disintegrating tablets, oral solution, IM injection, 2006).

b) Poor metabolizers (CYP-2D6) have been identified (speculated as 8% of population); these patients l active compounds (aripiprazole and dehydroaripiprazole) . Inhibitors of CYP-2D6 are capable of increasi (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006).

B) Metabolites

1) Dehydroaripiprazole (active) (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution,

a) Major metabolite, representing about 40% of aripiprazole AUC in plasma. This metabolite has affinitie compound and appears to contribute to pharmacologic activity (Prod Info ABILIFY(R) oral tablets, orally- injection, 2006).

2.3.4 Excretion

A) Kidney

1) Renal Excretion (%)

a) 25% of dose (less than 1% unchanged aripiprazole) (Prod Info ABILIFY(R) oral tablets, orally-disinteg 2006).

B) Feces

1) FECES, 55% of a dose (about 18% unchanged aripiprazole) (Prod Info ABILIFY(R) oral tablets, orally-disi 2006).

2.3.5 Elimination Half-life

A) Parent Compound

1) ELIMINATION HALF-LIFE

a) 75 hours (extensive metabolizers) (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, ora

1) An elimination half-life of 146 hours has been reported in poor metabolizers (Prod Info ABILIFY(R solution, IM injection, 2006).

B) Metabolites

1) Dehydroaripiprazole, 94 hours (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solutio

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING

1) Oral (Tablet; Tablet, Disintegrating; Solution)

Increased Mortality In Elderly Patients With Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of d controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week c patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of dea to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Observa antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to wh observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the approved for the treatment of patients with dementia-related psychosis.

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in child term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the us antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk w adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with ages who are started on antidepressant therapy should be monitored appropriately and observed closely for changes in behavior. Families and caregivers should be advised of the need for close observation and comm not approved for use in pediatric patients with depression (Prod Info ABILIFY(R) oral tablets, oral solution, IM disintegrating tablets, 2008).

2) Intramuscular (Solution)

Increased Mortality In Elderly Patients With Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of d controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week c patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of dea to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Observa antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to wh observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the approved for the treatment of patients with dementia-related psychosis.

Suicidality and Antidepressant Drugs

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3.1 Contraindications

A) hypersensitivity to aripiprazole or any component of the product (Prod Info ABILIFY(R) oral tablets, oral solution, IM disintegrating tablets, 2008)

3.2 Precautions

A) elderly patients with dementia (unapproved use); increased risk of death mostly due to cardiovascular events (eg, (mostly pneumonia) reported when atypical antipsychotics were used off-label to treat behavorial disorders associated tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008)

B) first few months of therapy or following changes in dosage; increased risk of suicidal ideation and behavior or wors tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008)

C) suicidal ideation and behavior or worsening depression; increased risk, particularly in children, adolescents, and yo require therapy discontinuation (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) o

D) aspiration pneumonia, at-risk patients; esophageal dysmotility and aspiration have been reported, especially in the dementia (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tab

E) cardiovascular disease, preexisting (including history of myocardial infarction or ischemic heart disease, heart failu risk of orthostatic hypotension (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) or

F) cerebrovascular disease, preexisting; increased risk of orthostatic hypotension (Prod Info ABILIFY(R) oral tablets, (R) orally disintegrating tablets, 2008)

G) concomitant parenteral benzodiazepine therapy; monitor patient for orthostatic hypotension and for excessive seda solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008)

H) diabetes mellitus, preexisting or risk factors for (eg, obesity, family history of diabetes); may experience hyperglyce ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008)

I) elderly, increased risk of esophageal dysmotility, aspiration, and potentially-irreversible tardive dyskinesia (especial

oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008)
J) elevation in core body temperature; increased risk following strenuous exercise, exposure to extreme heat, concon
or dehydration (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrati
K) higher doses and longer treatment durations; increased risk of tardive dyskinesia, which may be irreversible (Prod
injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008)
L) hyperglycemia, severe and associated with ketoacidosis, hyperosmolar coma, or death has been reported with aty
tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008)
M) hypotension, predisposition (such as dehydration, hypovolemia, and antihypertensive drug therapy); increased risk
(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008)
N) neuroleptic malignant syndrome has occurred; discontinue aripiprazole therapy and provide treatment as needed (
solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008)
O) seizures, history or condition that may lower the seizure threshold (eg, Alzheimer's dementia); increased risk of se
solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008)
P) tardive dyskinesia; has been reported and may be irreversible (Prod Info ABILIFY(R) oral tablets, oral solution, IM
disintegrating tablets, 2008)
Q) report suspected adverse reactions to Bristol-Myers Squibb at 1-800-721-5072 or to the US Food and Drug Admin
www.fda.gov/medwatch (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally di

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Immunologic Effects

Musculoskeletal Effects

Neurologic Effects

Ophthalmic Effects

Psychiatric Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

Orthostatic hypotension

Prolonged QT interval

Summary

Tachycardia

3.3.1.A Orthostatic hypotension

1) Incidence: 0.6% to 4% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(
2) Compared with placebo, aripiprazole therapy resulted in a higher incidence of orthostatic hypotension am
(1% vs 0.3%; n=2467), pediatric patients 10 to 17 years of age receiving oral aripiprazole (1% vs 0%; n=399)

(0.6% vs 0%; n=501) during short-term trials. Aripiprazole should be used cautiously in patients with preexisti
would predispose patients to hypotension (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILI
2008).
3) The frequency of a significant orthostatic change in blood pressure (ie, a decrease of at least 20 mmHg in
increase in heart rate of 25 or greater when changing from a supine to standing position) was not significantly
compared with those treated with placebo in the placebo controlled trials of adult patients (4% aripiprazole, 2
years (0%, 0.5%), or in aripiprazole injection-treated patients (3%, 2%) (Prod Info ABILIFY(R) oral tablets, ora
(R) orally disintegrating tablets, 2008).

3.3.1.B Prolonged QT interval

1) Incidence: 0.1% to 1% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(
2) Prolongation of the QT-interval has been observed during clinical trials with a frequency between 1/1000 a
doses of aripiprazole at least 2 mg day. Aripiprazole should be used cautiously in patients with preexisting ca
abnormalities (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally dis

3.3.1.C Summary

1) Because orthostatic hypotension, prolonged QT interval, and tachycardia have been reported with aripipra
caution in patients with known cardiovascular disease or conduction abnormalities, or conditions which would
ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008)

3.3.1.D Tachycardia

1) Incidence: 2% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally
2) In a pooled analysis of trials in which adult patients with agitation associated with schizophrenia or bipolar
intramuscularly 5.25 mg/day or greater (n=501) or placebo (n=220), tachycardia was reported in 2% of patien
than 1% of patients receiving placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY
2008).

3.3.2 Dermatologic Effects

Acneiform drug eruption

Rash

3.3.2.A Acneiform drug eruption

1) Incidence: rare
2) A 23-year-old man developed acneiform drug eruptions 10 days after starting aripiprazole treatment for pa
year history of symptoms suggestive of paranoid schizophrenia. In the past had received an adequate trial of
treated with aripiprazole 20 mg/day with a good response. After 1 month of treatment with aripiprazole, the pa
remained symptomatic for 1 year. The patient was readmitted for aggravation of symptoms and upon admiss
hemogram, serum electrolytes, renal function and liver function. For acute control of his aggression, the patie
haloperidol 10 mg and promethazine 25 mg intramuscularly twice daily for 4 days. The patient was restarted
mg/day over 4 days. After 10 days of aripiprazole treatment, the patient developed papulopustular eruptions
worsened with sunlight exposure) The patient had no past history of the eruptions or aripiprazole exposure in
with aripiprazole-induced acneiform eruptions. Aripiprazole was discontinued and the patient was switched to
response. Consequently, the affected regions were treated with topical retinoic acid 0.25 mg ointment. Within
there was complete resolution of the acneiform eruptions with mild scarring. Because the patient was previou
rapid development of the acneiform lesions, the acneiform drug eruption may have been mediated through a
clinical signs of allergy were noted (Mishra et al, 2008).

3.3.2.B Rash

1) Incidence: 2% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally
2) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with schizophrenia or bipolar m
mg/day or greater) (n=399) or placebo (n=197), rash was reported in 2% of patients receiving aripiprazole co
(Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tab

3.3.3 Endocrine/Metabolic Effects

Blood glucose level - finding

Diabetes mellitus

Diabetic ketoacidosis

Hyperglycemia

Hyponatremia

Increased body temperature

Increased prolactin level

Metabolic syndrome

Summary

Triglyceride level - finding

Weight increased

3.3.3.A Blood glucose level - finding

1) Incidence: rare (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orall

2) Blood glucose fluctuation has been observed rarely in postmarketing surveillance of aripiprazole (Prod Inf injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

3.3.3.B Diabetes mellitus

See Drug Consult reference: ATYPICAL ANTIPSYCHOTIC AGENTS - EFFECT ON GLUCOSE AND RISK C

3.3.3.C Diabetic ketoacidosis

1) A 44-year-old, obese, African-American man developed new-onset diabetes and diabetic ketoacidosis (DK treatment for schizoaffective disorder. The patient's medical history included a 16-year diagnosis of schizoaff upon admission was 43.3 kg/m(2)), and he had no personal or family history of diabetes and no current medi prior for schizoaffective disorder with a good clinical response to fluphenazine and valproic acid. Upon admis exacerbation of schizoaffective disorder symptoms (auditory hallucinations), treatment with fluphenazine 5 m fluphenazine was increased to 5 mg twice daily and valproic acid 1750 mg/day was added. By day 27, the pa hallucinations and aripiprazole 15 mg/day was initiated. Additionally, the patient was receiving fluphenazine, atorvastatin for hyperlipidemia. On day 28 the aripiprazole was increased to 30 mg/day. On day 43, after 16 d experienced a episode of urinary incontinence. On day 44, the patient refused to eat, experienced somnolenc ability to take his medication or drink fluids without assistance. The patient was treated with intravenous fluids sinus tachycardia. On day 45, the patient was lethargic, stopped communicating, had difficulty walking and ha hours. Laboratory analysis revealed hyperglycemia (glucose, 813 mg/dL), metabolic acidosis (bicarbonate, 9 gases pH, 7.2), moderate serum ketone levels, elevated serum creatinine (2.7 mg/dL), bilirubinemia (2.6 mg/ 14.9%. The patient was diagnosed with DKA, transferred to the medical intensive care unit where all psychiat patient was given intravenous insulin and fluids. The psychiatric team recommended fluphenazine, benztropi metabolic acidosis and azotemia resolved, and the intravenous insulin was changed to subQ long-acting insu back to the psychiatric service after the serum glucose had stabilized. The patient's discharge medications in aspart in addition to benztropine, fluphenazine, divalproex sodium, and escitalopram. Within 4 months after h insulin. According to the Naranjo scale (score of 5), aripiprazole was the probable catalyst triggering DKA. Th associated DKA may be attributed to preexisting glucose impairment (evidenced by the strong correlation bet (Makhzoumi et al, 2008).

2) A case of new-onset diabetes and diabetic ketoacidosis with elevated lipase was described in a 33-year-o following treatment with aripiprazole. Prior to current presentation, the patient had been on aripiprazole therap had a body mass index (BMI) was 32 kg/m(2) prior to taking aripiprazole. At the time of presentation, the pati epigastric abdominal pain. The patient had progressively gained weight since initiating aripiprazole treatment Laboratory tests indicated hyperglycemia (blood glucose of 1769 mg/dL), diabetic ketoacidosis (anion gap of milliosmoles/kg, CO2 of 6 mmol/L), and hyperlipasemia (lipase of 4068 International Units/L). An abdominal u pancreatitis and gallstones, and thyroid function tests were normal. The patient did not have a prior medical h Aripiprazole was discontinued and the patient was treated with intravenous fluids and insulin. A diagnosis of a lipase, secondary to diabetic ketoacidosis, was made and the patient was discharged home with haloperidol a discontinuation of aripiprazole, the patient's BMI had decreased to 33 kg/m(2) and, while still diabetic, his insu proposed that patient's weight and blood glucose may need be monitored during aripiprazole therapy (Reddy

3.3.3.D Hyperglycemia

1) Hyperglycemia has been reported in patients treated with atypical antipsychotics; and in some instances, ketoacidosis, hyperosmolar coma, or death. There have been few reports of hyperglycemia in patients treate atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However risk of treatment-emergent hyperglycemia-related adverse events in patients treated with atypical antipsychot the time these studies were conducted, it is not known if aripiprazole is associated with this increased risk. Pa antipsychotics for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. If sy should undergo fasting blood glucose testing. Although hyperglycemia has resolved when the antipsychotic d

required continued antidiabetic treatment despite antipsychotic discontinuation (Prod Info ABILIFY(R) oral tab DISCMELT(R) orally disintegrating tablets, 2008).

3.3.3.E Hyponatremia

1) Hyponatremia was reported in a 69-year-old man when aripiprazole was added to sodium valproate maint His comorbid conditions included diabetes mellitus treated with metformin and glibenclamide, and hypothyroi While he was treated with a stable dose of sodium valproate 1000 mg/day, he experienced a relapse of mani mg/day was added. The patient developed persistent hiccoughs 2 days later, accompanied by a serum sodiu of 4.5 mEq/L, and urine specific gravity of 1.01; other laboratory and thyroid serology results were unremarka per day of water for the previous 3 weeks. When aripiprazole was withheld and water intake was restricted to mEq/L. However, sodium levels dropped again to 120 mEq/L one day following rechallenge with aripiprazole aripiprazole and was initiated on quetiapine (dose titrated to 400 mg/day over 2 weeks), his sodium levels gra later with spontaneous resolution of hiccoughs. Fluid restriction was then stopped. During the following 8 mor normal sodium levels (Behere et al, 2007).

3.3.3.F Increased body temperature

1) Disruption of the body's ability to reduce core body temperature has been associated with antipsychotic a appropriate care in patients who will be experiencing conditions that may contribute to an elevated core body exposure to extreme heat, or dehydration) (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABIL tablets, 2008).

3.3.3.G Increased prolactin level

1) Serum prolactin levels have been unaffected or increased only slightly by oral aripiprazole (2 to 30 mg dai Petrie et al, 1998; Kane et al, 2000b). Increases in prolactin levels were greater with haloperidol 10 mg daily i Saha et al, 1999a).

3.3.3.H Metabolic syndrome

See Drug Consult reference: ANTIPSYCHOTIC AGENTS - METABOLIC SYNDROME

3.3.3.I Summary

1) Blood glucose fluctuation, diabetic ketoacidosis, and hyperglycemia have been reported with aripiprazole factors for diabetes should be monitored for worsening glucose control and should undergo fasting blood gluc during aripiprazole treatment. Reports of weight gain, increased body temperature, a case report of hyponatr prolactin have been reported with aripiprazole use. Aripiprazole should be used cautiously in patients with the temperatures, dehydration, strenuous exercise, or other conditions which may increase core body temperatu solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

3.3.3.J Triglyceride level - finding

1) In pooled data of 2 placebo-controlled trials of adult patients with major depressive disorder receiving oral weeks in addition to continued antidepressant therapy (n=371) or antidepressant therapy alone (n=366), the triglycerides was 5% versus 0%, respectively (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, A tablets, 2008).

3.3.3.K Weight increased

1) Incidence: 2% to 30% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(

2) In a short-term study of aripiprazole as adjunctive therapy for bipolar disorder, increased weight was repo mg/day or 30 mg/day orally (n=253) compared with 1% of patients receiving placebo (n=130). Patients receiv aripiprazole or placebo for up to 6 weeks (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILI 2008).

3) In pooled data of 2 placebo-controlled trials of adult patients with major depressive disorder receiving arip in addition to continued antidepressant therapy (n=371), compared with antidepressant therapy only (n=366), of patients, respectively. Comparing the aripiprazole adjunctive group with the adjunctive placebo group, the respectively, and the percentage of patients gaining 7% or greater of body weight was 5% vs 1%, respectivel solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

4) In 4- to 6-week trials in which adult patients with schizophrenia were treated with either aripiprazole 5 to 3 was observed among patients treated with aripiprazole compared with a weight loss of 0.05 kg observed amo greater gain in body weight from baseline was observed in 8% of the aripiprazole-treated patients compared Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2

5) In 3-week trials in which adult patients with mania were treated with either aripiprazole or placebo, a weigl treated with aripiprazole compared with a weight loss of 0.2 kg observed among patients treated with placebo baseline was observed in 3% of the aripiprazole-treated patients compared with 2% of the placebo-treated pa solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

6) In a 6-week trial in which pediatric patients 13 to 17 years of age with schizophrenia were treated with eith 0.13 kg was observed among patients treated with aripiprazole compared with a weight loss of 0.83 kg obser 7% or greater gain in body weight from baseline was observed in 5% of the aripiprazole-treated patients com (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tab

7) In one large 4-week study, weight gain of more than 7% was observed in about 11% of patients treated w relationship) and 14% receiving haloperidol 10 mg daily (Saha et al, 1999a).

8) In a 26-week, placebo-controlled trial among patients treated with aripiprazole 15 mg daily for schizophrer greater body weight from baseline were as follows (Prod Info ABILIFY(R) oral tablets, oral solution, IM injecti disintegrating tablets, 2008):

Body-Mass Index (BMI)	Aripiprazole	Placebo
Less than 23	6.8%	3.7%
23 to 27	5.1%	4.2%
Greater than 27	5.7%	4.1%

p values not provided

9) In a 52-week, active-controlled trial with aripiprazole for schizophrenia, weight changes from baseline wer tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008):

Body-Mass Index (BMI)	Mean weight change from baseline (kg)	Weight gain
Less than 23	2.6	
23 to 27	1.4	
Greater than 27	-1.2	

p values not provided

3.3.4 Gastrointestinal Effects

Constipation

Diarrhea

Dysphagia

Excessive salivation

Increased appetite

Nausea

Summary

Vomiting

Xerostomia

3.3.4.A Constipation

1) Incidence: 5% to 11% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(I
2) In pooled data of 2 placebo-controlled trials of adult patients with major depressive disorder receiving oral weeks in addition to continued antidepressant therapy (n=371) or antidepressant therapy only (n=366), const respectively (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disin
3) In a pooled analysis of trials in which adult patients with schizophrenia or bipolar mania received either ari or placebo (n=1166), constipation was reported in 11% of patients receiving aripiprazole compared with 7% c ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008)

3.3.4.B Diarrhea

1) Incidence: 3% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally
2) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with schizophrenia or bipolar m mg/day or greater) (n=399) or placebo (n=197), diarrhea was reported in 3% of patients receiving aripiprazole placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegr

3.3.4.C Dysphagia

1) Esophageal dysmotility and aspiration have occurred with aripiprazole use. Dysphagia was reported infrec premarketing clinical trials. Nonetheless, like other antipsychotic drugs, aripiprazole should be used cautiousl (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tab

3.3.4.D Excessive salivation

1) Incidence: 3.1% to 8.1% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMEL
2) In a short-term study of aripiprazole as adjunctive therapy for bipolar disorder, salivary hypersecretion wa aripiprazole 15 mg/day or 30 mg/day orally (n=253) compared with 2% of patients receiving placebo (n=130).

in addition to aripiprazole or placebo for up to 6 weeks (Prod Info ABILIFY(R) oral tablets, oral solution, IM inj disintegrating tablets, 2008).
3) In a short-term, placebo-controlled trial in which pediatric patients age 10 to 17 years with bipolar mania re orally or placebo, salivary hypersecretion was reported in 8.1% of the aripiprazole 30-mg group and 3.1% of t placebo group (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally dis
4) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with schizophrenia or bipolar m mg/day or greater) (n=399) or placebo (n=197), salivary hypersecretion was reported in 4% of patients receiv receiving placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally
5) A 27-year-old man with bipolar affective disorder and current-episode mania with mood-congruent psycho gram/day developed sialorrhea 3 months after the institution of aripiprazole 10 mg/day for persistent psychoti any associated sign suggestive of extrapyramidal syndrome. A significant reduction in sialorrhea was noted c mg/day (Praharaj et al, 2009).

3.3.4.E Increased appetite

1) Incidence: 3% to 4% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R
2) In pooled data of 2 placebo-controlled trials of adult patients with major depressive disorder receiving oral weeks in addition to continued antidepressant therapy (n=371) or antidepressant therapy only (n=366), increa patients, respectively (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) o
3) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with schizophrenia or bipolar m mg/day or greater) (n=399) or placebo (n=197), increased appetite was reported in 4% of patients receiving a receiving placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally

3.3.4.F Nausea

1) Incidence: 8% to 15% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(I
2) In a short-term study of aripiprazole as adjunctive therapy for bipolar disorder, nausea was reported in 8% or 30 mg/day orally (n=253) compared with 5% of patients receiving placebo (n=130). Patients received lithiu aripiprazole or placebo for up to 6 weeks (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIF 2008).
3) In a pooled analysis of trials in which adult patients with schizophrenia or bipolar mania received either ari or placebo (n=1166), nausea was reported in 15% of patients receiving aripiprazole compared with 11% of pa (R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).
4) In a pooled analysis of trials in which adult patients with agitation associated with schizophrenia or bipolar mg/day or greater IM (n=501) or placebo (n=220), nausea was reported in 9% of patients receiving aripiprazo placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegr
5) In a short-term, placebo-controlled trial in which pediatric patients age 10 to 17 years with bipolar mania re orally or placebo, nausea was reported in 11% of the aripiprazole group (n=197) compared with 4% of the pla tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).
6) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with schizophrenia or bipolar m mg/day or greater) (n=399) or placebo (n=197), nausea was reported in 10% of patients receiving aripiprazol placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegr

3.3.4.G Summary

1) Nausea has been reported commonly in adult and pediatric patients treated with oral or injectable aripipra patients treated with oral or injectable aripiprazole. Constipation has been reported in adult patients treated w patients treated with oral aripiprazole have reported dry mouth and salivary hypersecretion. Diarrhea occurre aripiprazole. Although uncommon, dysphagia has been reported in patients treated with aripiprazole. Therefo patients at risk for aspiration pneumonia (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIF 2008).

3.3.4.H Vomiting

1) Incidence: 3% to 11% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(I
2) In a short-term study of aripiprazole as adjunctive therapy for bipolar disorder, vomiting was reported in 4% or 30 mg/day orally (n=253) compared with 0% of patients receiving placebo (n=130). Patients received lithiu aripiprazole or placebo for up to 6 weeks (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIF 2008).
3) In a pooled analysis of trials in which adult patients with schizophrenia or bipolar mania received either ari or placebo (n=1166), vomiting was reported in 11% of patients receiving aripiprazole compared with 6% of pa (R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).
4) In a pooled analysis of trials in which adult patients with agitation associated with schizophrenia or bipolar mg/day or greater IM (n=501) or placebo (n=220), vomiting was reported in 3% of patients receiving aripiprazo placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegr

3.3.4.I Xerostomia

1) Incidence: 2% to 5% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R
2) In a short-term study of aripiprazole as adjunctive therapy for bipolar disorder, dry mouth was reported in mg/day or 30 mg/day orally (n=253) compared with 1% of patients receiving placebo (n=130). Patients receiv aripiprazole or placebo for up to 6 weeks (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIF 2008).

3) In a pooled analysis of trials in which adult patients with schizophrenia or bipolar mania received either ari
or placebo (n=1166), dry mouth was reported in 5% of patients receiving aripiprazole compared with 4% of pa
(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).
4) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with schizophrenia or bipolar m
mg/day or greater) (n=399) or placebo (n=197), dry mouth was reported in 2% of patients receiving aripiprazo
placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegr

3.3.5 Hematologic Effects

3.3.5.A Leukopenia

1) A case report described leukopenia in a 32-year-old man following treatment with risperidone and aripipra
paranoid schizophrenia, had been initiated on risperidone 2 mg/day a few years earlier. Although he reported
physical exam were normal, laboratory assessment showed a WBC and absolute neutrophil count (ANC) of 2
Risperidone-induced leukopenia was suspected and the patient agreed to reduce the risperidone dose to 1 m
showed WBC count and ANC at 2.7 x 10(9) and 1.22 x 10(9), respectively. Subsequently, risperidone was di
aripiprazole 10 mg daily. He was evaluated every 4 weeks and reported no adverse effects. Six months later,
and 0.85 x 10(9), respectively, and aripiprazole was discontinued. Two weeks later, he experienced paranoid
hallucinations for which he was hospitalized. Upon admission, his WBC count and ANC were 6.4 x 10(9) and
after being reinitiated on aripiprazole 10 mg/day. At a follow-up appointment, his WBC count and ANC were a
respectively). It was decided to discontinue aripiprazole and treat the patient with paliperidone 6 mg and lithiu
change, his WBC count and ANC increased to 3.3 x 10(9) and 1.42 x 10(9). A full hematologic workup was p
& Rubin, 2008).

3.3.7 Immunologic Effects

3.3.7.A Immune hypersensitivity reaction

1) Incidence: rare (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orall
2) Allergic reactions (ie, anaphylactic reaction, angioedema, laryngospasm, pruritus/urticaria, or oropharynge
postmarketing surveillance of aripiprazole (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABIL
2008).

3.3.8 Musculoskeletal Effects

Arthralgia

Myalgia

3.3.8.A Arthralgia

1) Incidence: 2% to 4% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R
2) In pooled data of 2 placebo-controlled trials of adult patients with major depressive disorder receiving arip
in addition to continued antidepressant therapy (n=371) or antidepressant therapy alone (n=366), arthralgia o
respectively (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disin
3) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with schizophrenia or bipolar m
mg/day or greater) (n=399) or placebo (n=197), arthralgia was reported in 2% of patients receiving aripiprazo
placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegr

3.3.8.B Myalgia

1) Incidence: 3% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally
2) In pooled data of 2 placebo-controlled trials of adult patients with major depressive disorder receiving arip
in addition to continued antidepressant therapy (n=371) or antidepressant therapy only (n=366), myalgia occu
(Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tab

3.3.9 Neurologic Effects

Akathisia

Cerebrovascular accident

Dizziness

Dystonia

Extrapyramidal disease

Headache

Insomnia

Sedated

Seizure

Somnolence

Summary

Tardive dyskinesia

Transient ischemic attack

Tremor

3.3.9.A Akathisia

1) Incidence: 2% to 25% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(

2) In a short-term study of aripiprazole as adjunctive therapy for bipolar disorder, akathisia was reported in 1 mg/day or 30 mg/day orally (n=253) compared with 5% of patients receiving placebo (n=130). Patients receiv aripiprazole or placebo for up to 6 weeks (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILI 2008).

3) In pooled data of 2 placebo-controlled trials of adult patients with major depressive disorder receiving oral weeks in addition to continued antidepressant therapy (n=371) or antidepressant therapy only (n=366), akath respectively (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disin

4) In a pooled analysis of 3-week, placebo-controlled trials in which adult patients with bipolar mania receive placebo (n=753), akathisia was reported in 13% of aripiprazole-treated patients compared with 4% of placeb tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

5) In a pooled analysis of trials in which adult patients with schizophrenia or bipolar mania received either ari or placebo (n=1166), akathisia was reported in 10% of patients receiving aripiprazole compared with 4% of p (R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

6) In a pooled analysis of trials in which adult patients with agitation associated with schizophrenia or bipolar mg/day or greater IM injection (n=501) or placebo (n=220), akathisia was reported in 2% of patients receiving receiving placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orall

7) In a short-term, placebo-controlled trial in which pediatric patients age 10 to 17 years with bipolar mania re orally or placebo, akathisia was reported in 11.1% of the aripiprazole 30-mg group and 8.2% of the 10-mg gr (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tab

8) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with schizophrenia or bipolar m mg/day or greater) (n=399) or placebo (n=197), akathisia was reported in 9% of patients receiving aripiprazol placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegr

9) A case series reported dose-dependent akathisia following initiation of aripiprazole therapy in 4 patients (a had a history of schizoaffective disorder. All patients were concurrently receiving SSRI therapy. The patients weeks following aripiprazole initiation. Dose adjustments and/or changes to the patient's psychiatric medicati akathisia subsequently improved or resolved with no further issues (Basu & Brar, 2006).

3.3.9.B Cerebrovascular accident

1) In three, 10-week, placebo-controlled clinical studies (two flexible dose and one fixed dose study) of deme patients (mean age of 84 years; range: 78 to 88 years) were treated with aripiprazole or placebo, cerebrovas ischemic attack), including fatalities, were reported with greater incidence in the aripiprazole-treated patients the fixed-dose study, there was a significant dose response relationship for cerebrovascular adverse events i not approved for the treatment of dementia-related psychosis (Prod Info ABILIFY(R) oral tablets, oral solution disintegrating tablets, 2008).

3.3.9.C Dizziness

1) Incidence: 4% to 10% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(

2) In a short-term study of aripiprazole as adjunctive therapy for bipolar disorder, dizziness was reported in 4 or 30 mg/day orally (n=253) compared with 1% of patients receiving placebo (n=130). Patients received lithiu aripiprazole or placebo for up to 6 weeks (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILI 2008).

3) In pooled data of 2 placebo-controlled trials of adult patients with major depressive disorder receiving arip in addition to continued antidepressant therapy (n=371) or antidepressant therapy alone (n=366), dizziness o

respectively (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disin
4) In a pooled analysis of trials in which adult patients with schizophrenia or bipolar mania received either ora
placebo (n=1166), dizziness was reported in 10% of patients receiving aripiprazole compared with 7% of pati
oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).
5) In a pooled analysis of trials in which adult patients with agitation associated with schizophrenia or bipolar
injection of aripiprazole 5.25 mg/day or greater (n=501) or placebo (n=220), dizziness was reported in 8% of
5% of patients receiving placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISC
6) In a short-term, placebo-controlled trial in which pediatric patients age 10 to 17 years with bipolar mania re
orally or placebo, dizziness was reported in 5% of the aripiprazole group (n=197) compared with 1% of the pl
oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).
7) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with schizophrenia or bipolar m
mg/day or greater) (n=399) or placebo (n=197), dizziness was reported in 5% of patients receiving aripiprazo
placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegr

3.3.9.D Dystonia

1) Incidence: 2% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally
2) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with schizophrenia or bipolar m
mg/day or greater) (n=399) or placebo (n=197), dystonia was reported in 2% of patients receiving aripiprazole
placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegr
3) A 25-year-old female with schizophrenia developed characteristics associated with tardive dystonia follow
diagnosed with schizoaffective disorder that included 2 previous psychotic episodes and 3 previous manic ep
changing to various antipsychotic medications due to adverse events which included skin rashes with carbam
galactorrhea and severe extrapyramidal symptoms with risperidone , and tremors and drowsiness with valproc
mania with quetiapine, the patient switched to lithium. Lithium was reduced to 450 mg/day because of memor
lithium for 8 months with additional adverse effects. Aripiprazole 10 mg/day was added to lithium therapy due
treatment, aripiprazole was increased to 15 mg/day. After 2 months of lithium and aripiprazole therapy, she p
spasms over the latissimus dorsi, which worsened over time. The patient did not experience any other sympt
facial grimacing, or difficulty in breathing or chewing. However, the Extrapyramidal Symptom Rating Scale (E
from moderate to severe levels of extrapyramidal symptoms. The patient was started on trihexyphenidyl 6 mg
After 2 weeks, her dystonia improved and she had a ESRS score of zero. After 4 weeks, clozapine was adde
to 150 mg/day to treat her mood and psychotic symptoms. She remained symptom free 1 year after stopping
4) A 10-year-old boy with bipolar disorder developed dystonia following aripiprazole treatment. The child was
high energy and violent, impulsive behaviors with aggression toward his family and peers. His current medica
divided three times daily plus guanfacine 0.5 mg three times daily. Divalproex was discontinued and aripiprazo
was initiated the following day. Three days after initial aripiprazole therapy, the patient developed neck pain a
Upon examination, his symptoms were consistent with acute torticollis. His neck symptoms completely resolv
administration and aripiprazole discontinuation. The patient did not have any recurrence of dystonia after he w
times daily with bupropion SR 200 mg daily for mood disorder (Singh et al, 2007).

3.3.9.E Extrapyramidal disease

1) Incidence: 2% to 27.3% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT
2) In a short-term study of aripiprazole as adjunctive therapy for bipolar disorder, extrapyramidal disorder wa
aripiprazole 15 mg/day or 30 mg/day orally (n=253) compared with 1% of patients receiving placebo (n=130).
in addition to aripiprazole or placebo for up to 6 weeks (Prod Info ABILIFY(R) oral tablets, oral solution, IM inj
disintegrating tablets, 2008).
3) In pooled data of 2 placebo-controlled trials of adult patients with major depressive disorder receiving arip
in addition to continued antidepressant therapy (n=371) or antidepressant therapy alone (n=366), extrapyram
patients, respectively (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) o
4) In a pooled analysis of 3-week, placebo-controlled trials in which adult patients with bipolar mania receive
placebo (n=753), extrapyramidal disorder was reported in 5% of aripiprazole-treated patients compared with
ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008)
5) In a pooled analysis of trials in which adult patients with schizophrenia or bipolar mania received either ari
or placebo (n=1166), extrapyramidal disorder was reported in 5% of patients receiving aripiprazole compared
Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2
6) In a short-term, placebo-controlled trial in which pediatric patients age 13 to 17 years with schizophrenia r
extrapyramidal disorder was reported in 21.6% of the 30-mg aripiprazole group and 13% of the 10-mg aripipr
group (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrati
7) In a short-term, placebo-controlled trial in which pediatric patients age 10 to 17 years with bipolar mania re
mg/day or placebo, extrapyramidal disorder was reported in 27.3% of the aripiprazole 30-mg group and 12.2%
the placebo group (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orall
8) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with schizophrenia or bipolar m
mg/day or greater) (n=399) or placebo (n=197), extrapyramidal disorder was reported in 19% of patients rece
patients receiving placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT
9) A case report described the development of extrapyramidal symptoms (EPS) in a 56-year-old schizophrer
aripiprazole. The patient, who presented with psychiatric symptoms of paranoid and persecutory delusions, a
was started on aripiprazole 10 mg once daily. The dose was increased to 15 mg once daily the second week
Five weeks after the initiation of aripiprazole, including 3 weeks at the 30 mg dose, the patient developed stiff
mask-like facial expression, and hypersalivation. None of these symptoms had been documented in this patie

patient had not received treatment with any other antipsychotic agents previously. Akathisia was absent, and absence of opisthotonos, torticollis, oculogyric crisis, and the time of onset. Subsequently, the aripiprazole dc procyclidine 5 mg was added, which prompted resolution of the stiffness. However, the patient continued to h not improve. Aripiprazole treatment was stopped 7 days after the onset of EPS and nightly olanzapine therap followed by 5 mg thereafter. The hypersalivation resolved 10 days after discontinuation of aripiprazole and nc the exact mechanism for this adverse event was not elucidated, an idiosyncratic reaction to aripiprazole, rath as a possible cause for this effect (Salmoiraghi & Odiyoor, 2006).

10) Extrapyramidal symptoms have been minimal during oral aripiprazole therapy of schizophrenia in unpubl 1999a; Petrie et al, 1998; Inoue & Nakata, 2001a). In one 4-week study, the overall incidence of extrapyramic daily was similar to that in the placebo group; at least one dose of benztropine was required in 11 to 17% of p compared to 36% assigned to haloperidol 10 mg daily (Kane et al, 2000b). The frequency of extrapyramidal s than haloperidol in a phase II study (Saha et al, 1999a).

See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

3.3.9.F Headache

1) Incidence: 12% to 27% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT

2) In a pooled analysis of trials in which adult patients with schizophrenia or bipolar mania received either ari or placebo (n=1166), headache was reported in 27% of patients receiving aripiprazole compared with 23% of (R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

3) In a pooled analysis of trials in which adult patients with agitation associated with schizophrenia or bipolar mg/day or greater IM (n=501) or placebo (n=220), headache was reported in 12% of patients receiving aripip placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegr

4) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with schizophrenia or bipolar m mg/day or greater) (n=399) or placebo (n=197), headache was reported in 16% of patients receiving aripiprazole placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegr

3.3.9.G Insomnia

1) Incidence: 8% to 18% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(I

2) In a short-term study of aripiprazole as adjunctive therapy for bipolar disorder, insomnia was reported in 8 or 30 mg/day orally (n=253) compared with 4% of patients receiving placebo (n=130). Patients received lithiu aripiprazole or placebo for up to 6 weeks (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIF 2008).

3) In pooled data of 2 placebo-controlled trials of adult patients with major depressive disorder receiving oral weeks in addition to continued antidepressant therapy (n=371) or antidepressant therapy alone (n=366), inso respectively (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disin

4) In a pooled analysis in which adult patients with schizophrenia or bipolar mania received either aripiprazol placebo (n=1166), insomnia was reported in 18% of patients receiving aripiprazole compared with 3% of patie oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

3.3.9.H Sedated

1) Incidence: 1% to 8% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R

2) In a short-term study of aripiprazole as adjunctive therapy for bipolar disorder, sedation was reported in 4 or 30 mg/day orally (n=253) compared with 2% of patients receiving placebo (n=130). Patients received lithiu aripiprazole or placebo for up to 6 weeks (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIF 2008).

3) In pooled data of 2 placebo-controlled trials of adult patients with major depressive disorder receiving arip in addition to continued antidepressant therapy (n=371) or antidepressant therapy alone (n=366), sedation oc respectively (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disin

4) In a pooled analysis of trials in which adult patients with schizophrenia or bipolar mania received either ari or placebo (n=1166), sedation was reported in 7% of patients receiving aripiprazole compared with 4% of pat oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

5) In a pooled analysis of 3-week, placebo-controlled trials in which adult patients with bipolar mania receive placebo (n=753), sedation was reported in 8% of aripiprazole-treated patients compared with 3% of placebo- tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

6) In a pooled analysis of trials in which adult patients with agitation associated with schizophrenia or bipolar mg/day or greater IM injection (n=501) or placebo (n=220), sedation was reported in 3% of patients receiving receiving placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally

7) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with schizophrenia or bipolar m mg/day or greater) (n=399) or placebo (n=197), sedation was reported in 1% of patients receiving aripiprazol placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegr

3.3.9.I Seizure

1) Incidence: 0.1% to 0.3% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMEL

2) Seizures or convulsions have been reported with aripiprazole use. Use aripiprazole with caution in patient lower the seizure threshold (eg, Alzheimer's dementia) (Prod Info ABILIFY(R) oral tablets, oral solution, IM in disintegrating tablets, 2008).

3) In short-term, placebo-controlled trials, seizures or convulsions were reported in 0.1% (3 of 2467) of adult patients (ages 10 to 17 years) who received oral aripiprazole and 0.2% of adult patients (1 of 501) treated wit

oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

3.3.9.J Somnolence

1) Incidence: 5% to 26.3% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT

2) In a short-term, placebo-controlled trial in which pediatric patients age 10 to 17 years with bipolar mania re orally or placebo, somnolence was reported in 23% of the aripiprazole group (n=197) compared with 3% of th oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

3) In pooled data of 2 placebo-controlled trials of adult patients with major depressive disorder receiving arip in addition to continued antidepressant therapy (n=371) or antidepressant therapy alone (n=366), somnolenc respectively (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disin

4) In a pooled analysis of trials in which adult patients with schizophrenia or bipolar mania received either ari or placebo (n=1166), somnolence was reported in 5% of patients receiving aripiprazole compared with 3% of (R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

5) In a pooled analysis of trials in which adult patients with agitation associated with schizophrenia or bipolar mg/day or greater IM injection (n=501) or placebo (n=220), somnolence was reported in 7% of patients recei receiving placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orall

6) In a short-term, placebo-controlled trial in which pediatric patients age 13 to 17 years with schizophrenia r somnolence was reported in 21.6% of the 30-mg aripiprazole group and 11% of the 10-mg aripiprazole group (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tab

7) In a short-term, placebo-controlled trial in which pediatric patients age 10 to 17 years with bipolar mania re mg/day or placebo, somnolence was reported in 26.3% of the 30-mg aripiprazole group and 19.4% of the 10- the placebo group (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orall

8) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with schizophrenia or bipolar m mg/day or greater) (n=399) or placebo (n=197), somnolence was reported in 20% of patients receiving aripip placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegr

9) Excessive somnolence requiring hospitalization was observed in a 9-year-old girl weighing 25 kg within 3. 15 mg/day (0.6 mg/kg/day) for the treatment of oppositional defiant disorder. Although optimal dosing in pedia dose is up to three times higher than doses used in a clinical study including children of similar body weight t mg/day) (Davenport et al, 2004).

3.3.9.K Summary

1) Neuroleptic malignant syndrome (NMS), sometimes fatal, has been reported rarely in patients treated with aripiprazole is diagnosed with NMS, management should include immediate discontinuation of aripiprazole fo Cerebrovascular accident, lethargy, and tardive dyskinesia have been reported with aripiprazole use, particul for the treatment of dementia-related psychosis. Akathisia, dystonia, extrapyramidal disorder, insomnia and s should be used with caution in patients with a history of seizures or conditions that may lower the seizure thre somnolence, sedation, and tremor, there is the potential for cognitive and motor impairment. Patients who are use caution while operating machinery, including automobiles, until the effects of the drug are known (Prod In injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

3.3.9.L Tardive dyskinesia

1) Tardive dyskinesia may develop in patients treated with antipsychotic drugs, with a higher prevalence in th of developing tardive dyskinesia and the likelihood of it becoming irreversible appear to increase as treatmen drug increase. Although less common, the condition can develop after relatively brief treatment periods at low discontinuation of the antipsychotic drug; however, the antipsychotic drug itself may mask the underlying proc lowest dose and the shortest duration of therapy to produce a satisfactory clinical response to minimize the o receiving aripiprazole therapy develops symptoms of tardive dyskinesia, consideration should be given to dis require aripiprazole treatment regardless of the presence of tardive dyskinesia (Prod Info ABILIFY(R) oral tab DISCMELT(R) orally disintegrating tablets, 2008).

2) Two case reports (involving Taiwanese women, ages 41 and 52 years) suggest a relationship between us first patient was maintained on amisulpiride 200 mg/day no adverse effects. However, she was concerned ov treatment. A combination of amisulpiride 200 mg/day and aripiprazole 10 mg/day was initiated and the patien remained stable. After 11 months of therapy, the patient presented with Parkinsonian symptoms including rab which persisted for 4 months. Amisulpiride was withdrawn and aripiprazole 15 mg/day was given. Dyskinetic amisulpiride discontinuation. However, the patient was reluctant to change medication since her psychotic sy dyskinetic symptoms improved and sustained after 21 months of aripiprazole therapy. The second patient, wh medications (sulpiride 50 to 200 mg/day for 6 years) was admitted due to reoccurring psychotic symptoms. U initiated titrating up to 10 mg/day in one week. She was discharged on this dose. After 2 months of aripiprazo dyskinesia (involuntary chewing and crunching movements). Diphenhydramine 150 mg/day was added to her eventually disappeared within 3 to 4 months (Wang et al, 2009).

3.3.9.M Transient ischemic attack

1) In three, 10-week, placebo-controlled clinical studies (two flexible dose and one fixed dose study) of deme patients (mean age of 84 years; range: 78 to 88 years) were treated with aripiprazole or placebo, cerebrovas ischemic attack), including fatalities, were reported with greater incidence in the aripiprazole-treated patients the fixed-dose study, there was a significant dose response relationship for cerebrovascular adverse events i not approved for the treatment of dementia-related psychosis (Prod Info ABILIFY(R) oral tablets, oral solution disintegrating tablets, 2008).

3.3.9.N Tremor

1) Incidence: 2% to 11.8% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT
2) In a pooled analysis of 3-week, placebo-controlled trials in which adult patients with bipolar mania receive placebo (n=753), tremor was reported in 6% of aripiprazole-treated patients compared with 3% of placebo-tre tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).
3) In a short-term study of aripiprazole as adjunctive therapy for bipolar disorder, tremor was reported in 9% 30 mg/day orally (n=253) compared with 6% of patients receiving placebo (n=130). Patients received lithium or placebo for up to 6 weeks (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMEL
4) In pooled data of 2 placebo-controlled trials in adult patients with major depressive disorder receiving aripi in addition to continued antidepressant therapy (n=371) or antidepressant therapy alone (n=366), tremor occu (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tab
5) In a pooled analysis of short-term trials in which adult patients with schizophrenia or bipolar mania receive (n=1843) or placebo (n=1166), tremor was reported in 5% of patients receiving aripiprazole compared with 3 ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008)
6) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with schizophrenia or bipolar m mg/day or greater) (n=399) or placebo (n=197), tremor was reported in 5% of patients receiving aripiprazole placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegr
7) In a short-term, placebo-controlled trial in which pediatric patients age 13 to 17 years with schizophrenia r was reported in 11.8% of the 30-mg aripiprazole group and 2% of the 10-mg aripiprazole group compared wi (R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

3.3.10 Ophthalmic Effects

3.3.10.A Blurred vision

1) Incidence: 3% to 8% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R
2) In a pooled analysis of trials in which adult patients with schizophrenia or bipolar mania received either ari or placebo (n=1166), blurred vision was reported in 3% of patients receiving aripiprazole compared with 1% ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008)
3) In pooled data of 2 placebo-controlled trials of adult patients with major depressive disorder receiving oral weeks in addition to continued antidepressant therapy (n=371) or antidepressant therapy alone (n=366), blur patients, respectively (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) o
4) In a short-term, placebo-controlled trial in which pediatric patients age 10 to 17 years with bipolar mania re orally or placebo, blurred vision was reported in 8% of the aripiprazole group (n=197) compared with 0% of th oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).
5) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with schizophrenia or bipolar m mg/day or greater) (n=399) or placebo (n=197), blurred vision was reported in 5% of patients receiving aripip placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegr

3.3.12 Psychiatric Effects

Agitation

Anxiety

At risk for suicide

Feeling nervous

Restlessness

Suicidal behavior

3.3.12.A Agitation

1) A case report described severe agitation in a 45-year-old woman after abrupt clozapine discontinuation ar woman, who had a history of psychosis (schizophrenia and chronic paranoid), substance abuse (cocaine and hospitalizations, was transferred to a state psychiatric hospital from a jail facility. Her medical history also incl normal glycemic control. Upon admission, risperidone and haloperidol were stopped due to lack of response included valproic acid and nortriptyline, as well as an albuterol inhaler and ibuprofen as needed. Her clozapin titrated upward. Although her glucose levels remained within normal range, she continued to experience psyc frustration tolerance. Subsequently, haloperidol 10 mg twice daily was reinitiated as adjunctive therapy. Two epigastric pain with emesis, dizziness and lethargy. Because her blood glucose levels were in the range of 4 the patient was sent to an ER at an outside hospital where she was diagnosed with new-onset diabetes with discontinued due to the potential for diabetogenic effects. Aripiprazole 15 mg was then initiated in its place, a

to the psychiatric hospital 7 days after clozapine discontinuation, she was stable with no signs of delusions or she experienced more restlessness, showed emotional distress (crying inconsolably and verbally threatening hallways. These symptoms persisted for several days, resulting in the discontinuation of aripiprazole. She wa titrated upward to 75 mg twice daily while haloperidol was continued. Over the next week, her condition impro and greater cooperation and alertness. The patient remained clinically stable over the next 12 weeks. The au agitation: 1) a withdrawal reaction due to abrupt clozapine withdrawn, and 2) the partial dopamine agonist eff 2009).

3.3.12.B Anxiety

1) Incidence: 4% to 17% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R
2) In a short-term study of aripiprazole as adjunctive therapy for bipolar disorder, anxiety was reported in 4% or 30 mg/day orally (n=253) compared with 1% of patients receiving placebo (n=130). Patients received lithiu aripiprazole or placebo for up to 6 weeks (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIF 2008).
3) In a pooled analysis of short-term trials in which adult patients with schizophrenia or bipolar mania receive (n=1843) or placebo (n=1166), anxiety was reported in 17% of patients receiving aripiprazole compared with ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008)

3.3.12.C At risk for suicide

1) In pooled analysis of placebo-controlled trials of adult patients with major depressive disorder, or other psy antidepressant drugs in 77,000 patients, there was a tendency toward an increased risk of suicidality in the y and the absolute risk of suicidality was highest in patients with major depressive disorder. In patients less tha versus placebo, there were 14 additional cases per 1000 patients treated, and in patients age 18 to 24 years patients treated. Patients should be carefully monitored for clinical worsening of depression, suicidality, and u precursors to suicidality, especially if symptoms are severe, abrupt, or unusual. This is especially crucial duri therapy and during dose changes (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DIS
2) Because a suicide attempt is inherently possible in patients with a psychotic illness or bipolar disorder, hig receive close supervision (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R

3.3.12.D Feeling nervous

1) Incidence: 3% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally
2) In pooled data of 2 placebo-controlled trials of adult patients with major depressive disorder receiving oral weeks in addition to continued antidepressant therapy (n=371) or antidepressant therapy only (n=366), feelin respectively (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disin

3.3.12.E Restlessness

1) Incidence: 2% to 12% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R
2) In a short-term study of aripiprazole as adjunctive therapy for bipolar disorder, restlessness was reported mg/day or 30 mg/day orally (n=253) compared with 1% of patients receiving placebo (n=130). Patients receiv aripiprazole or placebo for up to 6 weeks (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIF 2008).
3) In pooled data of 2 placebo-controlled trials of adult patients with major depressive disorder receiving arip in addition to continued antidepressant therapy (n=371) or antidepressant therapy alone (n=366), restlessnes respectively (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disin
4) In a pooled analysis of 3-week, placebo-controlled trials in which adult patients with bipolar mania receive placebo (n=753), restlessness was reported in 6% of aripiprazole-treated patients compared with 3% of place tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).
5) In a pooled analysis of trials in which adult patients with schizophrenia or bipolar mania received either ari or placebo (n=1166), restlessness was reported in 5% of patients receiving aripiprazole compared with 3% of ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008)

3.3.12.F Suicidal behavior

1) Adult and pediatric patients with major depressive disorder may experience unusual changes in behavior Antidepressant therapy may be associated with the emergence of suicidality and inducing worsening of depre treatment phase and in children, adolescents, and young adults ages 18 to 24 years. It is important that famil depressive disorder or other psychiatric and nonpsychiatric disorders be vigilant in monitoring (daily) signs of aggressiveness, impulsivity, akathisia, hypomania, mania, irritability, or any unusual changes in behavior. Ch discontinuing the antidepressant medication may be considered in patients with persistent worsening depress symptoms are abrupt in onset, severe, or were not part of the patient's initial presentation (Prod Info ABILIFY ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

3.3.15 Respiratory Effects

3.3.15.A Upper respiratory infection

1) Incidence: 6% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally
2) In pooled data of 2 placebo-controlled trials of adult patients with major depressive disorder receiving arip in addition to continued antidepressant therapy (n=371), compared with antidepressant therapy only (n=366), 6% versus 4% of patients, respectively (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY

2008).

3.3.16 Other

Death

Extrapyramidal disease

Fatigue

Neuroleptic malignant syndrome

3.3.16.A Death

1) Elderly patients with dementia-related psychosis (unapproved use) treated with aripiprazole had a 1.6 to 1 placebo (4.5% vs 2.6%) in 17 placebo-controlled clinical studies (modal duration 10 weeks). The cause of de cardiovascular events including heart failure, or infectious events including pneumonia (Prod Info ABILIFY(R) ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

2) Results of a population-based, retrospective cohort study demonstrated that the use of conventional antip risk for death than atypical antipsychotics when administered to elderly patients (aged 66 years and older) wi use and conventional versus atypical antipsychotic use pair-wise comparisons were made. A total of 27,259 r dementia cohort was stratified based on place of residence (community versus long-term care facilities). In or status, propensity score matching was used. The primary outcome of the study was all-cause mortality. The r and 180 days after the antipsychotic medications were initially dispensed. There was a statistically significant associated with new use of atypical antipsychotic medications compared with nonuse in both the community- 1.31 (95% confidence interval (CI), 1.02 to 1.70); absolute risk difference, 0.2 percentage point) and long-ter 1.15 to 2.07); absolute risk difference, 1.2 percentage points). For both cohorts, the risk associated with atypi days. The risk for death associated with conventional antipsychotics was even greater than the risk identified adjusted HR for the community-dwelling cohort was 1.55 (95% CI, 1.19 to 2.02) and 1.26 (95% CI, 1.04 to 1.5 difference for both was 1.1 percentage points). The risk appeared to persist to 180 days for both groups. Som unknown or unmeasured confounders may influence the results and cause of death could not be examined (

3) Results of a population-based, retrospective cohort study demonstrated comparable to possibly greater ris conventional antipsychotic medications in the elderly (aged 65 years and older) compared with atypical antips patients with cancer and included only new users of antipsychotic medications. The primary study outcome w potential confounders was measured based on healthcare utilization data within 6 months before the initiatior elderly patients identified, 12,882 and 24,359 received conventional and atypical antipsychotic medications, r conventional drug group within the first 180 days was 14.1% compared with 9.6% in the atypical drug group (confidence interval (CI), 1.39 to 1.56). In the multi-variable analysis which controlled for potential confounders death within 180 days for conventional versus atypical drug therapy was 1.32 (95% CI, 1.23 to 1.42). When tl antipsychotic drugs were compared with risperidone, the mortality ratio associated with haloperidol was 2.14 (95% CI, 1.19 to 1.40), while there was no difference associated with olanzapine. The increased mortality risk was greatest when doses higher (above median) doses were used (mortality ratio 1.67; 95% CI, 1.5 to 1.86) (mortality ratio 1.6; 95% CI, 1.42 to 1.8). Confirmatory analyses consisting of multi-variable Cox regression, p estimation confirmed the results of the study (Schneeweiss et al, 2007).

4) The findings of one meta-analysis suggest that there may be a small increased risk of death associated w the treatment of dementia in elderly patients. The study analysis (n=5110), including 15 randomized, double-l of antipsychotic use (ie, aripiprazole (n=3), olanzapine (n=5), quetiapine (n=3), risperidone (n=5)) in elderly p dementia, found that death occurred more often in patients receiving atypical antipsychotic therapy as compa respectively). The overall odds ratio, as assessed by meta-analysis, for death in elderly patients receiving aty was 1.54 (95% CI, 1.06 to 2.23; p=0.02), and the risk difference was 0.01 (95% CI, 0.004 to 0.02; p=0.01). O antipsychotic use was 1.65 (95% CI, 1.19 to 2.29; p=0.003); however this increased risk was only identified w analyses of individual drugs did not show a statistically significant increased risk. A similar dropout rate was c treated patients (32.2% vs 31.4%, respectively), with no significant difference in dropouts found by meta-anal

5) The results of a retrospective cohort study indicate that conventional antipsychotic agents are at least as l increase the risk of death among elderly patients 65 years of age or older. The study included 9,142 new use years) and 13,748 new users of atypical agents (mean age, 83.5 years). A higher adjusted relative risk of dea conventional antipsychotics as compared with atypical antipsychotics at all time points studied after beginning 1.27 to 1.49; less than 40 days: RR, 1.56; 95% CI, 1.37 to 1.78; 40 to 79 days: RR, 1.37; 95% CI, 1.19 to 1.5 1.41). In addition, the adjusted risks of death observed in patients with dementia (RR, 1.29; 95% CI, 1.15 to 1 1.30 to 1.63), in a nursing home (RR, 1.26; 95% CI, 1.08 to 1.47), or not in a nursing home (RR, 1.42; 95% C of conventional antipsychotic therapy as compared with atypical antipsychotic use. This risk appeared to be c higher dose (ie, greater than the median) conventional antipsychotics (RR, 1.73; 95% CI, 1.57 to 1.90). Addit optimum care of elderly patients requiring antipsychotic therapy are needed so that appropriate guidance reg provided (Wang et al, 2005).

3.3.16.B Extrapyramidal disease

See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

3.3.16.C Fatigue

1) Incidence: 2% to 11% (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(

2) In pooled data of 2 placebo-controlled trials of adult patients with major depressive disorder receiving oral weeks in addition to continued antidepressant therapy (n=371) or antidepressant therapy alone (n=366), fatig respectively (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disin

3) In a pooled analysis of trials in which adult patients with schizophrenia or bipolar mania received either ari or placebo (n=1166), fatigue was reported in 6% of patients receiving aripiprazole compared with 4% of patie schizophrenia received acute therapy up to 6 weeks and patients with bipolar mania received treatment up to oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

4) In a pooled analysis of trials in which adult patients with agitation associated with schizophrenia or bipolar mg/day or greater IM injection (n=501) or placebo (n=220), fatigue was reported in 2% of patients receiving a receiving placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally

5) In a short-term, placebo-controlled trial in which pediatric patients age 10 to 17 years with bipolar mania re orally or placebo, fatigue was reported in 11% of the aripiprazole group (n=197) compared with 4% of the pla tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

6) In a pooled analysis of trials in which pediatric patients age 10 to 17 years with schizophrenia or bipolar m mg/day or greater) (n=399) or placebo (n=197), fatigue was reported in 7% of patients receiving aripiprazole placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegr

3.3.16.D Neuroleptic malignant syndrome

1) Incidence: rare (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orall

2) Neuroleptic malignant syndrome (NMS) has been reported rarely in the worldwide clinical database in pat may include hyperpyrexia, muscle rigidity, altered mental status, evidence of autonomic instability, elevated c (rhabdomyolysis), and acute renal failure. The diagnosis of patients with NMS is complicated; differential diag serious illness and untreated extrapyramidal signs, as well as central anticholinergic toxicity, heat stroke, drug diagnosed, antipsychotic drugs and other concomitant drugs that are not essential should be immediately dis and receive intensive treatment for presenting symptoms and any concomitant serious medical problems. Fo require antipsychotic drug treatment and reintroduction of such therapy should be carefully considered and th recurrence of NMS (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) oral

3) Neuroleptic malignant syndrome (NMS) was reported in a 71-year-old female with pre-hypertension and p to an abrupt change in her baseline mental status, skin flushing, and worsening tardive dyskinesia including g upper extremity choreiform movements. In the previous 9 months, the patient was receiving aripiprazole 15 m buccal oral muscle movement and upper arm athetosis 4 weeks prior to admission. Despite aripiprazole dose hospitalization and a 1-week treatment of benztropine 1 mg/day for extrapyramidal reactions, her clinical con revealed a rectal temperature of 106.5 Fahrenheit, pulse of 137 beats per minute, respiratory rate of 22 breat ranging between 99/54 mmHg and 147/100 mmHg. The patient exhibited distress, marked muscle rigidity, ch worsening slurred speech that became muted. CPK rose from 78 units/L at admission to 103 units/L eight ho leukocytosis, unremarkable metabolic panel, urine analysis, and normal aged-consistent atrophic changes or with NMS and aripiprazole was discontinued. She was given intravenous hydration, supportive cooling therap benztropine 1 mg/day, and lorazepam 1 to 2 mg as needed. Five days later, the patient stabilized aside from to the care of her psychiatrist in a psychiatric hospital (Molina et al, 2007).

4) In a case report, a 14-year-old girl with psychotic depression and mental retardation developed partial neu aripiprazole treatment. The patient had no prior experience with any extrapyramidal symptoms with her past during previous hospitalizations. She did not experience any side effects from quetiapine 300 mg daily which aripiprazole 5 mg daily. Within 48 hours of aripiprazole initiation, the patient presented with tremors, drooling, incontinence, and agitation. The patient was disoriented and had slurred, incoherent speech with fluctuating (rpm) and a pulse of 131 beats per minute (bpm). The patient's serum creatine phosphokinase (CPK) increas myoglobinuria. However, her temperature and blood pressure were within normal parameters. Her white bloo (9300 per millimeter cubed (mm(3)) of blood) and urine toxicology screen was negative. Along with other sup sodium bicarbonate to alkalinize the urine. After 2 days, the patients CPK decreased to 6157 international un every 4 hours was administered to treat the tremors and agitation. The patient eventually recovered and retu

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info Abilify(TM), 2002) (All Trime

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

See Drug Consult reference: PREGNANCY RISK CATEGORIES

2) Crosses Placenta: Unknown

3) Clinical Management

a) There is insufficient clinical experience with the use of aripiprazole in pregnancy to confirm its safety in tha a successful outcome in a 27-year-old, schizoaffective woman who was treated with aripiprazole during differ According to the manufacturer, aripiprazole was teratogenic and fetotoxic in animal studies (Prod Info Abilify(caution should be exercised with aripiprazole use pregnant women.

4) Literature Reports

a) In the case of a 27-year-old, medically healthy, schizoaffective woman, exposure to aripiprazole during dif
associated with fetal toxicity. The patient was being effectively treated with aripiprazole 15 mg/day when she
aripiprazole was withdrawn following a risk-to-benefit analysis. However, at week 20 of gestation, the patient
a revised risk-to-benefit analysis, aripiprazole was re-initiated at a 10 mg/day dose which was continued throu
weight gain at full term was 10 kg. Ultrasound scans and laboratory tests for serum glucose, thyroid function,
were normal. Although spontaneous labor occurred at term, development of unexplained fetal distress in the
section which resulted in the birth of a male infant weighing 3.25 kg. Failure to establish lactation led to the in
follow-up, the infant had achieved normal milestones (Mendhekar et al, 2006).

B) Breastfeeding

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

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

2) Clinical Management

a) It is not known whether aripiprazole is excreted into human breast milk and the potential for adverse effec
drug are unknown. It is not known if aripiprazole affects the quantity or composition of breastmilk. According t
into the milk of lactating rats (Prod Info Abilify(TM), 2002a).

3) Literature Reports

a) No reports describing the use of aripiprazole during human lactation or measuring the amount, if any, of th

4) Drug Levels in Breastmilk

a) Active Metabolites

1) dehydro-aripiprazole (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM

3.5 Drug Interactions

3.5.1 Drug-Drug Combinations

Carbamazepine

Fluoxetine

Itraconazole

Ketoconazole

Paroxetine

Quinidine

Ranolazine

3.5.1.A Carbamazepine

1) Interaction Effect: decreased aripiprazole concentrations

2) Summary: Coadministration of carbamazepine 200 milligrams (mg) twice daily with aripiprazole 30 mg on
concentration (Cmax) and the area under the concentration-time curve (AUC) values of both aripiprazole and
approximately 70%. Aripiprazole is partly metabolized by cytochrome P450 3A4 (CYP3A4) enzymes. Coadm
CYP3A4 inducer, could increase aripiprazole clearance causing decreased blood concentrations. The dose o
administered concurrently with carbamazepine. If therapy with carbamazepine is discontinued, the dose of ar
Info ABILIFY(R) oral tablets, oral solution, 2005).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Coadministration of aripiprazole and carbamazepine has resulted in decreased arip
aripiprazole should be doubled when it is administered concurrently with carbamazepine. If therapy with carb
aripiprazole should then be decreased.

7) Probable Mechanism: induction of CYP3A4-mediated aripiprazole metabolism

3.5.1.B Fluoxetine

1) Interaction Effect: increased aripiprazole levels

2) Summary: Aripiprazole is partly metabolized by cytochrome P450 2D6 (CYP2D6) enzymes. Coadministra
fluoxetine, may inhibit aripiprazole elimination causing increased blood concentrations. Consider a dosage re
coadministered. If therapy with fluoxetine is discontinued, the dose of aripiprazole should then be increased (
solution, 2005).

3) Severity: moderate

4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Increased aripiprazole plasma levels may result if used concomitantly with fluoxetin aripiprazole when these agents are coadministered. If therapy with fluoxetine is discontinued, the dose of arip
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of aripiprazole

3.5.1.C Itraconazole
1) Interaction Effect: increased aripiprazole concentrations
2) Summary: Coadministration of ketoconazole 200 milligrams (mg) per day for 14 days with a single 15 mg concentration-time curve (AUC) values of both aripiprazole and its active metabolite, dehydro-aripiprazole, by partly metabolized by cytochrome P450 3A4 (CYP3A4) enzymes. Ketoconazole, a potent CYP3A4 inhibitor, in increased blood concentrations. Coadministration of aripiprazole with itraconazole, also a strong CYP3A4 i Consider reducing aripiprazole dose by one-half when these agents are coadministered. If therapy with itracc aripiprazole should then be increased (Prod Info ABILIFY(R) oral tablets, oral solution, 2005).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Increased aripiprazole plasma levels may result if used concomitantly with itraconaz approximately one-half when these agents are coadministered. If therapy with itraconazole is discontinued, th increased.
7) Probable Mechanism: inhibition of CYP3A4-mediated aripiprazole metabolism

3.5.1.D Ketoconazole
1) Interaction Effect: increased aripiprazole concentrations
2) Summary: Coadministration of ketoconazole 200 milligrams (mg) daily for 14 days with a single 15 mg arip under the concentration-time curve (AUC) values of both aripiprazole and its active metabolite, dehydro-aripip Aripiprazole is partly metabolized by cytochrome P450 3A4 (CYP3A4) enzymes. Coadministration with ketoc inhibit aripiprazole elimination resulting in increased blood concentrations. Reduce the aripiprazole dose to or are coadministered. If therapy with ketoconazole is discontinued, the dose of aripiprazole should then be incr solution, 2005).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of aripiprazole and ketoconazole has resulted in increased aripipr dose to one-half of its normal dose when these agents are coadministered. If therapy with ketoconazole is dis then be increased.
7) Probable Mechanism: inhibition of CYP3A4-mediated aripiprazole metabolism

3.5.1.E Paroxetine
1) Interaction Effect: increased aripiprazole levels
2) Summary: Aripiprazole is partly metabolized by cytochrome P450 2D6 (CYP2D6) enzymes. Coadministra paroxetine, may inhibit aripiprazole elimination causing increased blood concentrations. Consider a dosage r are coadministered. If therapy with paroxetine is discontinued, the dose of aripiprazole should then be increas solution, 2005).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Increased aripiprazole plasma levels may result if used concomitantly with paroxeti aripiprazole when these agents are coadministered. If therapy with paroxetine is discontinued, the dose of ari
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of aripiprazole

3.5.1.F Quinidine
1) Interaction Effect: increased aripiprazole levels
2) Summary: Coadministration of quinidine 166 milligrams (mg) daily for 13 days with a single 10 mg dose of concentration-time curve (AUC) value of aripiprazole by 112% and decreased the AUC of its active metabolit is partly metabolized by cytochrome P450 2D6 (CYP2D6) enzymes. Coadministration with quinidine, a poten elimination resulting in increased blood concentrations. Reduce the aripiprazole dose to one-half of its norma If therapy with quinidine is discontinued, the dose of aripiprazole should then be increased (Prod Info ABILIF
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of aripiprazole and quinidine has resulted in increased aripiprazol dose to one-half of its normal dose when these agents are coadministered. If therapy with quinidine is discon increased.
7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of aripiprazole

3.5.1.G Ranolazine
1) Interaction Effect: an increase in aripiprazole serum concentration

2) Summary: Ranolazine, and/or its metabolites, partially inhibit cytochrome P450-2D6-mediated aripiprazole aripiprazole exposure. Use caution when these agents are coadministered. Monitor patients for signs of incre aripiprazole doses as needed (Prod Info RANEXA(R) extended-release oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of aripiprazole and ranolazine may increase aripiprazole these agents are coadministered. Monitor patients for signs of increased aripiprazole adverse effects and low RANEXA(R) extended-release oral tablets, 2008).
7) Probable Mechanism: ranolazine inhibition of cytochrome P450-2D6-mediated metabolism of aripiprazole

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters

A) Therapeutic
1) Physical Findings
a) Monitor patients for improvement of schizophrenic (positive and negative), bipolar, or depressive sympton

B) Toxic
1) Laboratory Parameters
a) Elevated creatine phosphokinase, myoglobinuria, and acute renal failure may be signs of neuroleptic mali experienced previous NMS, they should be closely monitored since NMS may reoccur (Prod Info ABILIFY(R) ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).
b) Monitor patients with an established diagnosis of diabetes mellitus for worsening of glucose control during Patients with risk factors for diabetes mellitus (eg, obesity, family history of diabetes) who are beginning treat undergo fasting blood glucose testing at the beginning of treatment and periodically throughout treatment. Pa during atypical antipsychotic treatment should undergo fasting blood glucose testing (Prod Info ABILIFY(R) o DISCMELT(R) orally disintegrating tablets, 2008).
2) Physical Findings
a) Clinical worsening, suicidality, or unusual changes in behavior, should be monitored closely, particularly d times of dose changes and especially in children, adolescents, and young adults age 24 years and younger. emerging suicidality include anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, in hypomania, and mania. Instruct family members and caregivers to monitor daily for these symptoms and to re discontinuing treatment if symptoms are severe, abrupt in onset, were not part of the patient's presenting sym persistently worse, or where emergent suicidality or symptoms are precursors of worsening depression or sui solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).
b) Elderly patients treated with aripiprazole for dementia-related psychosis (unapproved use) should be mon ischemic attack, and pneumonia; any cardiovascular, cerebrovascular, or infectious events.
c) Abnormal-movement detection (extrapyramidal symptoms) and early signs of tardive dyskinesia (eg, worm monitored, especially in the elderly and in elderly women. Longer duration of treatment and increased total cu tardive dyskinesia, but may also develop after brief treatment periods at low doses. Consider discontinuing tr dyskinesia appear following therapy (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DI 2008).
d) Blood pressure and heart rate determinations should be monitored, particularly in patients with preexisting conditions which predispose patients to hypotension (eg, dehydration, hypovolemia) or concomitant antihype
e) Body temperature regulation may be impaired especially in patients with conditions contributing to elevatio exercise, extreme heat exposure, dehydration) or concomitant drugs with anticholinergic effects.
f) ECG monitoring at baseline and periodically during therapy has been suggested (Pacher & Kecskemeti, 2
g) Esophageal dysmotility and aspiration should be monitored, especially elderly patients and in patient with use).
h) Excessive sedation and orthostatic hypotension should be monitoring in patients receiving concomitant pa (R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).
i) Hyperpyrexia, muscle rigidity, altered mental status, irregular pulse or blood pressure, tachycardia, diapho

indicative of neuroleptic malignant syndrome (NMS). If patients have experienced previous NMS, they should
(Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tab
j) Polydipsia, polyuria, polyphagia, and weakness may be symptoms of hyperglycemia. Patients who exhibit
antipsychotic treatment should undergo fasting blood glucose testing. In some instances, hyperglycemia has
stopped; however, some patients required ongoing antidiabetic treatment despite discontinuation of the susp
tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).
k) Seizures should be monitored in patients with a history of seizures, or with conditions that lower the seizu
tablets, oral solution, IM injection, ABILIFY DISCMELT(R) orally disintegrating tablets, 2008).

4.2 Patient Instructions

A) Aripiprazole (By mouth)

Aripiprazole

Treats mental illnesses, including schizophrenia and some symptoms of bipolar disorder (manic episodes). Also u
depression.

When This Medicine Should Not Be Used:
You should not use this medicine if you or your child have had an allergic reaction to aripiprazole.

How to Use This Medicine:
Liquid, Tablet, Dissolving Tablet

Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed
best for you. Do not use more medicine or use it more often than your doctor tells you to.
You may take this medicine with or without food.
Measure the oral liquid medicine with a marked measuring spoon, oral syringe, or medicine cup.
If you are using the oral disintegrating tablet, make sure your hands are dry before you handle the tablet. Do
tablet until you are ready to take it. Remove the tablet from the blister pack by peeling back the foil, then takir
through the foil. Place the tablet on your tongue. It should melt quickly. If possible, take the tablet without any
Do not split the tablet.
This medicine should come with a Medication Guide. Read and follow these instructions carefully. Ask your d
Ask your pharmacist for the Medication Guide if you do not have one. Your doctor might ask you to sign some
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
skip the missed dose. Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light. Ope
for up to 6 months after opening, but not beyond the expiration date on the bottle.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after
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

Make sure your doctor knows if you are also using medicine to lower blood pressure, such as hydrochlorothia
Accupril®, Cozaar®, Diovan®, Lotrel®, Norvasc®, Toprol®, Zestril®.
Tell your doctor if you are also using carbamazepine (Tegretol®), fluoxetine (Prozac®), ketoconazole (Nizora
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and a
sedatives.
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:

Make sure your doctor knows if you or your child are pregnant or breastfeeding, or if you have heart disease
have a history of heart attack, stroke, seizures, drug abuse, alcohol abuse, or if you have ever experienced s
(NMS) in the past.
For some children, teenagers, and young adults, this medicine can increase thoughts of suicide. Tell your do
your child start to feel more depressed and have thoughts about hurting yourselves. Report any unusual thou
child, especially if they are new or are getting worse quickly. Make sure the doctor knows if you or your child
big increase in energy, or start to act reckless. Also tell the doctor if you or your child have sudden or strong f
restless, violent, or scared. Let the doctor know if you, your child, or anyone in your family has bipolar disorde
tried to commit suicide.
This medicine may raise your blood sugar. Tell your doctor if you or your child have diabetes. It may be nece
more often. The oral liquid form of this medicine also contains sugar.
Tardive dyskinesia (a movement disorder) may occur and may not go away after you stop using the medicine
your child have any of the following symptoms while taking this medicine: lip smacking or puckering, puffing c
of the tongue, uncontrolled chewing movements, or uncontrolled movements of the arms and legs.

Older adults may be more sensitive to the side effects of this medicine, including stroke. Make sure the docto
medicine has Alzheimer's disease. This medicine is not used to treat behavioral problems in older adults with
The oral disintegrating tablet form of this medicine contains phenylalanine. Make sure your doctor knows if yo
This medicine may make you or your child dizzy or drowsy. Avoid driving, using machines, or doing anything
alert. You may also feel lightheaded when getting up suddenly from a lying or sitting position, so get up slowly
You or your child may get overheated more easily while you are using this medicine. It might reduce how mu
you do not sweat enough. Be careful if you exercise often or are in high heat or humidity. If your body gets to
confused. You might vomit or have an upset stomach. Call your doctor if you are too hot and can not cool dow

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
Anxiety, irritability, nervousness, restlessness, or trouble sleeping.
Change in how much or how often you urinate.
Chest pain, fast or slow heartbeat.
Confusion, unusual behavior, depressed mood, or thoughts of hurting yourself or others.
Excessive hunger or thirst, increased urination, and weakness.
Extreme sleepiness or weakness with nausea, vomiting, or diarrhea.
Fever, sweating, confusion, uneven heartbeat, or muscle stiffness.
Lightheadedness, dizziness, or fainting.
Problems with balance or walking.
Seizures or tremors.
Swelling in your hands, ankles, or feet.
Trouble swallowing.
Twitching or muscle movements you cannot control (often in your face, tongue, or jaw).
Unusual bleeding, bruising, or weakness.

If you notice these less serious side effects, talk with your doctor:
Blurred vision.
Change in appetite.
Dry mouth or drooling.
Headache or flu symptoms.
Muscle or joint pain.
Nausea, vomiting, constipation, or upset stomach.
Runny or stuffy nose.
Tiredness.
Unexpected weight gain or loss.

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

B) Aripiprazole (Injection)

Aripiprazole

Treats agitation associated with schizophrenia or bipolar disorder (manic or mixed).

When This Medicine Should Not Be Used:
You should not receive this medicine if you have had an allergic reaction to aripiprazole.

How to Use This Medicine:
Injectable
Your doctor will prescribe your exact dose and tell you how often it should be given. This medicine is given as
A nurse or other trained health professional will give you this medicine.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, a
Make sure your doctor knows if you are also using medicine to lower blood pressure, such as hydrochlorothia
Accupril®, Cozaar®, Diovan®, Lotrel®, Norvasc®, Toprol®, Zestril®.
Tell your doctor if you are also using carbamazepine (Tegretol®), fluoxetine (Prozac®), ketoconazole (Nizora
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and a
sedatives.
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant or breastfeeding, or if you have heart disease or low blood
of heart attack, stroke, seizures, drug abuse, alcohol abuse, or if you have ever experienced symptoms of ne
past.
For some children, teenagers, and young adults, this medicine can increase thoughts of suicide. Tell your do
your child start to feel more depressed and have thoughts about hurting yourselves. Report any unusual thou
child, especially if they are new or are getting worse quickly. Make sure the doctor knows if you or your child

big increase in energy, or start to act reckless. Also tell the doctor if you or your child have sudden or strong f
restless, violent, or scared. Let the doctor know if you, your child, or anyone in your family has bipolar disorde
tried to commit suicide.
Older adults may be more sensitive to the side effects of this medicine, including stroke. Make sure the docto
medicine has Alzheimer's disease. This medicine is not used to treat behavioral problems in older adults with
This medicine may raise your blood sugar. Tell your doctor if you have diabetes. It may be necessary to mea
Tardive dyskinesia (a movement disorder) may occur and may not go away after you stop using the medicine
your child have any of the following symptoms while taking this medicine: lip smacking or puckering, puffing c
of the tongue, uncontrolled chewing movements, or uncontrolled movements of the arms and legs.
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that cou
also feel lightheaded when standing or sitting up straight, so stand up or sit up slowly.
You or your child may get overheated more easily while you are using this medicine. It might reduce how mu
you do not sweat enough. Be careful if you exercise often or are in high heat or humidity. If your body gets to
confused. You might vomit or have an upset stomach. Call your doctor if you are too hot and can not cool do

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, c
Anxiety, irritability, nervousness, restlessness, or trouble sleeping.
Change in how much or how often you urinate.
Chest pain, fast or slow heartbeat.
Confusion, unusual behavior, depressed mood, or thoughts of hurting self or others.
Dry mouth, increased thirst or hunger, or muscle cramps.
Fever, sweating, confusion, uneven heartbeat, or muscle stiffness.
Lightheadedness, dizziness, or fainting.
Seizures or tremors.
Severe drowsiness or sleepiness.
Trouble swallowing.
Twitching or muscle movements you cannot control (often in your face, tongue, or jaw).
Unusual bleeding or bruising.
Unusual tiredness or weakness.

If you notice these less serious side effects, talk with your doctor:
Headache or flu symptoms.
Nausea, vomiting, or upset stomach.
Redness, pain, swelling, itching, blistering, or rash where the shot was given.
Weight gain or loss.

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

4.3 Place In Therapy

A) Current users of atypical antipsychotic drugs (including aripiprazole) and typical antipsychotic drugs had a similar c
according to a retrospective cohort of 93,300 adult users of antipsychotic drugs and 186,600 matched controls. The st
(mean 45.7 +/- 11.8 years) with similar cardiovascular risk at baseline who had at least one filled prescription and had
years. Sudden cardiac death was defined as occurring in the community and excluded deaths of patients admitted to t
extrinsic causes, or causes not related to ventricular tachyarrhythmia. Current use was defined as the interval betwee
end of the day's supply. Low and high doses was defined as comparable to less than 100 milligrams (mg) of chlorpron
chlorpromazine 300 mg or greater, respectively. The adjusted rate of sudden cardiac death (incidence-rate ratio) in cu
79,589 person-years was 2.26 (95% CI, 1.88 to 2.72, p less than 0.001) which was similar to the risk in current users c
years which was 1.99 (95% CI, 1.68 to 2.34, p less than 0.001). The risk of sudden cardiac death significantly increase
atypical antipsychotic drug groups. In atypical antipsychotic use, the incidence rate ratio increased from 1.59 (95% CI,
2.25 to 3.65) in high-dose use. To limit the effects of confounding of the study results, there was a secondary analysis
propensity score, which resulted in a similar risk of sudden death as the primary cohort analysis (Ray et al, 2009). In a
Medicine, it has been suggested that antipsychotic drugs continue to be used in patients with clear evidence of benefit
risk profiles (eg, elderly patients), there should be an age-dependent justification required prior to administration. It has
tested) that ECGs be performed before and shortly after initiation of antipsychotic therapy to screen for existing or eme
& Avorn, 2009).

B) Agitation Associated with Schizophrenia or Bipolar Mania

1) Aripiprazole as an intramuscular injection is approved for the treatment of agitation associated with schizophre
Info ABILIFY(R) oral tablets, oral solution, IM injection, DISCMELT(TM) orally disintegrating tablets, 2007).

2) Aripiprazole was more effective than placebo for the acute treatment of agitation in patients with schizophrenia
disorder in a dose-ranging, multicenter, randomized, double-blind clinical trial (Tran-Johnson et al, 2007).

3) A double-blind, placebo-controlled study demonstrated that intramuscular aripiprazole was noninferior to intrar
in voluntarily hospitalized agitated patients with schizophrenia or schizoaffective disorder (Andrezina et al, 2006).

4) In one short-term (24-hour), placebo-controlled trial (n=291), intramuscular aripiprazole was statistically superi
agitation in patients with Bipolar I Disorder (manic or mixed; using the Positive and Negative Syndrome Scale (PA
Clinical Global Impression of Improvement (CGI-I) scale scores) (Prod Info ABILIFY(R) oral tablets, oral solution,
disintegrating tablets, 2007).

C) Bipolar I Disorder, Mixed or Manic Episodes

1) Aripiprazole is indicated for the treatment of manic and mixed episodes associated with bipolar I disorder with and maintenance therapy) and pediatric patients age 10 to 17 years (acute therapy only) (Prod Info ABILIFY(R) o DISCMELT(TM) orally disintegrating tablets, 2007).

2) In a multicenter, randomized, double-blind, placebo-controlled study, aripiprazole was more effective than plac episodes in patients (n=262) with bipolar disorder (Keck et al, 2003).

3) In a randomized, double-blind, parallel-group trial (n=161), maintenance treatment with oral aripiprazole, at do to 26 weeks, resulted in a longer time to relapse compared to placebo in adults with a recent manic or mixed bipo aripiprazole (Keck et al, 2006).

D) Major Depressive Disorder, Adjunctive Treatment in Patients Receiving Antidepressants

1) Aripiprazole is indicated for use as an adjunctive treatment to antidepressants for major depressive disorder (F IM injection, DISCMELT(TM) orally disintegrating tablets, 2007).

2) In two 6-week, placebo-controlled trials (n=743), treatment with aripiprazole was superior to placebo in reducir depressive disorder (MDD) and an inadequate response to prior antidepressant therapies; additionally, one of the functioning with aripiprazole compared to placebo (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, D 2007).

E) Schizophrenia

1) Aripiprazole is indicated for the treatment of schizophrenia in adults and pediatric patients 13 to 17 years of ag solution, IM injection, DISCMELT(TM) orally disintegrating tablets, 2007).

2) Aripiprazole therapy was effective compared to placebo in the prevention of relapse in patients with chronic, st randomized, double-blind, placebo-controlled study (n=310) (Anon, 2003).

3) In a placebo-controlled, phase III study involving relapsed schizophrenic or schizoaffective patients (n=414), a 10 mg daily (fixed doses) were each statistically superior to placebo with regard to changes in Positive and Negat Psychiatric Rating Scale (BPRS) total scores; based on responder analysis (a 30% reduction in PANSS-total scor aripiprazole was significantly more effective than placebo, whereas haloperidol was not (Kane et al, 2000).

4) In a 6-week, placebo-controlled trial in adolescents 13 to 17 years of age, oral aripiprazole at doses of 10 or 3(placebo in the treatment of schizophrenia (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, DISCMEL

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

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) Aripiprazole is an atypical antipsychotic agent (quinolinone derivative). It exhibits relatively high affinity for dop HT1A and 5-HT2A receptors (Prod Info Abilify(TM), 2002b; Lawler et al, 1999; Inoue & Nakata, 2001). The efficac to partial agonist activity at D2 and 5-HT1A receptors (Lawler et al, 1999; Prod Info Abilify(TM), 2002b; Inoue & N antagonist activity at 5-HT2A receptors has also been speculated (Prod Info Abilify(TM), 2002b).

2) However, other actions may be involved. In vitro data have indicated D2- agonist activity of aripiprazole at pres at postsynaptic D2 receptors (regulating inhibition of cAMP synthesis) (Inoue et al, 2001; Inoue & Nakata, 2001; M Prioleau et al, 1998). These dual effects are seen at the same dose level (concentration) (Lawler et al, 1999), and drugs (typical and atypical). Preclinical and clinical data suggest that these actions minimize extrapyramidal and e (Inoue et al, 2001; Inoue & Nakata, 2001; Lawler et al, 1999).

3) Electrophysiological studies in animals suggest that aripiprazole acts as a dopamine-D2 agonist on dopaminer as a dopamine-D2 (and possibly D3) antagonist on striatal neurons and nucleus accumbens neurons (Matsubaya

4) In a small magnetoencephalographic study involving schizophrenic patients (n=5), treatment with aripiprazole decrease (normalizing effect) of abnormal delta and theta activity, loosely correlating with decreases in Positive a (Canive et al, 1998). The authors suggest evaluation of delta activity (near-normalization) as a predictor of respon accumulation in a larger number of patients is needed.

B) REVIEW ARTICLES

1) Pharmacologic basis for using partial agonists in schizophrenia (Inoue & Nakata, 2001).

4.5 Therapeutic Uses

Bipolar disorder - Psychomotor agitation

Bipolar I disorder, Adjunctive therapy with lithium or valproate for acute manic or mixed episodes

Bipolar I disorder, Monotherapy, manic or mixed episodes

Borderline personality disorder

Dementia

Major depressive disorder, Adjunctive treatment in patients also receiving antidepressants

Psychomotor agitation - Schizophrenia

Schizophrenia

4.5.A Bipolar disorder - Psychomotor agitation

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes (injectable only); Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Aripiprazole injection is approved for the treatment of agitation associated with schizophrenia and bipolar
(R) oral tablets, oral solution, IM injection, DISCMELT(TM) orally disintegrating tablets, 2007a).
In one short-term (24-hour), placebo-controlled trial, intramuscular aripiprazole was statistically superior
in patients with Bipolar I Disorder (manic or mixed; using the Positive and Negative Syndrome Scale [PA
Clinical Global Impression of Improvement [CGI-I] scale scores) (Prod Info ABILIFY(R) oral tablets, oral s
disintegrating tablets, 2007a).

3) Adult:

a) In one short-term (24-hour), placebo-controlled trial (n=291), intramuscular aripiprazole (fixed doses of 9.7
statistically superior to placebo in improving symptoms of agitation in patients with Bipolar I Disorder (manic o
Syndrome Scale [PANSS] Excited Component scores and the Clinical Global Impression of Improvement [CG
active comparator treatment arm of lorazepam injection. Agitated patients predominantly meeting DSM-IV cri
received up to 3 injections during the 24-hour treatment period, with the second injection administered after th
efficacy measure was evaluated. All enrolled patients were judged by the clinical investigators as clinically ag
treatment with intramuscular medication. Additionally, all patients exhibited a level of agitation that met or exc
the five items comprising the PANSS Excited Component (eg; poor impulse control, tension, hostility, uncoop
least 2 individual item scores of 4 or greater using a 1 to 7 scoring system (1=absent, 4=moderate, 7=extrem
Component score ranged from 15 to 24 (out of a maximum score of 35) with the mean baseline score of 19; t
agitation with some patients experiencing mild or severe levels of agitation. The primary efficacy measure in t
Component from baseline to 2 hours post-injection. The CGI-I scale was a key secondary measure. After the
15 mg) were statistically superior to placebo in the PANSS Excited Component and on the CGI-I scale. There
the 15 mg dose when compared to the 9.75 mg dose (Prod Info ABILIFY(R) oral tablets, oral solution, IM inje
tablets, 2007a).

4.5.B Bipolar I disorder, Adjunctive therapy with lithium or valproate for acute manic or mixed episodes

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; Pediatric, yes (age 10 years and older)
Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Aripiprazole is indicated for use in adults and children age 10 years or older as adjunctive therapy with lit
episodes of bipolar I disorder, with or without psychotic features (Prod Info ABILIFY(R) oral tablets, solut
2008).
Aripiprazole, added to either valproate or lithium, significantly improved symptoms of mania as early as o
who were partially nonresponsive to monotherapy during a randomized, placebo-controlled trial (Vieta et

3) Adult:

a) Aripiprazole, added to either valproate or lithium, significantly improved symptoms of mania as early as or
disorder (manic or mixed episodes) who were partially nonresponsive to monotherapy during a randomized, p
a 3 to 42 day screening phase to stabilize lithium (serum levels of 0.6 to 1 millimole/liter) or valproate (serum
therapy. Once stabilized, patients entered the baseline phase where they continued on valproate or lithium th
were allowed during week 1 (4 milligrams (mg) or less/day) and week 2 (3 mg or less/day) of this phase. Prop
daily) was also permitted during this time. If after 2 weeks there was an inadequate clinical response (Young
or greater during the screening phase and 25% or less improvement on the Y-MRS total score), patients were
with either placebo (n=131) or aripiprazole (n=253) 15 mg orally once a day for the 6 week double-blind phas
aripiprazole could be increased to 30 mg orally once a day after 7 days (mean aripiprazole dose at week 6 wa
treatment with benzodiazepines (2 mg or less of lorazepam or equivalents) were allowed for a maximum of 1
primary efficacy measure was the mean change from baseline to week 6 in Y-MRS total score (last observati
4 and weekly thereafter. A key secondary efficacy measure was the mean change from baseline to week 6 in
(CGI-BP) severity of illness (mania) score. At week 6, significantly greater improvements in Y-MRS total scor
treatment group compared with the placebo group (-13.3 (standard deviation (SD) 7.9) and -10.7 (SD 7.6), re
all subsequent endpoints, therapy with aripiprazole plus mood stabilizer resulted in significantly greater impro
than lithium/valproate monotherapy (p less than 0.05). Aripiprazole did not worsen manic symptoms and dem
elevated mood, sexual interest, irritability, speech, disruptive/aggressive behavior, and insight. Additionally, a

significant reductions in CGI-BP severity of illness mania score (-1.9 (SD 1.3)) compared with placebo (-1.6 (
depression was also significantly lower in patients receiving aripiprazole (7.7%) compared with patients recei
suggests that improvement in mania was not associated with a destabilization into depression. Tolerability ar
was similar to that demonstrated in previous aripiprazole monotherapy studies. The most frequently reported
occurred at a significantly greater rate with aripiprazole than with placebo (18.6% and 5.4%, respectively; p=(
adverse events occurred in 9% and 5% of patients receiving aripiprazole and placebo, respectively (Vieta et a

1) Maintenance Therapy

a) It is unclear how long a patient should remain on aripiprazole therapy for the treatment of bipolar
symptomatically stable on aripiprazole monotherapy for at least 6 weeks demonstrated a benefit fro
continued on treatment beyond 6 weeks should be reassessed at regular intervals to determine the
ABILIFY(R) oral tablets, solution, orally disintegrating tablets, IM injection, 2008).

4) Pediatric:

a) The efficacy of adjunctive aripiprazole therapy in pediatric patients 10 years of age and older with bipolar
additional pharmacokinetic comparisons in adults and pediatric patients (Prod Info ABILIFY(R) oral tablets, s
injection, 2008).

4.5.C Bipolar I disorder, Monotherapy, manic or mixed episodes

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; Pediatric, yes (10 to 17 years old (acute therapy))
Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Aripiprazole is indicated for the treatment of manic and mixed episodes associated with bipolar I disorde
(acute and maintenance therapy) and pediatric patients age 10 to 17 years (acute therapy only) (Prod In
disintegrating tablets, IV injection, 2008).
In a multicenter, randomized, double-blind, placebo-controlled study, aripiprazole was more effective tha
mixed episodes in patients (n=262) with bipolar disorder (Keck et al, 2003).
In a randomized, double-blind, parallel-group trial (n=161), maintenance treatment with oral aripiprazole,
for up to 26 weeks, resulted in a longer time to relapse compared to placebo in adults with a recent mani
stabilized on aripiprazole (Keck et al, 2006).
In a 4 week, double-blind, placebo-controlled study in pediatric patients with bipolar disorder (n=296), tre
symptomatology compared to placebo (Prod Info ABILIFY(R) oral tablets, solution, disintegrating tablets,

3) Adult:

a) Acute Therapy

1) Aripiprazole was more effective than placebo in the treatment of acute manic or mixed episodes in pa
randomized, double-blind, placebo-controlled study, patients (n=262) with bipolar disorder, mixed or mar
(Y-MRS) score of at least 20 received aripiprazole 30 milligrams (mg)/day (reduced to 15 mg/day if need
weeks. Patients were hospitalized for at least the first 2 weeks of treatment. Response was defined as a
50%. From baseline to endpoint, total Y-MRS scores of aripiprazole-treated patients were significantly m
received placebo (mean, -8.2 vs -3.4, respectively; p=0.002). This significant difference was present fron
also significantly higher in aripiprazole-treated patients as compared with placebo at all time points from
0.02) to endpoint (40% vs 19%, respectively; p less than or equal to 0.005). Adverse events were similar
constipation, somnolence, vomiting, akathisia, and accidental injury occurred more than twice as often in
placebo (Keck et al, 2003).

b) Maintenance Therapy

1) In a randomized, double-blind, parallel-group, placebo-controlled trial (n=161), oral aripiprazole, at do
more effective than placebo for preventing relapse in adults with a recent manic or mixed episode who w
double-blind phase, patients (n=567) with bipolar I disorder received open-label treatment with aripiprazo
stable. Stability was defined as a Young Mania Rating Scale (YMRS) total score of 10 or less and a Mon
(MADRS) total score of 13 or less during 4 consecutive visits over a minimum of 6 weeks. Mean YMRS s
and 2.6 +/- 0.3 for patients randomized to placebo and aripiprazole, respectively, at the start of double-bl
+/- 0.4 and 3.9 +/- 0.4, respectively. Following completion of the stabilization phase, 161 patients (mean
phase and were randomly assigned oral aripiprazole (n=78) or placebo (n=83) for up to 26 weeks. Aripip
during the open-label phase, with adjustments made to either 15 or 30 mg/day depending on clinical effe
medications were excluded, except for lorazepam (1 to 2 mg/day) and anticholinergic agents (up to benz
taken 12 hours before rating scale assessments). The primary efficacy measure, evaluated using Kaplar
mood episode, either manic, depressive, or mixed. Relapse was defined by study discontinuation due to
additional or increased doses of non-study medications for mood episode). Although 58% of study patier
n=55), mainly due to lack of efficacy (aripiprazole, n=19 ; placebo, n=36), patients receiving at least 1 do
primary outcome assessment were included in the analysis. The time to relapse was significantly longer
to the placebo-treated patients (p=0.02; hazard ratio (HR) 0.52, 95% confidence interval (CI), 0.3 to 0.91
lower in the aripiprazole group (25%; n=19/77) compared to the placebo group (43%; n=36/83; p=0.013)
the aripiprazole and placebo groups, respectively (p=0.009). Among key secondary efficacy endpoints, t
aripiprazole group vs placebo group (p=0.01; HR, 0.31; 95% CI, 0.12 to 0.77). The time to depressive rel
HR, 0.83; 95% CI, 0.35 to 2.01). However, the study was not powered to detect differences in secondary

episodes of manic (70%) or mixed (30%) symptoms at enrollment. Compared to placebo, the mean char
significantly in favor of aripiprazole during weeks 18 to 26 (p 0.01 to 0.05). There were no significant diffe
mean MADRS total scores. At week 26, the mean changes from baseline in the Clinical Global Impressic
score (aripiprazole, 0.7 vs placebo, 1.3; p=0.02) and mania score (aripiprazole, 0.4 vs placebo, 0.9; p=0.
events in the aripiprazole group included tremor (9.1%), akathisia (6.5%), vaginitis (6.4%) and pain in the
twice the incidence of placebo. Among aripiprazole-treated patients, 13% (n=7/56) experienced clinically
more) vs none of the placebo-treated patients (Keck et al, 2006).

4) Pediatric:

a) In a 4 week, double-blind, placebo-controlled study in pediatric patients with bipolar disorder (n=296), trea
symptomatology compared to placebo. Pediatric patients aged 10 to 17 years with manic and mixed episodes
without psychotic features and a Young Mania Rating Scale (Y-MRS) score of 20 or greater received a target
or 30 mg/day or placebo. Doses were initiated at 2 mg/day and increased to 5 mg after 2 days and then to a t
treatment arm) or 30 mg in 13 days (30 mg/day treatment arm). At week 4, both aripiprazole doses were supe
(Prod Info ABILIFY(R) oral tablets, solution, disintegrating tablets, IV injection, 2008).

4.5.D Borderline personality disorder

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Addition of aripiprazole may be beneficial for patients with borderline personality disorder who are resista
(Bellino et al, 2008).
Aripiprazole was superior to placebo for the treatment of multiple markers of borderline personality disor
Aripriprazole continued to demonstrate superior efficacy in the treatment of multiple markers of borderlin
follow up period (n=52) (Nickel et al, 2007).

3) Adult:

a) In a double-blind, placebo-controlled study, aripiprazole was superior to placebo for the treatment of multi
(n=52). Adult and adolescent patients, who met Diagnostic and Statistical Manual of Mental Disorders-IV (DS
disorder were randomized in a 1:1 fashion to receive either aripiprazole 15 milligrams (mg) tablets orally daily
women/4 men) for 8 weeks. The primary outcome was the mean change in score from baseline to week 8 in
D), the Hamilton Anxiety Rating Scale (HAM-A), the State-Trait Anger Expression Inventory (STAXI) and the
consisted of 9 symptoms: somatization, obsessive-compulsiveness, insecurity in social contact, depression, a
paranoid thinking and psychoticism. The intent-to-treat analysis revealed that aripiprazole was significantly su
and 8 of the 9 symptoms of SCL-90-R, excluding somatization as seen in the following table. The most comm
headache, insomnia, nausea, numbness, constipation and anxiety. Self injury occurred before and during stu
aripiprazole versus placebo during treatment, respectively. Limitations to this study include a small sample pc
(Nickel et al, 2006).

Change in scores over 8 weeks on 9 scales of the symptom check list, HAM-D, HAM-A and STAXI in pa
taking aripiprazole or placebo

Variable	Som SCL-90-R	OCD SCL-90-R	ISC SCL-90
Baseline	Mean/(SD)		
ARI-G	69.5 (9.1)	60.1 (6.4)	68.2 (6.9)
PL-G	68.8 (8.7)	58.3 (7.5)	67.3 (5.7)
Outcome	Mean/(SD)		
ARI-G	62.5 (7.3)	55.2 (4.3)	59.7 (5.3)
PL-G	65.4 (8.9)	58.6 (7.9)	64.2 (6.2)
difference in change in score between groups	95% CI -8.2 to 1	95% CI -8 to -2.4	95% CI -8 to -2.8
	p=0.15	p=0.01	p less than 0.001
KEY: Som = somatization; OCD = obsessiveness/compulsiveness; ISC = insecurity in social contacts; D AGG/HOS = aggression/hostility; PHOB/ANX = phobic anxiety; PAR = paranoid thinking; PSYCH = psy Rating Scale; HAM-D = Hamilton Depression Rating Scale; STAXI = State-Trait Anger Expression Inve placebo group; (SD) = standard deviation; CI = confidence interval.			

Change in scores over 8 weeks on 9 scales of the symptom check list, HAM-D, HAM-A and STAXI in pa
taking aripiprazole or placebo, continued

Variable	ANX SCL-90-R	AGG/HOS SCL-90-R	PHOB/ANX S
Baseline	Mean/(SD)		
ARI-G	72.3 (6.4)	78.6 (4.4)	72.1 (7.6)
PL-G	74.1 (5.9)	77.9 (3.9)	70.4 (8.3)
Outcome	Mean/(SD)		
ARI-G	61.1 (5.2)	64.6 (6.8)	61.4 (7.4)
PL-G	70.2 (7.3)	73.1 (7.8)	67.1 (9.5)
difference in change in score between groups	95% CI -9.9 to -4.7	95% CI -11.7 to -6.7	95% CI -10.9 to -3.9
	p less than 0.001	p less than 0.001	p less than 0.001
KEY: Som = somatization; OCD = obsessiveness/compulsiveness; ISC = insecurity in social contacts; D = aggression/hostility; PHOB/ANX = phobic anxiety; PAR = paranoid thinking; PSYCH = psychoticism; I HAM-D = Hamilton Depression Rating Scale; STAXI = State-Trait Anger Expression Inventory; ARI-G = (SD) = standard deviation; CI = confidence interval.			

Change in scores over 8 weeks on 9 scales of the symptom check list, HAM-D, HAM-A and STAXI in pa
taking aripiprazole or placebo, continued

Variable	PSYCH SCL-90-R	HAM-D	HAM-A
Baseline	Mean/(SD)		
ARI-G	60.5 (7.6)	20.3 (4.4)	23.3 (4.1)
PL-G	62.6 (7.9)	20.9 (3.9)	22.8 (5.3)
Outcome	Mean/(SD)		
ARI-G	54.3 (3.5)	13.9 (2.8)	16.3 (3.5)
PL-G	60.5 (6.2)	18.8 (4.7)	19.5 (5)
difference in change in score between groups	95% CI -6.9 to -1.3	95% CI -6.5 to -2.1	95% CI -6.2 to -1.2
	p=0.02	p=0.002	p=0.007
KEY: Som = somatization; OCD = obsessiveness/compulsiveness; ISC = insecurity in social contacts; D = aggression/hostility; PHOB/ANX = phobic anxiety; PAR = paranoid thinking; PSYCH = psychoticism; I HAM-D = Hamilton Depression Rating Scale; STAXI = State-Trait Anger Expression Inventory; ARI-G = (SD) = standard deviation; CI = confidence interval.			

change in scores over 8 weeks on 9 scales of the symptom check list, HAM-D, HAM-A and STAXI in pat
taking aripiprazole or placebo, continued

Variable	Trait Anger	Anger In	Anger Out
Baseline	Mean/(SD)		
ARI-G	30.5 (6.4)	24.5 (4.2)	25 (5.7)
PL-G	29.9 (5.8)	25.2 (4.8)	26.1 (5.5)
Outcome	Mean/(SD)		

ARI-G	18.1 (3)	16.3 (2.5)	14.3 (2.6)
PL-G	24 (4.7)	20.5 (3.3)	20.7 (4.1)
difference in change in score between groups	95% CI -9.3 to -3.7	95% CI -5.6 to -1.4	95% CI -7.8 to -2.8
	p less than 0.001	p=0.002	p less than 0.001
KEY: Som = somatization; OCD = obsessiveness/compulsiveness; ISC = insecurity in social contacts; D = aggression/hostility; PHOB/ANX = phobic anxiety; PAR = paranoid thinking; PSYCH = psychoticism; I HAM-D = Hamilton Depression Rating Scale; STAXI = State-Trait Anger Expression Inventory; ARI-G = (SD) = standard deviation; CI = confidence interval.			

1) Aripiprazole continued to demonstrate superior efficacy in the treatment of multiple markers of borde follow up, open-label, observational study (n=52). After final evaluation at 8 weeks in the previous study, discontinued (ex-placebo) and patients in the aripiprazole group continued 15 milligrams daily. The prima checklist (SCL-90-R), Hamilton Anxiety Rating Scale (HAM-A), Hamilton Depression Rating Scale (HAM at 18 months. Aripiprazole continued to demonstrate significantly superior efficacy compared with ex-pla HAM-A and HAM-D as indicated in the table. Self injury occurred in both groups during the 18 months of aripiprazole and ex-placebo, respectively. Two patients in the ex-placebo group attempted suicide. Both numbness, restlessness, constipation and anxiety (Nickel et al, 2007).

Changes in all scales of the symptom check list (SCL-90-R) HAM-D, HAM-A, and STAXI at 18 mont

Marker	ARI-G	
SCL-90-R, somatization	59 +/- 5.1	
SCL-90-R, obsessive/compulsiveness	53.1 +/- 6.9	
SCL-90-R, insecurity in social contact	57.2 +/- 7.3	
SCL-90-R, depression	45 +/-5.6	
SCL-90-R, anxiety	58 +/- 5.9	
SCL-90-R, hostility/aggression	61.7 +/- 3.4	
SCL-90-R, phobic anxiety	60 +/- 3.3	
SCL-90-R, paranoid thinking	58.8 +/- 3.6	
SCL-90-R, psychoticism	52.5 +/- 5.5	
HAM-A	13.9 +/- 3.1	
HAM-D	12 +/- 2.6	
STAXI	all scales	
KEY: < = less than; ARI-G = aripiprazole group; (SCL-90-R) = symptom checklist 90-R, (HAM-A) = Hamilton Depression Rating Scale; (STAXI) = State-Trait Anger Expression Inventory; p provided is		

2) An open-label study revealed addition of aripiprazole may be beneficial for patients with borderline pe sertraline treatment (n=21). Adult outpatients, (18 to 50 years of age) diagnosed with borderline persona respond to 12 weeks of sertraline 100 to 200 milligrams (mg) daily received aripiprazole 10 mg (initial do remained constant, for 12 weeks. Patients were considered responders if the Clinical Global Impression much improved or much improved) and a decrease of the Brief Psychiatric Rating Scale (BPRS) score w

to-treat analysis at week 12 revealed a statistically significant improvement in the responders (n=16) in n (p=0.018) and 34.63 +/- 3.89 (p=0.005), respectively. Statistically significant secondary outcomes that er Borderline Personality Disorder Severity Index (BPDSI) for impulsivity 5.66 +/- 1.18 (p=0.011), BPDSI fo 1.28 (p=0.036) and Barratt Impulsiveness Scale (BIS-11) 64.88 +/- 7.53 (p=0.017). However, no significa Rating Scale (HAM-D), the Hamilton Anxiety Rating Scale (HAM-A), Social Occupational Functioning As BPDSI. The most common adverse effects were headache (37.5%), insomnia and anxiety (25%). Limitat population size and short duration of treatment (Bellino et al, 2008).

4.5.E Dementia

See Drug Consult reference: BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

4.5.F Major depressive disorder, Adjunctive treatment in patients also receiving antidepressants

FDA Labeled Indication

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Aripiprazole is indicated for use as an adjunctive treatment to antidepressants for major depressive diso solution, IM injection, DISCMELT(TM) orally disintegrating tablets, 2007).
In two 6-week, placebo-controlled trials (n=743), treatment with aripiprazole was superior to placebo in re major depressive disorder (MDD) and an inadequate response to prior antidepressant therapies; additio patient functioning with aripiprazole compared to placebo (Prod Info ABILIFY(R) oral tablets, oral solutio disintegrating tablets, 2007).

3) Adult:

a) In two 6-week, placebo-controlled trials (n=381, n=362), treatment with aripiprazole was superior to placel patients with major depressive disorder (MDD) and an inadequate response to prior antidepressant therapy; improved patient functioning with aripiprazole compared to placebo. Patients with DSM-IV criteria for MDD, a 50% patient-perceived improvement after 6 weeks or greater of antidepressant therapy at or above the minim antidepressant therapies in the current depressive episode, and an inadequate response (defined as less tha the Hamilton Depression Rating Scale (HAMD17), a minimal HAMD17 score of 14, and a Clinical Global Imp minimal improvement) to 8 weeks of prospective antidepressant therapy were eligible. Prior therapies include extended-release, fluoxetine, escitalopram, or sertraline. Patients initially received oral aripiprazole 5 milligrar therapy. The aripiprazole dose was adjusted by 5 mg/day in 1-week intervals based on patient tolerability and (patients on potent CYP2D6 inhibitors (eg, fluoxetine, paroxetine)) or 2 to 20 mg/day (patients not on potent C aripiprazole doses were 10.7 and 11.4 mg/day in the two studies. Response to therapy was determined using Asberg Depression Rating Scale (MADRS), which assessed depressive symptoms and the 3-item, patient-ra assessed the impact of depression on work/school, social life, and family life functioning (0=not at all to 10=e aripiprazole was found to be superior in reducing mean MADRS total scores in both studies and in reducing r smaller mean reduction in total MADRS scores was observed in males compared to females; otherwise, resp prospective antidepressant choice, or race (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, DISC 2007).

4.5.G Psychomotor agitation - Schizophrenia

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes (injectable only); Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Aripiprazole injection is approved for the treatment of agitation associated with schizophrenia and bipolar (R) oral tablets, oral solution, IM injection, DISCMELT(TM) orally disintegrating tablets, 2007a).
A double-blind, placebo-controlled study demonstrated that intramuscular aripiprazole was noninferior to placebo in voluntarily hospitalized agitated patients with schizophrenia or schizoaffective disorder (Andre In placebo-controlled trials, intramuscular aripiprazole was statistically superior to placebo in improving s schizophrenia (Tran-Johnson et al, 2007; Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, DI 2007a).

3) Adult:

a) Aripiprazole was more effective than placebo for the acute treatment of agitation in patients with schizoph schizophreniform disorder in a dose-ranging, multicenter, randomized, double-blind clinical trial. Patients who Positive and Negative Syndrome Scale (PANSS)-Excited Component (PEC) scores of 15 to 32, and a score 5 PEC items (excitement, hostility, tension, uncooperativeness, and poor impulse control; scores range from receive one of 4 aripiprazole doses (1 milligram (mg) (n=57), 5.25 mg (n=63), 9.75 mg (n=57), or 15 mg (n=5 (n=62). All doses were administered intramuscularly within 1 hour of baseline assessment and repeated up to

but no more than 20 hours could elapse between the first and third doses. In the placebo arm, aripiprazole 15
required. A rescue benzodiazepine, such as lorazepam, was permitted only at least 60 minutes after the seco
antipsychotic medications were discontinued prior to the study. The primary endpoint was the mean change f
one dose of aripiprazole compared to placebo, with a p-value of 0.0167 indicating a statistically significant dif
score at 2 hours was noted between each dose of aripiprazole, except the 1-mg group, and haloperidol comp
versus placebo). Significant differences were observed as early as 45 minutes in the aripiprazole 9.75-mg gro
The PEC response (defined as at least a 40% reduction in the mean PEC score from baseline to 2 hours) for
the haloperidol group ($p < 0.05$). The secondary endpoint of the Agitation-Calmness Evaluation Scale (ACES
compared to placebo for the 9.75-mg aripiprazole group ($p < 0.01$) and the haloperidol group ($p < 0.01$). Addi
Agitated Behavior Scale (CABS) score, the Clinical Global Impressions-Severity of Illness (CGI-S) score, the
(CGI-I) score, and the Brief Psychiatric Rating Scale (BPRS) total score were significantly improved at 2 hour
aripiprazole groups and the haloperidol group. Only the CGI-I score was significantly improved in the 1-mg ar
were observed for the mean change in BPRS-positive scores after 2 hours in any group compared to placebo
the placebo group compared to the aripiprazole 5.25-mg to 15-mg groups and the haloperidol group ($p < 0.05$
adverse events in the aripiprazole groups were headache (13%), dizziness (10%), somnolence (7%), and na
of patients in the aripiprazole groups, 10.5% of patients in the haloperidol group, and no patients in the placel
1.8% of the aripiprazole groups, 7% of the haloperidol group, and 0% of the placebo group (Tran-Johnson et

b) A double-blind, placebo-controlled study demonstrated that intramuscular aripiprazole was noninferior to i
placebo in voluntarily hospitalized, agitated patients with schizophrenia or schizoaffective disorder as measur
excited components from the Positive and Negative Syndrome Scale (PANSS)) to 2 hours after the first injec
cooperation, excitement, poor impulse control, and tension on a scale of 1 (absent) to 7 (extreme). Patients w
9.75 mg intramuscularly (IM) (n=175), haloperidol 6.5 mg IM (n=185), or placebo (n=88). The noninferiority m
score was 2.5. Patients could receive up to three IM injections spaced at least 2 hours apart. Analysis of the
improvement in PEC score at 2 hours from baseline of -7.27 aripiprazole group, -7.75 haloperidol group, and
after the first injection the percentage of patients achieving a clinical response (defined as a reduction in PEC
achieved by 55% aripiprazole group, 58% haloperidol group, and 36% in the placebo group (p less than 0.00
occurred in 41% aripiprazole patients (n=70), 34% haloperidol patients (n=62), and 57% in placebo (n=50), w
second dose of -5.92, -6.73 and -2.16 (p less than 0.001 vs placebo), respectively. The most frequently repor
(n=175) was headache (7.4%), dizziness (6.3%), nausea (5.7%) and insomnia (5.7%), and in the haloperidol
headache (8.2%), and extrapyramidal disorder (5.5%) (Andrezina et al, 2006).

c) In two short-term (24-hour), placebo-controlled trials, intramuscular aripiprazole was statistically superior t
in patients with schizophrenia (using the Positive and Negative Syndrome Scale [PANSS] Excited Componer
Improvement [CGI-I] scale scores). Both trials included a single active comparator treatment arm of haloperic
meeting DSM-IV criteria for schizophrenia received up to 3 injections during the 24-hour treatment period, wit
initial 2-hour period, when the primary efficacy measure was evaluated. All enrolled patients were judged by t
and clinically appropriate candidates for treatment with intramuscular medication. Additionally, all patients exl
exceeded a threshold score of 14 or greater on the five items comprising the PANSS Excited Component (eg
uncooperativeness and excitement items) with at least 2 individual item scores of 4 or greater using a 1 to 7 s
7=extreme). In both studies, the baseline PANSS Excited Component score ranged from 15 to 24 (out of a m
score of 19; this suggested mainly moderate levels of agitation with some patients experiencing mild or sever
measure in both trials was the change in the PANSS Excited Component from baseline to 2 hours post-inject
measure. In the first study (n=350), four fixed aripiprazole injection doses of 1 milligram (mg), 5.25 mg, 9.75 r
2-hour period, the 5.25 mg, 9.75 mg, and 15 mg doses were statistically superior to placebo in the PANSS Ex
the second study (n=445), one fixed aripiprazole injection dose of 9.75 mg was evaluated. After the initial 2-h
statistically superior to placebo in the PANSS Excited Component and on the CGI-I scale (Prod Info ABILIFY
DISCMELT(TM) orally disintegrating tablets, 2007a)

4.5.H Schizophrenia

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; Pediatric, yes (13 to 17 years old)
Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Aripiprazole is indicated for the treatment of schizophrenia in adults and pediatric patients 13 to 17 years
solution, IM injection, DISCMELT(TM) orally disintegrating tablets, 2007a).
Aripiprazole has been more effective than placebo in treating adult patients with acutely relapsed schizo
improve cognitive function in some patients (Petrie et al, 1998a; Saha et al, 1999b).
Longer time to relapse was seen in adult patients with schizophrenia treated with aripiprazole therapy (A
Treatment with oral aripiprazole, at doses of 10 or 30 milligrams per day for 6 weeks, was superior to pla
adolescents 13 to 17 years of age (Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, DISCME

3) Adult:

a) General Information

1) Relatively large double-blind, placebo-controlled studies (unpublished) have indicated the efficacy of
in patients with acute relapse of schizophrenia or schizoaffective disorder (Petrie et al, 1998a; Kane et al
optimal dose appears to be 10 or 15 mg once daily; additional clinical benefit has not usually been obser

oral tablets, disintegrating tablets, solution, 2006). These studies indicated significant improvement relati
Syndrome Scale (PANSS)-total, PANSS-positive, PANSS-negative, Clinical Global Improvement (CGI)-s
(BPRS) scores. The drug demonstrated a low propensity for extrapyramidal symptoms. All studies have
extended open treatment phase was instituted in one study (Petrie et al, 1998a), although results were n

b) Clinical Trials

1) Aripiprazole therapy was effective in the prevention of relapse in patients with chronic, stable schizop
blind, placebo-controlled study, patients (n=310) with at least a 2-year history of schizophrenia and stabl
received oral aripiprazole (15 milligrams daily) or placebo for 26 weeks. Time to relapse after randomizat
treated patients as compared with patients who received placebo (p less than 0.001). Additionally, a high
relapsed as compared with those in the aripiprazole group (57% vs 33.8%, respectively). The relative ris
versus placebo was 0.59 (95% confidence interval, 0.45 to 0.75; p less than 0.001). Mean changes from
greater with aripiprazole therapy as compared with placebo for the Positive and Negative Syndrome Sca
subscale score, PANSS-derived Brief Psychiatric Rating Scale (BPRS) core score, Clinical Global Impre
or equal to 0.01, all values), and CGI-Severity score (p less than or equal to 0.05). Insomnia, tremor, aka
frequently reported adverse events with aripiprazole therapy (Pigott et al, 2003)(Anon, 2003).

2) In a placebo-controlled, phase III study involving relapsed schizophrenic or schizoaffective patients (r
haloperidol 10 mg daily (fixed doses) were each statistically superior to placebo with regard to changes i
on responder analysis (a 30% reduction in PANSS-total scores from baseline at last visit), each dose of a
than placebo, whereas haloperidol was not. There was evidence of better tolerability with aripiprazole co
requirements for extrapyramidal effects, prolactin increases, weight increase). Extrapyramidal symptoms
placebo, and fewer patients receiving aripiprazole discontinued treatment due to adverse events compar
2000). However, this study did not report statistical comparisons of aripiprazole and haloperidol for any p
effects); responder-analysis data revealed only a small difference between the two drugs. Overall, this st
aripiprazole is significantly more efficacious than haloperidol.

3) Some improvement in neurocognitive function (eg, verbal learning, executive functioning, vigilance) w
mg daily) in a randomized study (n=256); the drug tended to be superior to olanzapine (Kern et al, 2001a

4) Pediatric:

a) In a 6-week, placebo-controlled trial in adolescents 13 to 17 years of age, oral aripiprazole at doses of 10
placebo in the treatment of schizophrenia. Study patients (n=302) were outpatients who met the Diagnostic a
edition) criteria for schizophrenia and had a baseline Positive and Negative Syndrome Scale (PANSS) score
fixed daily doses of aripiprazole 10 mg, aripiprazole 30 mg, or placebo. Aripiprazole was initiated at 2 mg/day
and 11 days for the 10-mg and 30-mg groups, respectively. The mean improvement in PANSS total score fro
superior in both aripiprazole groups compared to placebo. The 30 mg/day dose was not found to be more effi
most common treatment-related adverse events with a possible dose-response relationship were extrapyram
21.6%; placebo, 5%); somnolence (incidence: 10 mg, 11%; 30 mg, 21.6%; placebo, 6%); and tremor (incider
(Prod Info ABILIFY(R) oral tablets, oral solution, IM injection, DISCMELT(TM) orally disintegrating tablets, 20

4.6 Comparative Efficacy / Evaluation With Other Therapies

Chlorpromazine

Haloperidol

Olanzapine

Perphenazine

4.6.A Chlorpromazine

4.6.A.1 Schizophrenia

a) Based upon comparisons of minimum effective dosages identified in placebo- controlled, fixed-dose and f
minimum effective dose of aripiprazole was 15 milligrams/day (equivalent to chlorpromazine 200 milligrams/d

4.6.B Haloperidol

4.6.B.1 Schizophrenia

a) SUMMARY: Aripiprazole (up to 30 mg daily) and haloperidol (up to 20 mg daily) appear similarly effective
schizophrenia or schizoaffective disorder; adverse effects may be less with aripiprazole.

b) Haloperidol 5 to 20 mg daily, but not aripiprazole (5 to 30 mg daily), was superior to placebo with respect
study involving acutely relapsed inpatients with DSM-III/IV schizophrenia (n=103). Both haloperidol and aripip
responder analysis based on CGI-severity scores (Prod Info Abilify(TM), 2002).

c) In a placebo-controlled, phase III study involving relapsed schizophrenic or schizoaffective patients (n=41
haloperidol 10 mg daily (fixed doses) were each statistically superior to placebo with regard to changes in PA
responder analysis (a 30% reduction in PANSS-total scores from baseline at last visit), each dose of aripipraz

placebo, whereas haloperidol was not. There was evidence of better tolerability with aripiprazole compared to extrapyramidal effects, prolactin increases, weight increase). Extrapyramidal symptoms were reportedly simil patients receiving aripiprazole discontinued treatment due to adverse events compared to haloperidol and pla did not report statistical comparisons of aripiprazole and haloperidol for any parameter (efficacy versus basel data revealed only a small difference between the two drugs. Overall, this study does not provide evidence th than haloperidol.

d) Results of phase II studies also suggested fewer adverse effects with aripiprazole compared to haloperido studies, lower changes from baseline in Simpson-Angus Scale scores (parkinsonian symptoms) and less req all doses of aripiprazole (2, 10, or 30 mg daily) than with haloperidol 10 mg daily; prolactin levels were not inc significant increases with haloperidol, and significantly less weight gain was evident in the aripiprazole groups not presented.

4.6.C Olanzapine

4.6.C.1 Schizophrenia

a) A trend toward greater improvement in some areas of neurocognitive function (eg, verbal learning, workin mg daily compared to olanzapine 15 mg daily in a randomized study (n=256) (Kern et al, 2001). However, a p study are unavailable (unpublished).

4.6.D Perphenazine

4.6.D.1 Schizophrenia, Treatment resistant

a) Both aripiprazole and perphenazine improved symptoms associated with treatment-resistant schizophreni study. Patients (n=416) with treatment-resistant schizophrenia (ie, failure of at least 2 trials of antipsychotic th last 2 years) with a Positive and Negative Syndrome Scale (PANSS) total score of at least a 75, a score grea of conceptual disorganization, suspiciousness, hallucinatory behavior, or delusions, and a Clinical Global Imp or greater. After a 2-day washout period, patients entered a 4 to 6 week open-label treatment phase receiving or risperidone 2 to 8 mg/day to confirm treatment resistance. At the end of this open-label screening period, 3 washout period then were randomized to 6 weeks of treatment with aripiprazole 15 to 30 mg/day or perphena was mean change in PANSS score during the 6-week double-blind treatment period. In the aripiprazole group 9.8 points (95% confidence interval (CI), -13.2 to -6.3) from a mean total baseline score of 97.5 (95% CI, 95 t decrease in PANSS total score was 10.5 points (95% CI, -14 to -7) from a mean total baseline score of 99.5 (groups was not statistically significant (p-value not reported). At the end of 6 weeks, 27% (40/150) of patients of patients responded to perphenazine treatment, with response defined as at least a 30% decrease in PANS Extrapyramidal symptoms were reported in 13.7% (n=21) of patients in the aripiprazole group and 19.4% (n= Serious adverse events were reported in 21% (n=32) and 17% (n=24) of patients treated with aripiprazole an common being psychosis (9.8% and 6.3%, respectively) (Kane et al, 2007).

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DRUGDEX® Evaluations

AMPHETAMINE/DEXTROAMPHETAMINE

0.0 Overview

1) Class
- **a)** This drug is a member of the following class(es):
  Central Nervous System Agent
  CNS Stimulant

2) Dosing Information
- **a)** Adult
  - **1)** Attention deficit hyperactivity disorder
    - **a)** extended-release, 20 mg ORALLY daily (Prod Info ADDERALL XR(R) extended-release oral capsules, 20
  - **2)** Narcolepsy
    - **a)** immediate-release, 5 to 60 mg/day ORALLY in divided doses (Prod Info ADDERALL(R) oral tablets, 2006
- **b)** Pediatric
  - **1)** (immediate-release) not FDA approved in children under 3 years of age with attention deficit hyperactivity diso 2006)
  - **2)** (extended-release) not FDA approved in children under 6 years of age with attention deficit hyperactivity disor release oral capsules, 2006)
    - **a)** Attention deficit hyperactivity disorder
      - **1)** immediate release (age 3 to 5 yr), initial 2.5 mg ORALLY every morning; may increase daily dose in 2 optimal response (Prod Info ADDERALL(R) oral tablets, 2006)
      - **2)** immediate release (age 6 yr and older), initial 5 mg ORALLY once or twice daily; may increase daily d optimal response; give first dose in the morning and subsequent doses at 4 to 6 hour intervals; MAX 40 m 2006)
      - **3)** extended release (6 to 12 yr), initial 10 mg ORALLY every morning (alternatively, 5 mg/day if appropr increments at weekly intervals until optimal response; MAX 30 mg/day (Prod Info ADDERALL XR(R) ext
      - **4)** extended release (13 to 17 yr), initial 10 mg ORALLY every morning; may increase to 20 mg/day afte extended-release oral capsules, 2006)
    - **b)** Narcolepsy
      - **1)** immediate release (age 6 to 12 yr) initial, 5 mg ORALLY once daily; may increase daily dose in 5 mg response (Prod Info ADDERALL(R) oral tablets, 2006)
      - **2)** immediate release (age 12 yr and older) initial, 10 mg ORALLY once daily; may increase daily dose in optimal response (Prod Info ADDERALL(R) oral tablets, 2006)

3) Contraindications
- **a)** advanced arteriosclerosis (Prod Info ADDERALL(R) oral tablets, 2006)
- **b)** agitated states; may aggravate symptoms (Prod Info ADDERALL(R) oral tablets, 2006)
- **c)** cardiovascular disease, symptomatic (Prod Info ADDERALL(R) oral tablets, 2006)
- **d)** concomitant use of monoamine oxidase inhibitors (MAOI), or within 14 days of MAOI use; hypertensive crisis may 2006)
- **e)** drug dependence, history of; potential for abuse (Prod Info ADDERALL(R) oral tablets, 2006)
- **f)** glaucoma (Prod Info ADDERALL(R) oral tablets, 2006)
- **g)** hypersensitivity/idiosyncrasy to sympathomimetic amines (Prod Info ADDERALL(R) oral tablets, 2006)
- **h)** hypertension, moderate to severe (Prod Info ADDERALL(R) oral tablets, 2006)
- **i)** hyperthyroidism (Prod Info ADDERALL(R) oral tablets, 2006)

4) Serious Adverse Effects
- **a)** Cardiomyopathy
- **b)** Cerebrovascular accident
- **c)** Dead - sudden death
- **d)** Mania
- **e)** Myocardial infarction
- **f)** Psychotic disorder
- **g)** Seizure

5) Clinical Applications
- **a)** FDA Approved Indications
  - **1)** Attention deficit hyperactivity disorder
  - **2)** Narcolepsy

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

1.2 Storage and Stability
A) Preparation
1) Oral
a) Give first dose (immediate-release) on awakening, and additional doses at 4 to 6-hour intervals. Avoid late
Info ADDERALL(R) oral tablets, 2006; Prod Info ADDERALL(R) XR extended release oral capsule, 2005).
b) Extended-release capsules may be swallowed whole with or without food. The entire capsule contents ma
immediately; the applesauce with sprinkled beads should be consumed in its entirety without chewing. Do no
ADDERALL(R) XR extended release oral capsule, 2005).

1.3 Adult Dosage

1.3.1 Normal Dosage

1.3.1.A Oral route

Attention deficit hyperactivity disorder

Narcolepsy

1.3.1.A.1 Attention deficit hyperactivity disorder
a) Extended-Release
1) The recommended initial dose for patients with attention deficit hyperactivity disorder is 20 milligr
extended-release oral capsules, 2006).

1.3.1.A.2 Narcolepsy
a) The recommended dose of immediate-release tablets is 5 to 60 milligrams/day ORALLY in divided do
2006).

1.4 Pediatric Dosage

1.4.1 Normal Dosage

1.4.1.A Oral route

Attention deficit hyperactivity disorder

Narcolepsy

1.4.1.A.1 Attention deficit hyperactivity disorder
a) Immediate-Release
1) For children aged 3 to 5 years, the recommended initial dose of immediate-release tablets is 2.5
be increased in 2.5-mg increments at weekly intervals until optimal response (Prod Info ADDERALL
2) For children aged 6 years and older, the recommended initial dose of immediate-release is 5 mill
increase in 5-mg increments at weekly intervals until optimal response, up to 40 mg/day. Give first d
to 6 hour intervals (Prod Info ADDERALL(R) oral tablets, 2006).
b) Extended-Release
1) For children 6 years of age and older, the starting dose of extended-release amphetamine/dextro
in the morning. Doses may be increased by 10 mg at weekly intervals to a MAXIMUM dose of 30 mg
XR(R) extended-release oral capsules, 2006).
2) For patients using immediate-release tablets, they should be switched to the same total daily dos
taken once daily in the morning (Prod Info Adderall XR(TM), 2001).

1.4.1.A.2 Narcolepsy
a) Immediate-Release

1) For children aged 6 to 12 years, the recommended initial dose of immediate-release tablets is 5 r
be increased in 5-mg increments at weekly intervals until optimal response (Prod Info ADDERALL(F
2) For children aged 12 years and older, the recommended initial dose of immediate-release tablet
dose increase in 10-mg increments at weekly intervals until optimal response. Take first dose on aw
intervals (Prod Info ADDERALL(R) oral tablets, 2006).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING

1) Oral (Tablet; Capsule, Extended Release)

a) Amphetamines have a high potential for abuse. Administration of amphetamines for prolonged periods of time
avoided. Particular attention should be paid to the possibility of subjects obtaining amphetamines for non-therape
should be prescribed or dispensed sparingly.

b) Misuse of amphetamine may cause sudden death and serious cardiovascular adverse events (Prod Info ADDI

3.1 Contraindications

A) advanced arteriosclerosis (Prod Info ADDERALL(R) oral tablets, 2006)
B) agitated states; may aggravate symptoms (Prod Info ADDERALL(R) oral tablets, 2006)
C) cardiovascular disease, symptomatic (Prod Info ADDERALL(R) oral tablets, 2006)
D) concomitant use of monoamine oxidase inhibitors (MAOI), or within 14 days of MAOI use; hypertensive crisis may
2006)
E) drug dependence, history of; potential for abuse (Prod Info ADDERALL(R) oral tablets, 2006)
F) glaucoma (Prod Info ADDERALL(R) oral tablets, 2006)
G) hypersensitivity/idiosyncrasy to sympathomimetic amines (Prod Info ADDERALL(R) oral tablets, 2006)
H) hypertension, moderate to severe (Prod Info ADDERALL(R) oral tablets, 2006)
I) hyperthyroidism (Prod Info ADDERALL(R) oral tablets, 2006)

3.2 Precautions

A) amphetamine misuse; may cause sudden death and serious cardiovascular events (Prod Info ADDERALL(R) oral
B) drug dependence, history of; potential for abuse (Prod Info ADDERALL(R) oral tablets, 2006)
C) bipolar disorder, comorbid; may precipitate a mixed/manic episode (Prod Info ADDERALL(R) oral tablets, 2006)
D) cardiovascular conditions which may be compromised by increases in blood pressure or heart rate (e.g., pre-existi
infarction, or ventricular arrhythmia) (Prod Info ADDERALL(R) oral tablets, 2006)
E) EEG abnormalities, especially with history of; may lower convulsive threshold (Prod Info ADDERALL(R) oral tablet
F) psychosis, pre-existing; may exacerbate symptoms of behavior disturbance and thought disorder (Prod Info ADDE
G) seizures, especially with a history of; may lower convulsive threshold (Prod Info ADDERALL(R) oral tablets, 2006)
H) structural cardiac abnormalities/conditions, serious, especially in children and adolescents; sudden death has beer
Info ADDERALL(R) oral tablets, 2006)
I) tics, motor and phonic, history of; risk of exacerbation (Prod Info ADDERALL(R) oral tablets, 2006)
J) Tourette's syndrome, history of; risk of exacerbation (Prod Info ADDERALL(R) oral tablets, 2006)

3.3 Adverse Reactions

Cardiovascular Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Neurologic Effects

Psychiatric Effects

3.3.1 Cardiovascular Effects

Cardiomyopathy

Chest pain

Dead - sudden death

Hypertension

Myocardial infarction

Palpitations

Tachycardia

3.3.1.A Cardiomyopathy

1) Cardiomyopathy has been associated with chronic amphetamine use (Prod Info ADDERALL(R) oral capsı extended-release oral capsules, 2007).

3.3.1.B Chest pain

1) In a placebo controlled, 4-week, study of adults with ADHD, 0.5% of 191 patients discontinued Adderall XI symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac dise a prompt cardiac evaluation (Prod Info ADDERALL XR(R) extended-release oral capsules, 2007).

3.3.1.C Dead - sudden death

1) Incidence: rare

2) Children and Adolescents - With Preexisting Cardiac Risk

a) Sudden death has been reported in children and adolescents with structural cardiac abnormalities or medications at usual doses. Patients, including adults with serious structural or other cardiac abnormaliti abnormalities) should generally not be treated with stimulant medications. A cardiac evaluation (eg, elect performed in any patient experiencing exertional chest pain, unexplained syncope, or other symptoms in ADDERALL(R) oral capsules, 2007; Prod Info ADDERALL XR(R) extended-release oral capsules, 2007)

3) Children and Adolescents - Healthy

a) A retrospective, case-controlled study examines the association between stimulant medication, incluc combination drugs, and unexplained sudden death in healthy children and adolescents. In a collection of across the United States, 564 cases of sudden death in children and adolescents between the ages of 7 564 youngsters who died as passengers in motor vehicle accidents. The study determined that 1.8% (n= unexplained deaths were taking stimulant medication compared with only 0.4% (n=2) of youths in the mc 95% CI, 1.4 to 74.9; p=0.02). Limitations to this study included the time lag between the youths stimulant collected, family recall of information regarding clinical diagnoses, inconsistent postmortem inquiry, and t conditions. The authors stated that this finding should be considered when evaluating the overall risk and and adolescents (Gould et al, 2009). Given the limitations of this study, the U.S. Food and Drug Adminis benefits associated with stimulant medications (US Food and Drug Administration, 2009).

3.3.1.D Hypertension

1) Incidence: 7% to 22%, pediatric (Prod Info ADDERALL XR(R) extended-release oral capsules, 2007)

2) An average elevation of blood pressure of 2 to 4 mmHg has been reported following administration of Adc have larger increases. Larger increases in blood pressure should be monitored. Because stimulant medicatic with caution in patients with cardiac conditions which may be exacerbated by further blood pressure increase recent myocardial infarction, ventricular arrhythmia) (Prod Info ADDERALL(R) oral capsules, 2007; Prod Info capsules, 2007).

3) A 4-week controlled study was conducted in adolescents with ADHD. Isolated systolic blood pressure elev of patients in the Adderall XR treatment group compared to 11% of placebo-treated patients. Isolated diastoli were observed in 22% of patients in the Adderall XR treatment group compared to 25% of placebo-treated pa release oral capsules, 2007).

4) A single-dose study of 23 adolescents showed isolated increases in systolic blood pressure in patients tre patients treated with Adderall XR 20 mg (35%). All increases were transitory, appeared maximal at 2 to 4 hou (Prod Info ADDERALL XR(R) extended-release oral capsules, 2007).

3.3.1.E Myocardial infarction

1) Myocardial infarction has been reported in adults receiving amphetamine therapy at normal doses. Patien

other cardiac abnormalities (eg, cardiomyopathy, heart rhythm abnormalities) should generally not be treated (eg, electrocardiogram, echocardiogram) should be performed in any patient experiencing exertional chest pa indicative of cardiac disease (Prod Info ADDERALL(R) oral capsules, 2007; Prod Info ADDERALL XR(R) ext

3.3.1.F Palpitations

1) Palpitation has been associated with amphetamine use (Prod Info ADDERALL(R) oral capsules, 2007; Pr capsules, 2007).

3.3.1.G Tachycardia

1) Incidence: 6% (Prod Info ADDERALL XR(R) extended-release oral capsules, 2007)

2) Average heart rate increases of 3 to 6 bpm have been reported with stimulant medications. Patients shoul Because stimulant medications can cause increases in blood pressure, use with caution in patients with card further blood pressure increases (eg, preexisting hypertension, heart failure, recent myocardial infarction, ver (R) extended-release oral capsules, 2007).

3) Tachycardia has been reported in 6% of patients in the Adderall XR treatment group (n=191) compared to randomized, double-blind, placebo-controlled, parallel-group study conducted in adults with ADHD (Prod Info capsules, 2007). Tachycardia has been reported with Adderall also (Prod Info ADDERALL(R) oral capsules,

3.3.3 Endocrine/Metabolic Effects

3.3.3.A Weight loss

1) Incidence: 4% to 9%, pediatric; 11%, adults (Prod Info ADDERALL XR(R) extended-release oral capsules

2) Weight loss has occurred in 4% of pediatric patients in the Adderall XR treatment group (n=374) compare in a randomized, double-blind, placebo-controlled, parallel-group study conducted in children ages 6 to 12 wi extended-release oral capsules, 2007).

3) Weight loss has occurred in 9% of patients in the Adderall XR treatment group (n=233) compared to 0% c randomized, double-blind, placebo-controlled, multicenter, parallel-group study conducted in adolescents age XR(R) extended-release oral capsules, 2007).

4) Weight loss has occurred in 11% of patients in the Adderall XR treatment group (n=191) compared to 0% randomized, double-blind, placebo-controlled, parallel-group study conducted in adults with ADHD (Prod Info capsules, 2007).

3.3.4 Gastrointestinal Effects

Abdominal pain

Loss of appetite

Xerostomia

3.3.4.A Abdominal pain

1) Incidence: 11% to 14%, pediatrics (Prod Info ADDERALL XR(R) extended-release oral capsules, 2007)

2) Abdominal pain has occurred in 14% of pediatric patients in the Adderall XR treatment group (n=374) com (n=210) in a randomized, double-blind, placebo-controlled, parallel-group study conducted in children ages 6 extended-release oral capsules, 2007).

3) Abdominal pain has been reported in 11% of patients in the Adderall XR treatment group (n=233) compar in a randomized, double-blind, placebo-controlled, multicenter, parallel-group study conducted in adolescents ADDERALL XR(R) extended-release oral capsules, 2007).

3.3.4.B Loss of appetite

1) Incidence: 22% to 36% (Prod Info ADDERALL XR(R) extended-release oral capsules, 2007)

2) Loss of appetite has been reported in 22% (n=374) of pediatric patients in the Adderall XR treatment grou placebo group (n=210) in a randomized, double-blind, placebo-controlled, parallel-group study conducted in ADDERALL XR(R) extended-release oral capsules, 2007).

3) Loss of appetite has been reported in 36% of patients in the Adderall XR treatment group (n=233) compa in a randomized, double-blind, placebo-controlled, multicenter, parallel-group study conducted in adolescents ADDERALL XR(R) extended-release oral capsules, 2007).

4) Loss of appetite has been reported in 33% of patients in the Adderall XR treatment group (n=191) compa in a randomized, double-blind, placebo-controlled, parallel-group study conducted in adults with ADHD (Prod capsules, 2007).

3.3.4.C Xerostomia

1) Incidence: 35% (Prod Info ADDERALL XR(R) extended-release oral capsules, 2007)

2) Aptyalism has been reported in 35% of patients in the Adderall XR treatment group (n=191) compared to randomized, double-blind, placebo-controlled, parallel-group study conducted in adults with ADHD (Prod Info

capsules, 2007).

3.3.9 Neurologic Effects

Central nervous system stimulation, Overstimulation

Cerebrovascular accident

Gilles de la Tourette's syndrome

Headache

Insomnia

Seizure

Tic

Tremor

3.3.9.A Central nervous system stimulation, Overstimulation

1) Overstimulation has been associated with amphetamine use (Prod Info ADDERALL(R) oral capsules, 200 release oral capsules, 2007).

3.3.9.B Cerebrovascular accident

1) Cerebrovascular accident has been associated with amphetamine use (Prod Info ADDERALL(R) oral cap extended-release oral capsules, 2007).

3.3.9.C Gilles de la Tourette's syndrome

1) Summary

a) Exacerbation of Tourette's syndrome has been reported following administration of amphetamines (P Prod Info ADDERALL XR(R) extended-release oral capsules, 2007).

3.3.9.D Headache

1) Incidence: 26% (Prod Info ADDERALL XR(R) extended-release oral capsules, 2007)

2) Headache has been reported in 26% of patients in the Adderall XR treatment group (n=191) compared to randomized, double-blind, placebo-controlled, parallel-group study conducted in adults with ADHD (Prod Info capsules, 2007).

3.3.9.E Insomnia

1) Incidence: 12% to 17%, pediatric; 27%, adults (Prod Info ADDERALL XR(R) extended-release oral capsu

2) Insomnia occurred in 17% of pediatric patients in the Adderall XR treatment group (n=374) compared to 2 randomized, double-blind, placebo-controlled, parallel-group study conducted in children ages 6 to 12 with AI release oral capsules, 2007).

3) Insomnia occurred in 12% of patients in the Adderall XR treatment group (n=233) compared to 4% of pati randomized, double-blind, placebo-controlled, multicenter, parallel-group study conducted in adolescents age XR(R) extended-release oral capsules, 2007).

4) Insomnia was reported in 27% of patients in the Adderall XR treatment group (n=191) compared to 13% c randomized, double-blind, placebo-controlled, parallel-group study conducted in adults with ADHD (Prod Info capsules, 2007).

3.3.9.F Seizure

1) Some clinical evidence suggests patients with a history of seizures or EEG abnormalities may have a low XR should be discontinued if seizures are present (Prod Info ADDERALL(R) oral capsules, 2007; Prod Info A capsules, 2007).

3.3.9.G Tic

1) Exacerbation of motor and phonic tics has been reported following administration of amphetamines (Prod Info ADDERALL XR(R) extended-release oral capsules, 2007).

3.3.9.H Tremor

1) Tremors have been reported following administration of amphetamines (Prod Info ADDERALL(R) oral cap extended-release oral capsules, 2007).

3.3.12 Psychiatric Effects

Dysphoric mood

Euphoria

Feeling nervous

Mania

Psychotic disorder

Restlessness

3.3.12.A Dysphoric mood

1) Dysphoria has been associated with amphetamine use (Prod Info ADDERALL(R) oral capsules, 2007; Pro capsules, 2007).

3.3.12.B Euphoria

1) Euphoria has been associated with amphetamine use (Prod Info ADDERALL(R) oral capsules, 2007; Proc capsules, 2007).

3.3.12.C Feeling nervous

1) Incidence: 6% (Prod Info ADDERALL XR(R) extended-release oral capsules, 2007)

2) Nervousness has been reported in 6% of pediatric patients in the Adderall XR treatment group (n=374) co (n=210) in a randomized, double-blind, placebo-controlled, parallel-group study conducted in children ages 6 extended-release oral capsules, 2007).

3) Nervousness has been reported in 6% of patients in the Adderall XR treatment group (n=233) compared t a randomized, double-blind, placebo-controlled, multicenter, parallel-group study conducted in adolescents a XR(R) extended-release oral capsules, 2007).

3.3.12.D Mania

1) In a review of 49 randomized, controlled pediatric ADHD clinical trials involving pscyhostimulant medicatic hydrochloride, modafinil and dextromethylphenidate hydrochloride), the rate of psychosis/mania events in pe (95% CI, 0.74 to 2.65) per 100 person-years, with no comparable adverse events recorded in the placebo gro Administration to manufacturers of marketed ADHD drugs for submission of postmarketing case reports of ps 2005, yielded a total of 865 reports (pediatrics and adults) in which signs and/or symptoms of psychoses or n involved pediatric subjects, with almost half of the reports in children 10 years-old or younger, and approxima similar psychiatric conditions. Visual and/or tactile sensations of insects, snakes, or worms were commonly re each of the psychostimulant medications (methylphenidate hydrochloride, atomoxetine hydrochloride, and mi product) included in the analysis; and in many cases a strong temporal association was identified. The onset weeks, but in some cases it was months or years from the start of ADHD treatment and symptom onset (Mos

3.3.12.E Psychotic disorder

1) In a review of 49 randomized, controlled pediatric ADHD clinical trials involving pscyhostimulant medicatic hydrochloride, modafinil and dextromethylphenidate hydrochloride), the rate of psychosis/mania events in pe (95% CI, 0.74 to 2.65) per 100 person-years, with no comparable adverse events recorded in the placebo gro Administration to manufacturers of marketed ADHD drugs for submission of postmarketing case reports of ps 2005, yielded a total of 865 reports (pediatrics and adults) in which signs and/or symptoms of psychoses or n involved pediatric subjects, with almost half of the reports in children 10 years-old or younger, and approxima similar psychiatric conditions. Visual and/or tactile sensations of insects, snakes, or worms were commonly re each of the psychostimulant medications (methylphenidate hydrochloride, atomoxetine hydrochloride, and mi product) included in the analysis; and in many cases a strong temporal association was identified. The onset weeks, but in some cases it was months or years from the start of ADHD treatment and symptom onset (Mos

2) Psychotic or manic symptoms may occur among patients without prior history of psychosis, or may worse Chronic intoxication may result in severe psychosis, often similar to schizophrenia. Symptoms of psychosis o (4/3482) exposed to methylphenidate or amphetamine for several weeks at usual doses, in a pooled analysis studies (Prod Info ADDERALL XR(R) extended-release oral capsules, 2007).

3.3.12.F Restlessness

1) Restlessness has been associated with amphetamine use (Prod Info ADDERALL(R) oral capsules, 2007; oral capsules, 2007).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) Amphetamine

a) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info ADDERALL XR(R) oral

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

See Drug Consult reference: PREGNANCY RISK CATEGORIES

b) Crosses Placenta: Yes

c) Clinical Management

1) Because there is evidence of developmental and behavioral adverse effects in humans and animals f ADDERALL XR(R) oral capsules, 2007; Eriksson & Zetterstrom, 1994a; Levin, 1971a), amphetamines sl potential benefit to the mother outweighs the potential risk to the fetus (Prod Info ADDERALL XR(R) oral

d) Literature Reports

1) There are no adequate and well-controlled studies in pregnant women. There has been one report of esophageal fistula, and anal atresia (vater association) in a baby born following maternal exposure to de trimester of pregnancy. The risk of premature delivery and low birth weight is increased in infants born to infants may also experience symptoms of withdrawal as demonstrated by dysphoria, including agitation, XR(R) oral capsules, 2007). A statistically significant correlation between aggressive behavior and amph reported (Eriksson & Zetterstrom, 1994a).

2) Eleven infants were born with biliary atresia to mothers who had taken amphetamines in various dose development of a biliary tree). In a controlled group of 50 normal infants, it was noted that 3 of 50 mother

3) A large prospective, observational study of pregnancy and child development was undertaken relatec phenmetrazine) prescribed to gravid women during different stages of pregnancy and evaluated for their rate (SCA) per 100 live-born children at age 5 years did not differ from the SCA rate of the group of child There was, however, an excess of oral clefts in the infants of mothers who had amphetamines prescribe period. A rough test of efficacy of anorectic drugs was made by comparing mean weight gain in 4-week p showed only short-term and limited reduction of weight gain (Milkovich & Van Den Berg, 1977a).

4) In animal studies, there was no evidence of adverse effects on embryofetal morphological developme amphetamine/dextroamphetamine product (amphetamine d- to l-enantiomer ratio of 3:1) was orally admi up to 6 mg/kg/day (1.5 times the maximum recommended human dose (MRHD) of 30 mg/day on a body the MRHD), respectively, throughout the period of organogenesis. Fetal malformations and death and se mice following parenteral administration of d-amphetamine doses of 50 mg/kg/day (approximately 6 time term neurochemical and behavioral alterations (ie, learning and memory deficits, altered locomotor activi prenatal or early postnatal exposure to amphetamine (d- or d,l-), at doses similar to those used clinically 2007).

e) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info ADDERALL XR(R) oral

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

See Drug Consult reference: PREGNANCY RISK CATEGORIES

f) Crosses Placenta: Yes

g) Clinical Management

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h) Literature Reports

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2) Dextroamphetamine

a) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info Dexedrine(R), 2002) (A
1) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or ot
women or studies in women and animals are not available. Drugs should be given only if the potential be
See Drug Consult reference: PREGNANCY RISK CATEGORIES
b) Crosses Placenta: Unknown
c) Clinical Management
1) Amphetamines are not recommended for use during pregnancy except possibly in the case of narcol
which the drug is indicated and according to established regimens, amphetamines are not expected to c
However, maternal abuse of amphetamines does increase the potential risk of maternal, fetal, and neona
controversial, limited evidence suggests an increased incidence of cardiac defects and cleft palate in ne
during pregnancy (Berkowitz et al, 1981).
d) Literature Reports
1) Eleven infants were born with biliary atresia to mothers who had taken amphetamines in various dose
development of a biliary tree) (Levin, 1971). In a controlled group of 50 normal infants, it was noted that
2) A large prospective, observational study of pregnancy and child development was undertaken relatec
phenmetrazine) prescribed to gravid women during different stages of pregnancy and evaluated for their
1977). The severe congenital anomaly rate (SCA) per 100 live-born children at age 5 years did not differ
whose mothers did not use these drugs. There was, however, an excess of oral clefts in the offspring of
the first 55 days from the last menstrual period. A rough test of efficacy of anorectic drugs was made by
before and after the prescription; it showed only short-term and limited reduction of weight gain.
3) In a further report, clinicians evaluated the outcome of pregnancy in 52 women who had abused intra
throughout pregnancy, with results being compared to a control group of 52 nonabusing women (Little et
circumference was decreased significantly in neonates born to mothers abusing methamphetamine durir
congenital anomalies was not increased significantly compared to the control group.
4) A statistically significant correlation between aggressive behavior and amphetamine exposure during
Zetterstrom, 1994).
e) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info Dexedrine(R), 2002) (A
1) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or ot
women or studies in women and animals are not available. Drugs should be given only if the potential be
See Drug Consult reference: PREGNANCY RISK CATEGORIES
f) Crosses Placenta: Unknown
g) Clinical Management
1) Amphetamines are not recommended for use during pregnancy except possibly in the case of narcol
which the drug is indicated and according to established regimens, amphetamines are not expected to c
However, maternal abuse of amphetamines does increase the potential risk of maternal, fetal, and neona
controversial, limited evidence suggests an increased incidence of cardiac defects and cleft palate in ne
during pregnancy (Berkowitz et al, 1981).
h) Literature Reports
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development of a biliary tree) (Levin, 1971). In a controlled group of 50 normal infants, it was noted that
2) A large prospective, observational study of pregnancy and child development was undertaken relatec
phenmetrazine) prescribed to gravid women during different stages of pregnancy and evaluated for their
1977). The severe congenital anomaly rate (SCA) per 100 live-born children at age 5 years did not differ
whose mothers did not use these drugs. There was, however, an excess of oral clefts in the offspring of
the first 55 days from the last menstrual period. A rough test of efficacy of anorectic drugs was made by
before and after the prescription; it showed only short-term and limited reduction of weight gain.
3) In a further report, clinicians evaluated the outcome of pregnancy in 52 women who had abused intra
throughout pregnancy, with results being compared to a control group of 52 nonabusing women (Little et
circumference was decreased significantly in neonates born to mothers abusing methamphetamine durir
congenital anomalies was not increased significantly compared to the control group.
4) A statistically significant correlation between aggressive behavior and amphetamine exposure during
Zetterstrom, 1994).

B) Breastfeeding
1) Amphetamine
a) American Academy of Pediatrics Rating: Drugs of abuse for which adverse effects on the infant during bre
b) Thomson Lactation Rating: Infant risk has been demonstrated.
1) Evidence and/or expert consensus has demonstrated harmful infant effects when used during breastf
prescribed or patients should be advised to discontinue breastfeeding.
c) Clinical Management
1) Amphetamines have been shown to be excreted in human breast milk (Prod Info ADDERALL XR(R)
al, 1984). Adverse effects reported in exposed infants include irritability and poor sleeping patterns (Proc
Therefore, nursing mothers who are using amphetamines should be advised to avoid nursing (Prod Info
d) Literature Reports
1) Two case reports described methylamphetamine and amphetamine exposure in 4- and 2-month-old r
methylamphetamine by the 2 mothers ages 29 and 26 years, respectively, who were recruited from the i
HIT trial. The women self-injected a single methylamphetamine dose of unknown purity and quantity. Fo
collected. A 5- to 10-mL breast milk sample was collected just prior to drug use and then in 2 to 6 hour ir
methylamphetamine use. Methylamphetamine and amphetamine were estimated using high-performanc

detected in the urine and breast milk of both subjects was methylamphetamine with a small quantity of a methylamphetamine and amphetamine half-lives were 13.6 and 43 hours, respectively, in subject 1, and average concentration (Cavg) of methylamphetamine in the breast milk was 111 and 281 mcg/L for subje absolute infant dose of 16.7 and 42.2 mcg/kg/day. The Cavg of amphetamine in the breast milk was 4 ar resulting in an absolute infant dose of 0.8 and 2.5 mcg/kg/day (Bartu et al, 2009).

2) Concentrations of amphetamine were 3 and 7 times higher in breast milk than maternal plasma on th respectively, following administration of amphetamine 20 mg daily to a nursing mother with narcolepsy. A in the urine of the infant. Although only a small fraction of maternal dose is expected to be transferred to that patients abstain from long-term nursing during amphetamine treatment (Steiner et al, 1984).

e) American Academy of Pediatrics Rating: Drugs of abuse for which adverse effects on the infant during bre

f) Thomson Lactation Rating: Infant risk has been demonstrated.

1) Evidence and/or expert consensus has demonstrated harmful infant effects when used during breastf prescribed or patients should be advised to discontinue breastfeeding.

g) Clinical Management

1) Amphetamines have been shown to be excreted in human breast milk (Prod Info ADDERALL XR(R) al, 1984). Adverse effects reported in exposed infants include irritability and poor sleeping patterns (Proc Therefore, nursing mothers who are using amphetamines should be advised to avoid nursing (Prod Info

h) Literature Reports

1) Two case reports described methylamphetamine and amphetamine exposure in 4- and 2-month-old r methylamphetamine by the 2 mothers ages 29 and 26 years, respectively, who were recruited from the i HIT trial. The women self-injected a single methylamphetamine dose of unknown purity and quantity. Fo collected. A 5- to 10-mL breast milk sample was collected just prior to drug use and then in 2 to 6 hour ir methylamphetamine use. Methylamphetamine and amphetamine were estimated using high-performanc detected in the urine and breast milk of both subjects was methylamphetamine with a small quantity of a methylamphetamine and amphetamine half-lives were 13.6 and 43 hours, respectively, in subject 1, and average concentration (Cavg) of methylamphetamine in the breast milk was 111 and 281 mcg/L for subje absolute infant dose of 16.7 and 42.2 mcg/kg/day. The Cavg of amphetamine in the breast milk was 4 ar resulting in an absolute infant dose of 0.8 and 2.5 mcg/kg/day (Bartu et al, 2009).

2) Concentrations of amphetamine were 3 and 7 times higher in breast milk than maternal plasma on th respectively, following administration of amphetamine 20 mg daily to a nursing mother with narcolepsy. A in the urine of the infant. Although only a small fraction of maternal dose is expected to be transferred to that patients abstain from long-term nursing during amphetamine treatment (Steiner et al, 1984).

2) Dextroamphetamine

a) Thomson Lactation Rating: Infant risk has been demonstrated.

1) Evidence and/or expert consensus has demonstrated harmful infant effects when used during breastf prescribed or patients should be advised to discontinue breastfeeding.

b) Clinical Management

1) Amphetamines are concentrated in human breast milk. Adverse effects reported in exposed infants ir (Anon, 2001). The manufacturer of Adderal(R) suggests that breastfeeding women taking amphetamines Adderal(R), 2003).

c) Literature Reports

1) One study reported that concentrations of amphetamine were 3 and 7 times higher in breast milk thar delivery, respectively, following administration of dextroamphetamine 20 mg daily to a nursing mother wi effects occurred in the infant. Although only a small fraction of the maternal dose is expected to be transf suggest that patients abstain from long-term nursing during amphetamine treatment.

d) Thomson Lactation Rating: Infant risk has been demonstrated.

1) Evidence and/or expert consensus has demonstrated harmful infant effects when used during breastf prescribed or patients should be advised to discontinue breastfeeding.

e) Clinical Management

1) Amphetamines are concentrated in human breast milk. Adverse effects reported in exposed infants ir (Anon, 2001). The manufacturer of Adderal(R) suggests that breastfeeding women taking amphetamines Adderal(R), 2003).

f) Literature Reports

1) One study reported that concentrations of amphetamine were 3 and 7 times higher in breast milk thar delivery, respectively, following administration of dextroamphetamine 20 mg daily to a nursing mother wi effects occurred in the infant. Although only a small fraction of the maternal dose is expected to be transf suggest that patients abstain from long-term nursing during amphetamine treatment.

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Food Combinations

3.5.1 Drug-Drug Combinations

Acetazolamide

Acetazolamide

Amitriptyline

Amoxapine

Calamus

Chlorpromazine

Citalopram

Clomipramine

Clorgyline

Clorgyline

Desipramine

Dothiepin

Doxepin

Furazolidone

Furazolidone

Guanethidine

Imipramine

Iproniazid

Iproniazid

Isocarboxazid

Isocarboxazid

Lofepramine

Moclobemide

Moclobemide

Nialamide

Nialamide

Nortriptyline

Opipramol

Pargyline

Pargyline

Phenelzine

Phenelzine

Procarbazine

Procarbazine

Protriptyline

Rasagiline

Selegiline

Selegiline

Sibutramine

Sodium Bicarbonate

Sodium Bicarbonate

Toloxatone

Toloxatone

Tranylcypromine

Tranylcypromine

Trimipramine

Venlafaxine

3.5.1.A Acetazolamide

1) Interaction Effect: amphetamine toxicity (hypertension, hyperpyrexia, seizures)
2) Summary: Concomitant acetazolamide and amphetamine therapy resulted in enhanced amphetamine effe
and the renal excretion of amphetamine is decreased due to increased reabsorption (Rowland, 1969; Anggar
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Lower doses of dextroamphetamine may be required with urinary alkalizers. Monito
7) Probable Mechanism: decreased renal clearance

3.5.1.B Acetazolamide

1) Interaction Effect: amphetamine toxicity (hypertension, hyperpyrexia, seizures)
2) Summary: Acetazolamide tends to alkalinize the urine, increasing the unionized amphetamine urine conce
tubular reabsorption. Enhanced effects of amphetamines may occur due to increased amphetamine concentr
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor for amphetamine toxicity and adjust the dose or discontinue the acetazolan
7) Probable Mechanism: decreased clearance

3.5.1.C Amitriptyline

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been rep & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCA monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.D Amoxapine

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

ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt
appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.E Calamus

1) Interaction Effect: reduced effect of amphetamines
2) Summary: Calamus antagonized spontaneous motor activity and amphetamine-induced hyperactivity in m
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Use caution with concomitant use of calamus and amphetamines.
7) Probable Mechanism: not specified
8) Literature Reports
a) Calamus antagonized spontaneous motor activity and amphetamine-induced hyperactivity in mice. C
(0.2 milliliters of 10, 25, 50 milligrams/kilogram (mg/kg)). One group of mice received 4 mg/kg chlorproma
spontaneous motor activity was compared to untreated mice. In another test, mice were injected IP with
calamus followed by amphetamine. Calamus significantly reduced spontaneous motor activity in a mann
and 25 mg/kg and significantly reduced amphetamine-induced hyperactivity at 25 mg/kg (Panchal et al,

3.5.1.F Chlorpromazine

1) Interaction Effect: decreased amphetamine and chlorpromazine effectiveness
2) Summary: Amphetamine may inhibit the antipsychotic effects of chlorpromazine (Casey, 1961) and chlorp
amphetamine (Modell & Hussar, 1965; Espelin & Done, 1968).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Avoid combining amphetamines and chlorpromazine where possible.
7) Probable Mechanism: antagonism

3.5.1.G Citalopram

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Concurrent use of citalopram and dextroamphetamine resulted in symptoms of serotonin syndr
citalopram and dextroamphetamine are used concomitantly, monitor closely for symptoms of serotonin syndr
threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care ar
Shannon, 2005).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: A case of serotonin syndrome was reported with coadministration of citalopram and
citalopram and dextroamphetamine are used concomitantly, monitor closely for symptoms of serotonin syndr
(including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic h
diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation an
threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care ar
Shannon, 2005).
7) Probable Mechanism: additive pharmacologic effects
8) Literature Reports
a) A 32-year-old male on dextroamphetamine experienced serotonin syndrome approximately 1 week a
dextroamphetamine 5 mg three times daily for attention deficit hyperactivity disorder. He started 75 mg a
was increased to 150 mg daily. Approximately 2 weeks after starting venlafaxine he experienced markec
admission he was alert and oriented. He experienced diaphoresis, shivering, and fine motor tremor. His
pressure was 142/93 mmHg, and temperature was 37.3 degrees Celsius. No nystagmus or ocular clonus
reactive. He had generalized hypertonia, hyperreflexia, inducible ankle clonus, frequent myoclonic jerkin
oris muscle. No abnormality was shown on ECG, except sinus tachycardia with a baseline tremor. Dextr
discontinued and cyproheptadine (up to a total of 32 mg over 3 hours) was administered. Symptoms res
morning. Dextroamphetamine was restarted 3 days later. Four days later citalopram was started. Approx
symptoms as he did with dextroamphetamine and venlafaxine. Agitation, nausea, diarrhea, and teeth cle
was discontinued. Two doses of cyproheptadine were given and within 2 days he was asymptomatic (Pri

3.5.1.H Clomipramine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte
from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit
Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m
most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh
moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo
& Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs
monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed

5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism c imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.I Clorgyline

1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of dextroamphetamine concomitantly or within 14 days following the administration of a mo (Prod Info Dexedrine(R), 1995c). Amphetamines stimulate the release of norepinephrine, and the use of mon more norepinephrine being made available at nerve receptor sites through inhibition of catecholamine degrad of norepinephrine, which increases sympathetic activity (Gilman et al, 1990d). Coadministration of indirect-ac in severe hypertension and hyperpyrexia (Krisko et al, 1969d; Lloyd & Walker, 1965d; Mason, 1962d; Dally, 1 dextroamphetamine or pemoline in addition to a MAOI was observed during a study of patients with treatmen
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Dextroamphetamine use during or within 14 days following the administration of a n
7) Probable Mechanism: increased norepinephrine availability
8) Literature Reports
a) Severe headaches and hypertensive crises are well-documented in the literature as being associated include cardiac arrhythmias, chest pain, hyperpyrexia, and death (Goldberg, 1964b).
b) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a (pemoline or dextroamphetamine) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the tricyclic antidepressants and lithium, in addition to the study medications. Most of the patients (78%) exp months during coadministration, and 31% of the patients continued treatment after the study. Four of the discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or sha dextroamphetamine and a MAOI discontinued the medications due to memory problems, parkinsonian s patients experienced mood cycling, five to hypomania and one to mania. No patients developed symptor (Fawcett et al, 1991h).

3.5.1.J Clorgyline

1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: The concurrent use of amphetamine and monoamine oxidase inhibitors (MAOIs) is contraindic the discontinuation of MAOIs before amphetamine therapy is instituted (Prod Info Biphetamine(R), 1995j). An norepinephrine, and the use of MAO inhibitors results in more norepinephrine being made available at nerve catecholamine degradation; concurrent use leads to greater amounts of norepinephrine which increases sym
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: established
6) Clinical Management: Amphetamine use is contraindicated during or within 14 days of administration of m
7) Probable Mechanism: increased norepinephrine availability
8) Literature Reports
a) Severe headaches and hypertensive crises are well-documented in the literature as being associated include cardiac arrhythmias, chest pain, hyperpyrexia, and death (Goldberg, 1964o).

3.5.1.K Desipramine

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

from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with
Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m
most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sho
moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo
& Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs
monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho
increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf
capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if
closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen
amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet
VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab
2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o
imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in
effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb
methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th
pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g
fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical
doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc
1969). However, a systemic review of stimulants in the treatment of depression concluded that although
ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt
appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.L Dothiepin

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported
from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with
Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m
most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sho
moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo
& Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs
monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho
increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf
capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if
closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen
amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet
VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab
2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o
imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in
effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb
methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th
pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g
fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical
doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc
1969). However, a systemic review of stimulants in the treatment of depression concluded that although
ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt
appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.M Doxepin

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

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

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

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

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

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

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

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

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

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

3.5.1.N Furazolidone

1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)

2) Summary: Furazolidone has significant MAOI activity (Pettinger et al, 1968; Pettinger et al, 1966). Use of days following the administration of a monoamine oxidase inhibitor is contraindicated (Prod Info Dexedrine(R activity such as dextroamphetamine cause the release of norepinephrine, and the use of MAOIs results in m nerve receptor sites through inhibition of catecholamine degradation; concurrent use leads to greater amount sympathetic activity (Gilman et al, 1990e). Coadministration of indirect-acting sympathomimetics and MAOIs & Bermudez, 1982; Cuthbert et al, 1969; Terry et al, 1975; Horler & Wynne, 1965).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Dextroamphetamine use during or within 14 days following the administration of a

7) Probable Mechanism: increased norepinephrine availability

3.5.1.O Furazolidone

1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)

2) Summary: Furazolidone has significant MAOI activity (Pettinger et al, 1968a; Pettinger et al, 1966a) and s sympathomimetics. Sympathomimetics with indirect/mixed activity such as amphetamine cause the release results in more norepinephrine being made available at nerve receptor sites through inhibition of catecholami amounts of norepinephrine which increases sympathetic activity (Gilman et al, 1990p). Coadministration of in Inhibitors has resulted in serious hypertension (Smookler & Bermudez, 1982a; Cuthbert et al, 1969a; Terry e

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of amphetamines and an MAO inhibitor, or medications with MAO I

7) Probable Mechanism: increased norepinephrine availability

3.5.1.P Guanethidine

1) Interaction Effect: decreased guanethidine effectiveness

2) Summary: Amphetamines displace guanethidine from the neuron and interfere with neuron uptake. If pos (Ober & Wang, 1973).

3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Monitor patient for signs of decreased guanethidine effectiveness. Adjust the dosag
7) Probable Mechanism: antagonism
8) Literature Reports
a) Concomitant guanethidine and amphetamine administration has been reported to result in antagonisr appears that amphetamine displaces guanethidine from its site of action thereby reversing its hypotensiv 1971).
b) Available data indicate that amphetamine does not alter the orthostatic hypotension seen with guanet systolic blood pressure (Ober & Wang, 1970; Ober & Wang, 1971).

3.5.1.Q Imipramine
1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs n most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCA monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism c imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.R Iproniazid
1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of dextroamphetamine concomitantly or within 14 days following the administration of a m (Prod Info Dexedrine(R), 1995h). Amphetamines stimulate the release of norepinephrine, and the use of mor more norepinephrine being made available at nerve receptor sites through inhibition of catecholamine degrad of norepinephrine, which increases sympathetic activity (Gilman et al, 1990i). Coadministration of indirect-act in severe hypertension and hyperpyrexia (Krisko et al, 1969h; Lloyd & Walker, 1965h; Mason, 1962h; Dally, 1 dextroamphetamine or pemoline in addition to a MAOI was observed during a study of patients with treatmen
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Dextroamphetamine use during or within 14 days following the administration of a n
7) Probable Mechanism: increased norepinephrine availability
8) Literature Reports
a) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a (pemoline or dextroamphetamine) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the tricyclic antidepressants and lithium, in addition to the study medications. Most of the patients (78%) exp months during coadministration, and 31% of the patients continued treatment after the study. Four of the discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or sha dextroamphetamine and a MAOI discontinued the medications due to memory problems, parkinsonian s

patients experienced mood cycling, five to hypomania and one to mania. No patients developed symptor (Fawcett et al, 1991n).

3.5.1.S Iproniazid

1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: The concurrent use of amphetamine and monoamine oxidase inhibitors (MAOIs) is contraindic the discontinuation of MAOIs before amphetamine therapy is instituted (Prod Info Biphetamine(R), 1995h). A norepinephrine, and the use of MAO inhibitors results in more norepinephrine being made available at nerve catecholamine degradation; concurrent use leads to greater amounts of norepinephrine which increases sym potential reactions include cardiac arrhythmias, chest pain, hyperpyrexia, and death (Goldberg, 1964m).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Amphetamine use is contraindicated during or within 14 days of administration of m
7) Probable Mechanism: increased norepinephrine availability

3.5.1.T Isocarboxazid

1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of dextroamphetamine concomitantly or within 14 days following the administration of a m (Prod Info Dexedrine(R), 1995a; Prod Info Marplan(R), 1998). Amphetamines cause the release of norepinep norepinephrine being made available at nerve receptor sites through inhibition of catecholamine degradation. norepinephrine, which increases sympathetic activity (Gilman et al, 1990b). Coadministration of indirect-actin severe hypertension and hyperpyrexia (Krisko et al, 1969b; Lloyd & Walker, 1965b; Mason, 1962b; Dally, 196 dextroamphetamine or pemoline in addition to a MAOI was observed during a study of patients with treatmen
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Dextroamphetamine use during or within 14 days following the administration of a r
7) Probable Mechanism: increased norepinephrine availability
8) Literature Reports
a) Severe headaches and hypertensive crises are well-documented in the literature with this combinatio arrhythmias, chest pain, hyperpyrexia, and death (Goldberg, 1964a).
b) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a (pemoline or dextroamphetamine) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the tricyclic antidepressants and lithium, in addition to the study medications. Most of the patients (78%) exp months during coadministration, and 31% of the patients continued treatment after the study. Four of the discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or sha dextroamphetamine and a MAOI discontinued the medications due to memory problems, parkinsonian s patients experienced mood cycling, five to hypomania and one to mania. No patients developed symptor (Fawcett et al, 1991d).

3.5.1.U Isocarboxazid

1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: The concurrent use of amphetamine and monoamine oxidase inhibitors (MAOIs) is contraindic days should elapse following the discontinuation of MAOIs before amphetamine therapy is instituted (Prod In cause the release of norepinephrine, and the use of MAO inhibitors results in more norepinephrine being ma inhibition of catecholamine degradation; concurrent use leads to greater amounts of norepinephrine which in Goldberg, 1964l).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: established
6) Clinical Management: Amphetamine use is contraindicated during or within 14 days of administration of m
7) Probable Mechanism: increased norepinephrine availability
8) Literature Reports
a) Severe headaches and hypertensive crises are well-documented in the literature with this combinatio arrhythmias, chest pain, hyperpyrexia, and death (Goldberg, 1964k).
b) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a (pemoline or dextroamphetamine) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the tricyclic antidepressants and lithium, in addition to the study medications. Most of the patients (78%) exp months during coadministration, and 31% of the patients continued treatment after the study. Four of the discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or sha dextroamphetamine and a MAOI discontinued the medications due to memory problems, parkinsonian s patients experienced mood cycling, five to hypomania and one to mania. No patients developed symptor (Fawcett et al, 1991r).

3.5.1.V Lofepramine

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

from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with
Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m
most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh
moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo
& Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs
monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho
increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf
capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if
closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen
amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet
VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab
2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o
imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i
effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb
methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th
pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g
fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical
doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc
1969). However, a systemic review of stimulants in the treatment of depression concluded that although
ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt
appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.W Moclobemide
1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of dextroamphetamine concomitantly or within 14 days following the administration of a mo
(Prod Info Dexedrine(R), 1995). Amphetamines stimulate the release of norepinephrine, and the use of monc
more norepinephrine being made available at nerve receptor sites through inhibition of catecholamine degrac
of norepinephrine, which increases sympathetic activity (Gilman et al, 1990). Coadministration of indirect-acti
in severe hypertension and hyperpyrexia (Krisko et al, 1969; Lloyd & Walker, 1965; Mason, 1962; Dally, 1962
dextroamphetamine or pemoline in addition to a MAOI was observed during a study of patients with treatmen
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Dextroamphetamine use during or within 14 days following the administration of a m
7) Probable Mechanism: increased norepinephrine availability
8) Literature Reports
a) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a c
(pemoline or dextroamphetamine) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the
tricyclic antidepressants and lithium, in addition to the study medications. Most of the patients (78%) exp
months during coadministration, and 31% of the patients continued treatment after the study. Four of the
discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or sha
dextroamphetamine and a MAOI discontinued the medications due to memory problems, parkinsonian s
patients experienced mood cycling, five to hypomania and one to mania. No patients developed symptor
(Fawcett et al, 1991).

3.5.1.X Moclobemide
1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: The concurrent use of amphetamine and monoamine oxidase inhibitors (MAOIs) is contraindic
the discontinuation of MAOIs before amphetamine therapy is instituted (Prod Info Biphetamine(R), 1995). Am
norepinephrine, and the use of MAO inhibitors results in more norepinephrine being made available at nerve
catecholamine degradation; concurrent use leads to greater amounts of norepinephrine which increases sym
potential reactions include cardiac arrhythmias, chest pain, hyperpyrexia, and death (Goldberg, 1964e).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Amphetamine use is contraindicated during or within 14 days of administration of m
7) Probable Mechanism: increased norepinephrine availability

3.5.1.Y Nialamide

1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)

2) Summary: Use of dextroamphetamine concomitantly or within 14 days following the administration of a mo (Prod Info Dexedrine(R), 1995j). Amphetamines stimulate the release of norepinephrine, and the use of mono more norepinephrine being made available at nerve receptor sites through inhibition of catecholamine degrad of norepinephrine, which increases sympathetic activity (Gilman et al, 1990k). Coadministration of indirect-ac in severe hypertension and hyperpyrexia (Krisko et al, 1969j; Lloyd & Walker, 1965j; Mason, 1962j; Dally, 19 dextroamphetamine or pemoline in addition to a MAOI was observed during a study of patients with treatmen

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Dextroamphetamine use during or within 14 days following the administration of a n

7) Probable Mechanism: increased norepinephrine availability

8) Literature Reports

a) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a c (pemoline or dextroamphetamine) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the tricyclic antidepressants and lithium, in addition to the study medications. Most of the patients (78%) exp months during coadministration, and 31% of the patients continued treatment after the study. Four of the discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or sha dextroamphetamine and a MAOI discontinued the medications due to memory problems, parkinsonian s patients experienced mood cycling, five to hypomania and one to mania. No patients developed symptor (Fawcett et al, 1991p).

3.5.1.Z Nialamide

1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)

2) Summary: The concurrent use of amphetamine and monoamine oxidase inhibitors (MAOIs) is contraindic the discontinuation of MAOIs before amphetamine therapy is instituted (Prod Info Biphetamine(R), 1995b). A norepinephrine, and the use of MAOIs results in more norepinephrine being made available at nerve recepto degradation; concurrent use leads to greater amounts of norepinephrine which increases sympathetic activity indirect-acting sympathomimetics and MAOIs has resulted in severe hypertension and hyperpyrexia (Krisko e 1962k; Dally, 1962k).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Amphetamine use is contraindicated during or within 14 days of administration of m

7) Probable Mechanism: increased norepinephrine availability

3.5.1.AA Nortriptyline

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

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

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

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

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

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

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

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

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical

doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc
1969). However, a systemic review of stimulants in the treatment of depression concluded that although
ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt
appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.AB Opipramol

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte
from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit
Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m
most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh
moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo
& Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs
monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho
increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf
capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if
closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen
amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet
VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab
2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o
imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i
effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb
methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th
pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g
fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical
doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc
1969). However, a systemic review of stimulants in the treatment of depression concluded that although
ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt
appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.AC Pargyline

1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of dextroamphetamine concomitantly or within 14 days following the administration of a mo
(Prod Info Dexedrine(R), 1995i). Amphetamines cause the release of norepinephrine, and the use of MAOIs
available at nerve receptor sites through inhibition of catecholamine degradation; concurrent use leads to gre
sympathetic activity (Gilman et al, 1990j). Coadministration of indirect-acting sympathomimetics and MAOIs h
hyperpyrexia (Krisko et al, 1969i; Lloyd & Walker, 1965i; Mason, 1962i; Dally, 1962i).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Dextroamphetamine use during or within 14 days following the administration of a n
7) Probable Mechanism: increased norepinephrine availability

3.5.1.AD Pargyline

1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: The concurrent use of amphetamine and monoamine oxidase inhibitors (MAOIs) is contraindica
the discontinuation of MAOIs before amphetamine therapy is instituted (Prod Info Biphetamine(R), 1995e). A
norepinephrine, and the use of MAO inhibitors results in more norepinephrine being made available at nerve
catecholamine degradation; concurrent use leads to greater amounts of norepinephrine which increases sym
potential reactions include cardiac arrhythmias, chest pain, hyperpyrexia, and death (Goldberg, 1964i).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Amphetamine use is contraindicated during or within 14 days of administration of m
7) Probable Mechanism: increased norepinephrine availability

3.5.1.AE Phenelzine

1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)

2) Summary: Amphetamines cause the release of norepinephrine, and the use of monoamine oxidase inhibit being made available at nerve receptor sites through inhibition of catecholamine degradation. Concurrent use which increases sympathetic activity (Gilman et al, 1990a). Coadministration of indirect-acting sympathomime hypertension and hyperpyrexia (Krisko et al, 1969a; Lloyd & Walker, 1965a; Mason, 1962a; Dally, 1962a). So dextroamphetamine or pemoline in addition to a MAOI was observed during a study of patients with treatmen However, the concurrent use of dextroamphetamine and phenelzine is contraindicated (Prod Info Nardil(R), 1

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Dextroamphetamine use during or within 14 days following the administration of a n

7) Probable Mechanism: increased norepinephrine availability

8) Literature Reports

a) Severe headaches and hypertensive crises are well-documented in the literature with this combinatio arrhythmias, chest pain, hyperpyrexia, and death (Goldberg, 1964).

b) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a (pemoline or dextroamphetamine) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the tricyclic antidepressants and lithium, in addition to the study medications. Most of the patients (78%) exp months during coadministration, and 31% of the patients continued treatment after the study. Four of the discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or sha dextroamphetamine and a MAOI discontinued the medications due to memory problems, parkinsonian s patients experienced mood cycling, five to hypomania and one to mania. No patients developed symptor (Fawcett et al, 1991b).

3.5.1.AF Phenelzine

1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)

2) Summary: The concurrent use of amphetamine and monoamine oxidase inhibitors (MAOIs) is contraindic the discontinuation of MAOIs before amphetamine therapy is instituted (Prod Info Biphetamine(R), 1995c). A norepinephrine, and the use of MAO inhibitors results in more norepinephrine being made available at nerve catecholamine degradation; concurrent use leads to greater amounts of norepinephrine which increases sym potential reactions include cardiac arrhythmias, chest pain, hyperpyrexia, and death (Goldberg, 1964g).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: established

6) Clinical Management: Amphetamine use is contraindicated during or within 14 days of administration of m

7) Probable Mechanism: increased norepinephrine availability

3.5.1.AG Procarbazine

1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)

2) Summary: Use of dextroamphetamine concomitantly or within 14 days following the administration of a mo (Prod Info Dexedrine(R), 1995f). Amphetamines stimulate the release of norepinephrine, and the use of mon more norepinephrine being made available at nerve receptor sites through inhibition of catecholamine degrad of norepinephrine, which increases sympathetic activity (Gilman et al, 1990g). Coadministration of indirect-ac in severe hypertension and hyperpyrexia (Krisko et al, 1969f; Lloyd & Walker, 1965f; Mason, 1962f; Dally, 19 dextroamphetamine or pemoline in addition to a MAOI was observed during a study of patients with treatmen

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Dextroamphetamine use during or within 14 days following the administration of a n

7) Probable Mechanism: increased norepinephrine availability

8) Literature Reports

a) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a (pemoline or dextroamphetamine) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the tricyclic antidepressants and lithium, in addition to the study medications. Most of the patients (78%) exp months during coadministration, and 31% of the patients continued treatment after the study. Four of the discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or sha dextroamphetamine and a MAOI discontinued the medications due to memory problems, parkinsonian s patients experienced mood cycling, five to hypomania and one to mania. No patients developed symptor (Fawcett et al, 1991l).

3.5.1.AH Procarbazine

1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)

2) Summary: The concurrent use of amphetamine and monoamine oxidase inhibitors (MAOIs) is contraindic the discontinuation of MAOIs before amphetamine therapy is instituted (Prod Info Biphetamine(R), 1995d). A norepinephrine, and the use of MAO inhibitors results in more norepinephrine being made available at nerve catecholamine degradation; concurrent use leads to greater amounts of norepinephrine which increases sym potential reactions include cardiac arrhythmias, chest pain, hyperpyrexia, and death (Goldberg, 1964h).

3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Amphetamine use is contraindicated during or within 14 days of administration of m
7) Probable Mechanism: increased norepinephrine availability

3.5.1.AI Protriptyline

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

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

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

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

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

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

3.5.1.AJ Rasagiline

1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension) and serotonin syndrome (hy status changes)
2) Summary: Amphetamines cause the release of norepinephrine, and the use of MAO inhibitors results in m nerve receptor sites through inhibition of catecholamine degradation; concurrent use leads to greater amount sympathetic activity (Gilman et al, 1990o). Severe hypertensive reactions have been reported following the a and sympathomimetics. A minimum of 14 days should elapse after discontinuing rasagiline before initiating th oral tablets, 2006).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of amphetamine and rasagiline is contraindicated. Allow 14 day rasagiline and the initiation of therapy with amphetamine.
7) Probable Mechanism: increased norepinephrine availability

3.5.1.AK Selegiline

1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of dextroamphetamine concomitantly or within 14 days following the administration of a mo (Prod Info Dexedrine(R), 1995g). Amphetamines cause the release of norepinephrine, and the use of MAOIs available at nerve receptor sites through inhibition of catecholamine degradation; concurrent use leads to gre sympathetic activity (Gilman et al, 1990h). Coadministration of indirect-acting sympathomimetics and MAOIs hyperpyrexia (Krisko et al, 1969g; Lloyd & Walker, 1965g; Mason, 1962g; Dally, 1962g).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Dextroamphetamine use during or within 14 days following the administration of a r

7) Probable Mechanism: increased norepinephrine availability
8) Literature Reports
a) Severe headaches and hypertensive crises are well-documented in the literature as being associated include cardiac arrhythmias, chest pain, hyperpyrexia, and death (Goldberg, 1964d).

3.5.1.AL Selegiline
1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension) and serotonin syndrome (hy status changes)
2) Summary: The concurrent use of amphetamine and selegiline is contraindicated. At least 14 days should before amphetamine therapy is instituted and a minimum of 7 days should elapse after discontinuing propoxy (Prod Info EMSAM(R) transdermal patch, 2006; Prod Info Biphetamine(R), 1995f). Amphetamines cause the inhibitors results in more norepinephrine being made available at nerve receptor sites through inhibition of ca to greater amounts of norepinephrine which increases sympathetic activity (Gilman et al, 1990o).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: established
6) Clinical Management: The concurrent use of amphetamine and selegiline is contraindicated. Allow 14 day selegiline and the initiation of therapy with amphetamine or allow a minimum of 7 days to elapse between the initiation of therapy with selegiline.
7) Probable Mechanism: increased norepinephrine availability
8) Literature Reports
a) Severe headaches and hypertensive crises are well-documented in the literature as being associated include cardiac arrhythmias, chest pain, circulatory failure, hyperpyrexia, and death (Goldberg, 1964j).

3.5.1.AM Sibutramine
1) Interaction Effect: an increased risk of hypertension and tachycardia
2) Summary: Sibutramine has been associated with substantial increases in blood pressure and heart rate ir administration of sibutramine and other centrally acting appetite suppressants has not been systematically ev and tachycardia may result. Therefore, the concurrent administration of sibutramine with another centrally act (Prod Info Meridia(R), 1997).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concomitant administration of sibutramine with other centrally active appetite s
7) Probable Mechanism: additive pharmacologic effects

3.5.1.AN Sodium Bicarbonate
1) Interaction Effect: amphetamine toxicity (hypertension, hyperpyrexia, seizures)
2) Summary: Sodium bicarbonate (ie, greater than 2 grams daily) may alkalinize the urine, increasing the un allowing for increased renal tubular reabsorption. Enhanced effects of amphetamine may occur due to increa al, 1973a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Lower doses of dextroamphetamine may be required with urinary alkalinizers. Moni
7) Probable Mechanism: decreased dextroamphetamine clearance

3.5.1.AO Sodium Bicarbonate
1) Interaction Effect: amphetamine toxicity (hypertension, hyperpyrexia, seizures)
2) Summary: Sodium bicarbonate (ie, greater than 2 grams daily) may alkalinize the urine, increasing the un allowing for increased renal tubular reabsorption. Enhanced effects of amphetamine may occur due to increa (Anggard et al, 1973b).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor for possible amphetamine toxicity (eg, hypertension, hyperpyrexia, or seizu
7) Probable Mechanism: decreased renal clearance

3.5.1.AP Toloxatone
1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of dextroamphetamine concomitantly or within 14 days following the administration of a m (Prod Info Dexedrine(R), 1995b). Amphetamines stimulate the release of norepinephrine, and the use of mor more norepinephrine being made available at nerve receptor sites through inhibition of catecholamine degrad of norepinephrine, which increases sympathetic activity (Gilman et al, 1990c). Coadministration of indirect-ac in severe hypertension and hyperpyrexia (Krisko et al, 1969c; Lloyd & Walker, 1965c; Mason, 1962c; Dally, 1 dextroamphetamine or pemoline in addition to a MAOI was observed during a study of patients with treatmen
3) Severity: contraindicated
4) Onset: rapid

5) Substantiation: probable
6) Clinical Management: Dextroamphetamine use during or within 14 days following the administration of a r
7) Probable Mechanism: increased norepinephrine availability
8) Literature Reports
a) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a (pemoline or dextroamphetamine) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the tricyclic antidepressants and lithium, in addition to the study medications. Most of the patients (78%) exp months during coadministration, and 31% of the patients continued treatment after the study. Four of the discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or sha dextroamphetamine and a MAOI discontinued the medications due to memory problems, parkinsonian s patients experienced mood cycling, five to hypomania and one to mania. No patients developed symptor (Fawcett et al, 1991f).

3.5.1.AQ Toloxatone
1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: The concurrent use of amphetamine and monoamine oxidase inhibitors (MAOIs) is contraindic the discontinuation of MAOIs before amphetamine therapy is instituted (Prod Info Biphetamine(R), 1995a). A norepinephrine, and the use of MAO inhibitors results in more norepinephrine being made available at nerve catecholamine degradation; concurrent use leads to greater amounts of norepinephrine which increases sym potential reactions include cardiac arrhythmias, chest pain, hyperpyrexia, and death (Goldberg, 1964f). As a inhibitor, toloxatone may not potentiate the effects of amphetamine to the same frequency, extent, and durati further studies confirm the safety and efficacy of this combined therapy, concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Amphetamine use is contraindicated during or within 14 days of administration of m
7) Probable Mechanism: increased norepinephrine availability

3.5.1.AR Tranylcypromine
1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of dextroamphetamine concomitantly or within 14 days following the administration of a mo (Prod Info Dexedrine(R), 1995e). Amphetamines cause the release of norepinephrine, and the use of monoa norepinephrine being made available at nerve receptor sites through inhibition of catecholamine degradation. norepinephrine, which increases sympathetic activity (Gilman et al, 1990f). Coadministration of indirect-acting severe hypertension and hyperpyrexia (Krisko et al, 1969e; Lloyd & Walker, 1965e; Mason, 1962e; Dally, 196 dextroamphetamine or pemoline in addition to a MAOI was observed during a study of patients with treatmen
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Dextroamphetamine use during or within 14 days following the administration of a r
7) Probable Mechanism: increased norepinephrine availability
8) Literature Reports
a) Severe headaches and hypertensive crises are well-documented in the literature with this combinatio arrhythmias, chest pain, hyperpyrexia, and death (Goldberg, 1964c).
b) In a study of 32 patients with treatment-refractory depression, efficacy of combination therapy with a (pemoline or dextroamphetamine) with a monoamine oxidase inhibitor (MAOI) was studied. Some of the tricyclic antidepressants and lithium, in addition to the study medications. Most of the patients (78%) exp months during coadministration, and 31% of the patients continued treatment after the study. Four of the discontinued the medications due to impotence, orthostatic hypotension, elevated blood pressure, or sha dextroamphetamine and a MAOI discontinued the medications due to memory problems, parkinsonian s patients experienced mood cycling, five to hypomania and one to mania. No patients developed symptor (Fawcett et al, 1991j).

3.5.1.AS Tranylcypromine
1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: The concurrent use of amphetamine and monoamine oxidase inhibitors (MAOIs) is contraindic the discontinuation of MAOIs before amphetamine therapy is instituted (Prod Info Biphetamine(R), 1995i). An norepinephrine, and the use of MAO inhibitors results in more norepinephrine being made available at nerve catecholamine degradation; concurrent use leads to greater amounts of norepinephrine which increases sym potential reactions include cardiac arrhythmias, chest pain, hyperpyrexia, and death (Goldberg, 1964n).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: established
6) Clinical Management: Amphetamine use is contraindicated during or within 14 days of administration of m
7) Probable Mechanism: increased norepinephrine availability

3.5.1.AT Trimipramine
1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs n most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCA monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.AU Venlafaxine

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Two weeks of concurrent use of dextroamphetamine and venlafaxine resulted in symptoms of et al, 2002). If dextroamphetamine and venlafaxine are used concomitantly, monitor closely for symptoms of life-threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive car Shannon, 2005).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: A case of serotonin syndrome was reported with coadministration of dextroamphet dextroamphetamine and venlafaxine are used concomitantly, monitor closely for symptoms of serotonin synd (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic h diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation an threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care a Shannon, 2005).
7) Probable Mechanism: additive pharmacologic effects
8) Literature Reports
a) A 32-year-old male on dextroamphetamine experienced serotonin syndrome approximately 2 weeks dextroamphetamine 5 mg three times daily for attention deficit hyperactivity disorder. He started 75 mg a was increased to 150 mg daily. Approximately 2 weeks after starting venlafaxine he experienced marked admission he was alert and oriented. He experienced diaphoresis, shivering, and fine motor tremor. His pressure was 142/93 mmHg, and temperature was 37.3 degrees Celsius. No nystagmus or ocular clonus reactive. He had generalized hypertonia, hyperreflexia, inducible ankle clonus, frequent myoclonic jerking oris muscle. No abnormality was shown on ECG, except sinus tachycardia with a baseline tremor. Dextr discontinued and cyproheptadine (up to a total of 32 mg over 3 hours) was administered. Symptoms res morning. Dextroamphetamine was restarted 3 days later. Four days later citalopram was started. Approx symptoms as he did with dextroamphetamine and venlafaxine. Agitation, nausea, diarrhea, and teeth cle was discontinued. Two doses of cyproheptadine were given and within 2 days he was asymptomatic (Pri

3.5.2 Drug-Food Combinations

3.5.2.A Acidic Food

1) Interaction Effect: altered serum concentrations
2) Summary: Maximal absorption of amphetamines occurs in the alkaline environment of the small intestine

taken with amphetamines may impair gastrointestinal absorption. Foods that increase urinary pH may decrea reabsorption of the amphetamine and increased serum levels. Foods that acidify urine increase renal clearan levels (Prod Info Dexedrine(R), 1998; Beckett & Rowland, 1965).
3) Severity: minor
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Dextroamphetamine should not be administered with acidic foods, such as citric fru
7) Probable Mechanism: pH-dependent absorption and clearance

4.0 Clinical Applications

Monitoring Parameters

Therapeutic Uses

4.1 Monitoring Parameters

A) Therapeutic
1) Physical Findings
a) Attention Deficit Hyperactivity Disorder (ADHD)
1) Improvement in mental and behavioral symptoms, including inappropriate inattention, impulsivity, hyp
b) Narcolepsy
1) Decreased frequency of narcoleptic attacks.
B) Toxic
1) Physical Findings
a) It is not conclusive whether chronic use of stimulants in children may be associated with suppression of gr during treatment (Prod Info Adderall (R) XR, 2005).
1) Attention Deficit Hyperactivity Disorder (ADHD)
a) The American Academy of Pediatrics (AAP) does not recommend the routine use of electrocardi cardiology evaluations (which were previously recommended by the American Heart Association (AH conditions that might place the child at risk for sudden cardiac death) before initiating stimulant thera ADHD in most children. The APA cited specific reasons for changing the recommendation including between stimulant drugs used to treat ADHD and sudden cardiac death (SCD), the frequency of suc stimulant drugs is not higher than that in the general population of children, and lack of cost-effective evaluation by pediatric cardiologist (Perrin et al, 2008).
b) Based on the American Academy of Pediatrics (AAP) and the American Heart Association (AHA monitoring recommendations have been established to assist clinicians in the evaluation of children amphetamine/dextroamphetamine combinations, for ADHD (Perrin et al, 2008; Vetter et al, 2008):
- Conduct a thorough examination prior to initiating amphetamine/dextroamphetamine combinat attention should be given to symptoms indicative of a cardiac condition, including palpitations, r
- Obtain a complete family and patient history for conditions associated with SCD, and determir the-counter medications.
- Conduct a complete physical evaluation of the patient for hypertension, cardiac murmurs, phys and signs of irregular cardiac rhythms.
- Perform further evaluation if family history, patient history or physical exam is suggestive of ca visits, and if indicated, consult pediatric cardiologist .
- Continue to assess the patient for cardiac symptoms and any changes in family history at follo
- Blood pressure and heart rate should be evaluated at baseline, during routine follow-up within 12 months. Increases in blood pressure and heart rate have been reported with stimulant use.

4.5 Therapeutic Uses

Attention deficit hyperactivity disorder

Narcolepsy

4.5.A Attention deficit hyperactivity disorder

FDA Labeled Indication
1) Overview
FDA Approval: Adult, yes; Pediatric, yes (immediate-release, age 3 years and older; extended-release, a
Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Amphetamine aspartate/amphetamine sulfate/dextroamphetamine saccharate/dextroamphetamine sulfa
treatment of attention deficit hyperactivity disorder (ADHD) (Prod Info ADDERALL XR(R) extended-relea

3) Adult:

a) Adderall(R), a mixture of L- and D-amphetamine, was effective in some cases of adult attention deficit hyp
study (n=24). Dosing of Adderall was initiated at 5 milligrams (mg) twice daily orally and titrated according to
a positive response was shown by 54% of patients (13 of 24) using the Clinical Global Impression scale to de
much improved and 3 (12%) were much improved. Two patients (8%) were minimally improved. Among thes
10.33 mg or 0.14 mg/kg/day, and side effects were decreased appetite, insomnia, and sedation. Overall, 9 pa
of 7 with comorbid anxiety experienced immediate acute anxiety (diaphoresis, tremor, shortness of breath, ar
after day 1. Excluding those 4, mean score on the Copeland Symptom Checklist for adult ADD decreased fro
ADD scales dropped from 76.75 to 50.85 (p less than 0.001 and 0.0001, respectively) (Horrigan and Barnhill,

4) Pediatric:

a) Extended-Release

1) In a double-blind, randomized, placebo-controlled, parallel-group study, extended release Adderall (A
treatment of attention deficit hyperactivity disorder (ADHD) in children ages 6 to 12 years old. Patients (n
Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for hyperactive-impulsive or combined subt
placebo (n=210), or 10 milligrams per day (mg/day; n=129), 20 mg/day (n=121), or 30 mg/day (n=124) A
for a 1-week washout period. Once active treatment began, a dose escalation regimen was used for the
10 mg once daily was administered to all Adderall XR(TM) groups and increased each week by 10 mg p
Efficacy was evaluated using the Conners Global Index Scale (teacher's version, CGIS-T or parent's ver
Adderall XR (TM) groups showed significant improvement in CGIS scores compared to baseline and pla
scores were 10.6, 11.5, 12.1, and 11.2 for the placebo, 10 mg/d, 20 mg/d, and 30 mg/day groups, respe
study endpoint was -0.9, -5.3, -6.0, and -6.4, respectively. Adverse events that occurred more frequently
group were anorexia (21.9% in Adderall XR(TM) groups versus 1.9% in placebo), insomnia (16.6% versu
emotional lability (8.6% versus 1.9%), vomiting (7.2% versus 3.8%), and nervousness (5.6% versus 1.9%
withdrawn from the study due to adverse events (Biederman et al, 2002).

b) Immediate-Release

1) Seven-day courses of oral Adderall(R) (a mixture of AMPHETAMINE AND DEXTROAMPHETAMINE
(mg/kg) and 0.3 mg/kg, both twice daily, were found to be an efficacious treatment for attention-deficit/hy
adolescents 5 to 18 years of age, based on a randomized, double-blind, crossover study. A 54% respons
criteria requiring positive assessments seen by both parent and teacher, 81% were seen to respond as r
to teachers. Overall, 137 of 154 subjects (89%) responded based on either parent or teacher positive ev
by parent and teacher), 60% of children 5 to 7 years of age responded; 71% of those 8 to 9 years respor
older. Side effects of Adderall(R) included decreased appetite, stomachache, insomnia, and headache; d
prominent with the 0.3 mg/kg dose. According to the study design, subjects were randomized to start on
7-day treatment periods (Adderall(R), placebo, Adderall(R), placebo; or vice versa starting with placebo).
hours, a washout period between the 7-day treatment periods was not thought to be necessary. The low
dose, with a maximum Adderall(R) dose of 40 mg/day (Ahmann et al, 2001).

4.5.B Narcolepsy

FDA Labeled Indication

1) Overview
FDA Approval: Adult, yes (immediate release formulation only); Pediatric, yes ((6 years and older) imme
Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Amphetamine aspartate/amphetamine sulfate/dextroamphetamine saccharate/dextroamphetamine sulfa
treatment of narcolepsy (Prod Info ADDERALL XR(R) extended-release oral capsules, 2006)

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DRUGDEX® Evaluations

CLOMIPRAMINE

0.0 Overview

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

2) Dosing Information
- **a)** Clomipramine Hydrochloride
  - **1)** Adult
    - **a)** Delusional disorder
      - **1)** initial, 25 mg/day ORALLY, may increase dosage to 100 mg/day during the first 2 weeks (MAX dose 250 mg/day, mean dose 140 mg/day)
    - **b)** Depression
      - **1)** initial, 75 mg/day ORALLY (3 divided doses); may increase dosage slowly as needed and tolerated to a range of 100-250 mg/day (3 divided doses)
    - **c)** Obsessive-compulsive disorder
      - **1)** initial, 25 mg/day ORALLY, may increase dosage to 100 mg per day during the first 2 weeks (MAX dose 250 mg/day outpatients, 300 mg/day inpatients)
    - **d)** Panic disorder
      - **1)** 25-75 mg/day ORALLY
  - **2)** Pediatric
    - **a)** safety and effectiveness in children up to 10 years of age have not been established
      - **1)** Depression
        - **a)** 20-30 mg/day ORALLY; may increase dosage by 10 mg/day at 4-5 day intervals as needed and tolerated
      - **2)** Obsessive-compulsive disorder
        - **a)** 10 yrs and older, initial, 25 mg/day ORALLY, may increase the dosage as needed and tolerated up to 100 mg/day; MAX dose 200 mg/day OR 3 mg/kg of body weight (whichever is less)

3) Contraindications
- **a)** Clomipramine Hydrochloride
  1) coadministration with an MAOI or use within 14 days of discontinuing an MAOI; may cause serious reactions (eg, hyperpyretic crisis, seizures, coma, death) (Prod Info ANAFRANIL(R) oral capsules, 2007)
  2) hypersensitivity to clomipramine hydrochloride or other tricyclic antidepressant (Prod Info ANAFRANIL(R) oral capsules, 2007)
  3) myocardial infarction, during the acute recovery period (Prod Info ANAFRANIL(R) oral capsules, 2007)

4) Serious Adverse Effects
- **a)** Clomipramine Hydrochloride
  1) Agranulocytosis
  2) Body temperature above normal
  3) Depression, worsening
  4) Hepatotoxicity
  5) Hyperglycemia
  6) Leukopenia
  7) Myocardial infarction
  8) Orthostatic hypotension
  9) Pancytopenia
  10) Seizure
  11) Suicidal thoughts
  12) Suicide
  13) Thrombocytopenia

5) Clinical Applications
- **a)** Clomipramine Hydrochloride
  - **1)** FDA Approved Indications
    - **a)** Obsessive-compulsive disorder
  - **2)** Non-FDA Approved Indications
    - **a)** Delusional disorder
    - **b)** Depression
    - **c)** Panic disorder

1.0 Dosing Information

Drug Properties

Adult Dosage

Pediatric Dosage

1.1 Drug Properties

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

B) Synonyms

Chlorimipramine
Chlorimipramine Hydrochloride
Clomipramine
Clomipramine HCl
Clomipramine Hydrochloride

C) Physicochemical Properties

1) Molecular Weight

a) Clomipramine hydrochloride: 351.3 (Prod Info Anafranil(R), 2001)

2) pH

a) Clomipramine hydrochloride: pH of a 10% solution in water is 3.5 to 5 (Sweetman, 2004)

3) Solubility

a) Clomipramine hydrochloride: Freely soluble in water, in methanol, and in methylene chloride; insoluble in ethyl ether and in hexane (Prod Info Anafranil(R), 2001)

1.3 Adult Dosage

1.3.1 Normal Dosage

Clomipramine

Clomipramine Hydrochloride

1.3.1.A Clomipramine

1.3.1.A.1 Cataplexy - Narcolepsy

See Drug Consult reference: NARCOLEPSY AND CATAPLEXY - DRUG THERAPY

1.3.1.B Clomipramine Hydrochloride

Intravenous route

Oral route

1.3.1.B.1 Intravenous route

a) In a study evaluating the effects of intravenous pulse loading of clomipramine in obsessive-compulsive disorder, 7 patients were given clomipramine 150 milligrams (mg) intravenously, over 90 minutes. The next day, clomipramine 200 mg intravenously, was given. The doses were preceded by trimethobenzamide hydrochloride 250 mg to reduce nausea. Oral clomipramine 150 mg was started 4.5 days after the second dose. This was increased by 25 mg every fourth day to 250 mg/day. Six out of 7 patients had responded before the oral dosing was started (Koran et al, 1997).

b) One worker has commented on his experience in treating over 60 patients with severe OCD with intravenous clomipramine (CMI) (Warneke, 1992). These patients had not responded to oral CMI and approximately 2/3 showed marked reduction in Y-BOCS scores. As much as 350 milligrams was used in a single infusion and induration and inflammation were the only reason (2 cases) that infusions had to be stopped. Duration of treatment was 14 days (one infusion each day). Patients were then changed to oral treatment.

c) A 62-year-old patient with a long history of obsessive compulsive disorder, whose symptoms were not adequately controlled with oral clomipramine (CMI) was treated with intravenous (IV) CMI. A daily dose of 25 milligrams in 500 milliliters of a dextrose-saline mixture (infused over 2 hours) was given followed by increases to 250 milligrams. Intravenous CMI was stopped after 10 days and replaced with oral CMI 250 milligrams. The patient took oral treatment for 18 months at which time the dose was

gradually decreased and the drug was eventually stopped.

1.3.1.B.2 Oral route

a) Treatment for obsessive-compulsive disorder with clomipramine should be initiated at a dosage of 25 milligrams daily and gradually increased, as tolerated, to approximately 100 milligrams during the first 2 weeks. During initial titration, clomipramine should be given in divided doses with meals to reduce gastrointestinal side effects. Thereafter, the dosage may be increased gradually over the next several weeks, up to a maximum of 250 milligrams daily. After titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation (Prod Info Anafranil(R), 2001b).

b) When clomipramine is administered concomitantly with another drug that inhibits cytochrome P450 2D6, the dose of clomipramine or of the other drug may need to be lower than that usually prescribed. And, when either drug is withdrawn, the dose of the other may need to be increased (Prod Info Anafranil (R), 2001b).

c) During clinical trials for the treatment of OBSESSIVE-COMPULSIVE DISORDER, the usual therapeutic oral dose of clomipramine ranged from 75 to 300 milligrams/day in divided doses (Yaryura-Tobias et al, 1976; Marks et al, 1980a; Ananth et al, 1981a). Therapy usually starts at 25 milligrams at night with gradual increases over 4 weeks as tolerated.

d) The usual therapeutic oral dose of clomipramine for DEPRESSION ranges from 100 to 250 milligrams/day in 3 divided doses although daily doses as low as 50 or 75 milligrams have also been used (De Wilde et al, 1983a; Dimitriou et al, 1984a; Dunbar et al, 1985a; Larsen et al, 1984).

e) Clomipramine in low doses (25 to 75 milligrams orally per day) was reported effective in the treatment of panic ANXIETY and AGORAPHOBIA in outpatients in an uncontrolled clinical trial (Gloger et al, 1989). There was a trend towards the need for higher doses in agoraphobia (mean, 56 milligrams) as opposed to panic disorder (mean, 40 milligrams). Low-dose clomipramine 60 mg/day was as effective as high-dose clomipramine 150 mg/day in the treatment of phobias, anxiety, and panic attacks in a multi-center study (Caillard et al, 1999).

1.4 Pediatric Dosage

1.4.1 Normal Dosage

Clomipramine

Clomipramine Hydrochloride

1.4.1.A Clomipramine

1.4.1.A.1 Anorexia nervosa

See Drug Consult reference: ANOREXIA NERVOSA - DRUG THERAPY

1.4.1.B Clomipramine Hydrochloride

Intravenous route

Oral route

1.4.1.B.1 Intravenous route

a) A single pulse dose of clomipramine 200 milligrams intravenously has been administered to depressed adolescents (14-to 18-years-old), demonstrating dramatic and rapid reduction in depressive symptoms at day 6 post-clomipramine infusion as compared to placebo. The clomipramine effect may persist for up to 8 weeks in some patients (Sallee et al, 1997).

b) The use of intravenous clomipramine (CMI) in a 15-year-old female patient with obsessive compulsive disorder was reported (Warneke, 1985). After oral treatment with 200 milligrams of CMI plus 4 grams of L-tryptophan at bedtime for 3 weeks and no response, the patient was started on intravenous CMI. Doses ranged from 200 to 300 milligrams in 8 of 14 infusions. Dramatic response was seen, with marked reduction of obsessional thoughts and some reduction of compulsive rituals.

1.4.1.B.2 Oral route

a) As with adults, the starting dose for treating OBSESSIVE-COMPULSIVE DISORDER with clomipramine is 25 milligrams daily and should be gradually increased during the first 2 weeks, as tolerated, up to a daily maximum of 3 milligrams/kilogram or 100 milligrams, whichever is smaller. These initial doses should be divided and taken with meals to reduce gastrointestinal side effects. Thereafter, the dosage may be increased gradually over the next several weeks up to a daily maximum

of 3 milligrams/kilogram or 200 milligrams, whichever is smaller. After titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation (Prod Info Anafranil(R), 2001b).
b) Oral clomipramine in the range of 100 to 200 milligrams/day in divided doses was successful in treating obsessive compulsive disorder in children aged 10 to 18 years (Flament et al, 1985a). The dose was started at 50 milligrams/day and was gradually increased to a maximum of 200 milligrams/day if tolerated.

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset
- **1)** Initial Response
  - **a)** Obsessive-compulsive disorder, oral: 4 to 10 weeks (Marks et al, 1980b).
  - **b)** Obsessive-compulsive disorder, intravenous: 5.5 days (Koran et al, 1997a).
  - **c)** Depression, oral: 2 weeks (Wolfersdorf et al, 1987a).

2.2 Drug Concentration Levels

A) Therapeutic Drug Concentration
- **1)** Obsessive-compulsive disorder, 100 to 250 ng/mL (clomipramine) plus 230 to 550 ng/mL (desmethylclomipramine) (Insel et al, 1983a; Stern et al, 1980a).
- **2)** Depression, greater than 160 to 200 ng/mL clomipramine plus desmethylclomipramine (Faravelli et al, 1984).
  - **a)** In a dose-effect study, there was a pronounced inter-patient variability in response. The authors attributed this to a variability in clomipramine steady state kinetics, clomipramine dose-dependent kinetics, and genetic polymorphism related to CYP2D6 (Anon, 1999).

B) Time to Peak Concentration
- **1)** Oral: 2 to 6 hours (mean, 4.7 hours) (Prod Info Anafranil(R), 2001a; Della Corte et al, 1993).

C) Area Under the Curve
- **1)** 600 ng/ml (0.7 mg/kg) (Della Corte et al, 1993).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption

A) Bioavailability
- **1)** Oral: 20% to 78% (Kuss & Jungkunz, 1986; de Cuyper et al, 1981).

B) Effects of Food
- **1)** None (Prod Info Anafranil(R), 2001a).

2.3.2 Distribution

A) Distribution Sites
- **1)** Protein Binding
  - **a)** 97% (Prod Info Anafranil(R), 2001a; Reynolds, 1988).
    - **1)** Principally bound to albumin (Prod Info Anafranil(R), 2001a).
- **2)** OTHER DISTRIBUTION SITES
  - **a)** Cerebrospinal fluid (CSF), CSF:plasma ratio is 2.6 (Prod Info Anafranil(R), 2001a).

B) Distribution Kinetics

1) Volume of Distribution
a) 12 L/kg (range, 7 to 20 L/kg) (Nagy & Johansson, 1977).

2.3.3 Metabolism
A) Metabolism Sites and Kinetics
1) Liver (Nagy & Johansson, 1977).
a) Extensive first-pass effect (Nagy & Johansson, 1977).
b) The metabolism of CLOMIPRAMINE and desmethylclomipramine may be capacity limited (Prod Info Anafranil(R), 2001a).
B) Metabolites
1) Desmethylclomipramine, active (Nagy & Johansson, 1977).
a) Responders have a trend towards lower plasma CLOMIPRAMINE to desmethylclomipramine ratios (Mavissakalian et al, 1990).
2) 8-OH clomipramine and 8-OH desmethylclomipramine (Insel et al, 1983a).

2.3.4 Excretion
A) Kidney
1) Renal Excretion (%)
a) 51% to 60% recovered in the urine (Prod Info Anafranil(R), 2001a).
B) Total Body Clearance
1) 12.7 TO 56.5 L/hr (Shimoda et al, 1999).
a) In an interethnic study comparing the clearance of clomipramine between Japanese and Swedish patients, Japanese patients had a much lower clearance (12.7 L/hr) than the Swedish patients (62.7 L/hr) (Shimoda et al, 1999).
C) Other
1) OTHER EXCRETION
a) Feces, 24% to 32% recovered in the feces (Prod Info Anafranil(R), 2001a).

2.3.5 Elimination Half-life
A) Parent Compound
1) ELIMINATION HALF-LIFE
a) 19 hours to 37 hours (mean, 32 hours) (Prod Info Anafranil(R), 2001a; Dawling et al, 1980).
1) The half-life of CLOMIPRAMINE may be lengthened at higher doses (200 to 250 mg/day) (Prod Info Anafranil(R), 2001a).
B) Metabolites
1) Desmethylclomipramine, 54 to 77 hours (mean, 69 hours) (Prod Info Anafranil(R), 2001a).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

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

3.1 Contraindications

A) Clomipramine Hydrochloride

1) coadministration with an MAOI or use within 14 days of discontinuing an MAOI; may cause serious reactions (eg, hyperpyretic crisis, seizures, coma, death) (Prod Info ANAFRANIL(R) oral capsules, 2007)

2) hypersensitivity to clomipramine hydrochloride or other tricyclic antidepressant (Prod Info ANAFRANIL(R) oral capsules, 2007)

3) myocardial infarction, during the acute recovery period (Prod Info ANAFRANIL(R) oral capsules, 2007)

3.2 Precautions

A) Clomipramine Hydrochloride

1) suicidal ideation and behavior or worsening depression; increased risk, particularly in children, adolescents, and young adults during the first few months of therapy or following changes in dosage (Prod Info ANAFRANIL (R) oral capsules, 2007)

2) abrupt withdrawal; serious discontinuation symptoms have been reported (Prod Info ANAFRANIL(R) oral capsules, 2007)

3) adrenal medulla tumor (eg, pheochromocytoma, neuroblastoma); may cause hypertensive crisis (Prod Info ANAFRANIL(R) oral capsules, 2007)

4) bipolar disorder; increased risk of precipitation of a mixed/manic episode with only antidepressant treatment (Prod Info ANAFRANIL(R) oral capsules, 2007)

5) cardiovascular disease; may increase risk of ECG changes (Prod Info ANAFRANIL(R) oral capsules, 2007)

6) concurrent use with electroshock therapy; may increase hazards of electroshock therapy (Prod Info ANAFRANIL(R) oral capsules, 2007)

7) condition that may lower the seizure threshold (ie, alcoholism, brain damage, concomitant use of other drugs that lower seizure threshold); increased risk of seizure (Prod Info ANAFRANIL(R) oral capsules, 2007)

8) glaucoma, history of narrow-angle; exacerbation of condition due to cholinergic antagonism (Prod Info ANAFRANIL(R) oral capsules, 2007)

9) hyperthyroidism or concurrent use of thyroid medications; may cause cardiac toxicity (Prod Info ANAFRANIL (R) oral capsules, 2007)

10) intraocular pressure, increased; exacerbation of condition due to cholinergic antagonism (Prod Info ANAFRANIL(R) oral capsules, 2007)

11) liver disease; risk of hepatotoxicity (Prod Info ANAFRANIL(R) oral capsules, 2007)

12) mania/hypomania; risk of disease activation (Prod Info ANAFRANIL(R) oral capsules, 2007)

13) neuroleptic malignant syndrome; has been reported with clomipramine therapy (Prod Info ANAFRANIL(R) oral capsules, 2007)

14) renal function, significantly impaired (Prod Info ANAFRANIL(R) oral capsules, 2007)

15) schizophrenia, unrecognized; may precipitate psychosis (Prod Info ANAFRANIL(R) oral capsules, 2007)

16) seizures, history; may lower the convulsive threshold (Prod Info ANAFRANIL(R) oral capsules, 2007)

17) surgery, elective with general anesthetics (Prod Info ANAFRANIL(R) oral capsules, 2007)

18) urinary retention, history of; exacerbation of condition due to cholinergic antagonism (Prod Info ANAFRANIL (R) oral capsules, 2007)

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Musculoskeletal Effects

Neurologic Effects

Psychiatric Effects

Renal Effects

Reproductive Effects

Other

3.3.1 Cardiovascular Effects

3.3.1.A Clomipramine Hydrochloride

Cardiac arrest

Hypotension

3.3.1.A.1 Cardiac arrest

a) According to one study, the use of higher-dose tricyclic antidepressants (TCAs) was associated with an increased risk of SUDDEN CARDIAC DEATH, while lower doses did not increase this risk. In a cohort study including 481,744 persons and 1487 cases of sudden cardiac death occurring in a community setting, researchers found that compared to non-use, the current use of TCAs was associated with a dose-related increase in the risk of sudden cardiac death. For doses lower than 100 milligrams (mg) (amitriptyline or its equivalent), the rate ratio was 0.97 (95% CI, 0.72 to 1.29), however this increased to 2.53 (95% CI, 1.04 to 6.12) for doses of 300 mg or more (p=0.03, test for dose-response). In the entire cohort, users of TCAs in doses of 100 mg or higher (amitriptyline or its equivalent) had a 41% increased rate of sudden cardiac death (rate ratio, 1.41; 95% CI, 1.02 to 1.95). However, TCAs taken in doses of less than 100 mg (amitriptyline or its equivalent) were not associated with an increased risk of sudden cardiac death in the entire cohort or in any subgroups, including persons with treated cardiovascular disease. Use of selective serotonin reuptake inhibitors was not associated with an increased risk of sudden cardiac death (rate ratio, 0.95; 95% CI, 0.42 to 2.15) (Ray et al, 2004).

b) In a case report, a 31-year-old severely depressed woman developed severe epileptic convulsions followed by cardiac ARREST during a 300 mg infusion of parenteral clomipramine (Singh, 1972a). The patient had been started on parenteral clomipramine 25 mg/day which was slowly increased to 250 mg/day over 14 days. The cardiac arrest occurred on day 15 of treatment. She was resuscitated by external cardiac massage; EKG showed slight T wave flattening. One week later the patient restarted on oral clomipramine and was discharged 6 weeks later with no further cardiac problems.

3.3.1.A.2 Hypotension

a) Orthostatic hypotension worsened in both younger (less than 55 years of age, n=74) and older (55 to 70 years of age, n=28) people after taking clomipramine 150 milligrams per day for 2 weeks, but the fall in blood pressure was more severe in the older population (Stage et al, 2002).

b) A 57-year-old man who had been taking clomipramine 150 milligrams at bedtime for 2 years developed hypotension when he received general anesthesia in preparation for mitral valve repair. Anesthesia was induced with sodium thiopental and fentanyl and maintained with isoflurane. Forty-five minutes after induction of anesthesia, blood pressure and vascular resistance declined. Blood pressure was unresponsive to ephedrine, phenylephrine, and dopamine. After skin incision and sternotomy, systolic blood pressure decreased precipitously, to 55 millimeters of mercury. Despite multiple boluses of ephedrine and an infusion of norepinephrine, the patient developed third-degree atrioventricular block. Cardiopulmonary bypass was begun, and the surgery proceeded. The dosage of norepinephrine was increased before weaning from cardiopulmonary bypass. Prior to surgery, the patient had experienced postural hypotension, which was attributed to clomipramine. Therefore, a presumptive diagnosis of clomipramine-induced hypotension precipitated by anesthesia was made, and clomipramine was withheld. The patient was gradually weaned from norepinephrine (Malan et al, 2001).

c) Hypotension, TACHYCARDIA, and DIZZINESS have been reported at therapeutic doses of oral clomipramine (75 to 300 mg/day) (Dunbar et al, 1985a; De Wilde et al, 1983a; Pinder et al, 1980a). Most cases were mild and did not require any treatment.

3.3.2 Dermatologic Effects

3.3.2.A Clomipramine Hydrochloride

Diaphoresis

Discoloration of skin

3.3.2.A.1 Diaphoresis

a) Increased SWEATING was experienced by significantly more patients on clomipramine 50 to 300 mg/day than those on placebo during clinical trials of agoraphobic and obsessive compulsive patients (Johnston et al, 1988; Stern et al, 1980).

3.3.2.A.2 Discoloration of skin

a) A case of pseudocyanotic PIGMENTATION has occurred with clomipramine (Tunca et al, 1989).

3.3.3 Endocrine/Metabolic Effects

3.3.3.A Clomipramine Hydrochloride

Body temperature above normal

Galactorrhea

Hyperglycemia

Syndrome of inappropriate antidiuretic hormone secretion

Weight change finding

3.3.3.A.1 Body temperature above normal

a) More than 30 cases of hyperthemia have been associated with clomipramine. Most instances occurred when clomipramine was used in combination with other drugs. NEUROLEPTIC MALIGNANT SYNDROME has developed when clomipramine was administered concomitantly with a neuroleptic agent (Prod Info Anafranil(R), 2001b).

b) Sixteen of 38 inpatients with DSM-IIIR major depression treated with clomipramine alone developed at least one sympton of the serotonin syndrome in a prospective study (Lejoyeux et al, 1993). This syndrome includes confusion, agitation, myoclonus, diaphoresis, tremor, and diarrhea. In 14 cases, tremor and myoclonus occurred simultaneously and 10 patients presented tremor, myoclonus, diaphoresis, and shivering. With the exception of 2 patients, symptoms were transient, lasted less than 1 week, and resolved with treatment.

c) Two cases of clomipramine-moclobemide overdose resulted in fatal serotonin syndrome (Neuvonen et al, 1993j). A 23-year-old male and 19-year-old female ingested 1000-1500 mg moclobemide, an MAO-A selective inhibitor and 225 to 500 mg clomipramine in order to "get high". Two to 3 hours later they were euphoric, but developed extreme tremor within the next 2 hours followed by convulsions and loss of consciousness. Both patients died 9 to 10 hours after ingestion, one in status epilepticus and the other while in hyperthermia following generalized epileptiform convulsions. Blood levels of both drugs at autopsy were lower than expected, based on the estimated amount of drug ingested. This may reflect prolonged absorption or postmortem redistribution. There were no levels of desmethyl or hydroxy metabolites of clomipramine reported.

3.3.3.A.2 Galactorrhea

a) Summary

1) Clomipramine therapy has been associated with the development of galactorrhea, hyperprolactinemia, and amenorrhea.

b) Several cases of HYPERPROLACTINEMIA and galactorrhea have been reported with clomipramine therapy. A severely depressed woman in her late twenties was admitted to a psychiatric unit and started on oral clomipramine 75 mg twice daily and L-tryptophan 1 g 3 times daily. Two days later the patient developed profuse galactorrhea which was associated with AMENORRHEA. L-tryptophan was reduced and eventually stopped over a 3-week period with no change in breast secretion. Clomipramine was reduced to 25 mg twice daily and bromocriptine 2.5 mg twice daily was initiated. Galactorrhea gradually resolved after 6 weeks of this therapy and menstruation also returned at this time (Anand, 1985).

c) A woman who had been on oral clomipramine 10 mg twice daily for several years for anxiety developed galactorrhea, loss of libido, and uncomfortable breast engorgement 6 months after an increase of clomipramine to 50 mg at night (Fowlie & Burton, 1987). Her plasma prolactin levels were also above normal. Clomipramine was discontinued and within 2 weeks galactorrhea was reduced; within 3 months her breasts became normal and galactorrhea had resolved.

3.3.3.A.3 Hyperglycemia

a) Hyperglycemia, glucosuria and diabetes mellitus has been reported with the use of clomipramine (Prod Info ANAFRANIL(R) oral capsules, 2007a).

b) An 84-year-old woman developed severe hyperglycemia within 5 months following the initiation of clomipramine 25 mg/day. The patient had a medical history of well-controlled hypertension, atrial fibrillation and concomitant medications included aspirin and irbesartan. Her BMI was 23 kg/m(2) and she had a negative family history of diabetes or glucose intolerance. Upon physical examination the patient was dehydrated and neurological examination noted obtunded consciousness without other abnormalities. Laboratory analysis revealed severe hyperglycemia (serum glucose, 459 mg/dL (25.5 mmol/L)), ketonemia, metabolic acidosis, elevated HbA1C level (12%), serum sodium (158 mmol/L), SCr (1.8 mg/dL), glycosuria and ketonuria. Additional laboratory test results were within normal ranges (eg, CBC, serum lipase and serum amylase) and chest radiography and CT of the head and abdomen were unremarkable. Upon hospitalization, the clomipramine was discontinued and the patient was treated with IV insulin (30 units/day) and IV fluids. The patient's blood glucose level normalized with treatment and after 10 days, the insulin therapy was discontinued and the patient was discharged from the hospital. Three months after hospital discharge, laboratory analysis reported HbA1C level at 5% and the patient agreed to restart the clomipramine under medical surveillance. One week after restarting the clomipramine, the patient developed hyperglycemia (serum glucose, 250 mg/dL (13.88 mmol/L)), glycosuria, and ketonuria. Again, the clomipramine was discontinued and the blood glucose normalized after 2 days. A temporal relationship appears to exist between the administration of clomipramine and the development of hyperglycemia and with the resolution of the hyperglycemia upon withdrawal of clomipramine(Mumoli & Cei, 2008).

3.3.3.A.4 Syndrome of inappropriate antidiuretic hormone secretion

a) HYPONATREMIA secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) has been attributed to clomipramine (Pledger & Mathew, 1989). Hyponatremia developed in a 64-year-old woman 2 days following initiation of clomipramine 25 g three times daily. The patient was not receiving other medications. Clomipramine was discontinued and electrolyte levels a week later were normal.

3.3.3.A.5 Weight change finding

a) Weight gain was reported in 18% of patients in controlled studies receiving clomipramine compared to 1% of patients administered placebo. Twenty-eight percent of these patients had weight gain of at least 7% of their initial body weight and several patients had weight gains in excess of 25% of their initial body weight. Conversely, 5% of patients receiving clomipramine and 1% receiving placebo had weight losses of at least 7% of their body weight (Prod Info Anafranil(R), 2001b).

3.3.4 Gastrointestinal Effects

3.3.4.A Clomipramine Hydrochloride

3.3.4.A.1 Gastrointestinal tract finding

a) Mild to moderate CONSTIPATION has been reported as an adverse effect by patients on clomipramine therapy (75 to 300 mg/day) (Dick & Ferrero, 1983)(Stern et al, 1980; Langohr et al, 1985a).

b) DRY MOUTH has been reported to occur in over 50% of patients on clomipramine therapy (75 to 300 mg/day) (Dunbar et al, 1985a); (Dick & Ferrero, 1983)(Flament et al, 1985; Johnston et al, 1988; Stern et al, 1980).

3.3.5 Hematologic Effects

3.3.5.A Clomipramine Hydrochloride

Agranulocytosis

Hematology finding

Pancytopenia

3.3.5.A.1 Agranulocytosis

a) Incidence: rare

b) Agranulocytosis has been reported with tricyclic antidepressants (Miller, 1963; Bird, 1960; Crammer & Elkes, 1967) and clomipramine has been associated with this syndrome. A 37-year-old depressed woman received a total of 2.65 grams of both oral and parenteral clomipramine over a 26-day period (Souhami et al, 1976). She developed a sore throat and fever 3 weeks after stopping treatment. A white cell count revealed a complete absence of neutrophils. The patient developed a candida infection and was admitted to the hospital for antibiotic therapy. After 12 days of NEUTROPENIA, there was an increase in the lymphocyte count followed by a sudden reappearance of neutrophils. Clinical

improvement was noted with the reappearance of neutrophils and the patient was discharged 40 days after admission. In a second report, a 49-year-old postmenopausal caucasian female was treated with clomipramine 150 mg at bedtime for 38 days. Four days after stopping the drug, a routine hemogram revealed leukopenia: 1200/mm(3) from 4500/mm(3) one month earlier. One week later, the white blood cell count was 4200 and the agranulocytosis had resolved (Gravenor et al, 1986).
c) A 67-year-old man developed concurrent severe agranulocytosis with elevation of hepatic transaminases after treatment with clomipramine (CMI) for 1 month at 175 mg/day. The white count returned to normal 14 days after discontinuation of CMI (Alderman et al, 1993).

3.3.5.A.2 Hematology finding

a) Clomipramine has caused LEUKOPENIA, agranulocytosis, THROMBOCYTOPENIA, ANEMIA, and pancytopenia. Leukocyte and differential blood counts should be obtained in patients who develop fever and sore throat during treatment with clomipramine (Prod Info Anafranil(R), 2001b).

3.3.5.A.3 Pancytopenia

a) Incidence: rare
b) A 54-year-old man developed pancytopenia after being treated with oral clomipramine 50 mg/day for approximately 40 days and parenteral clomipramine 50 mg/day for several days before the onset of symptoms (Magni et al, 1987). Several days after admission the patient experienced increased fatigue, drowsiness, pallor and ecchymoses on the arms. A complete blood count revealed a progressive reduction of all cell lines, with platelets and white blood cells leading the way. On day 20 after admission clomipramine was discontinued and his blood count began to rise. The patient was discharged on day 49 with his blood count still below baseline, but continuing to rise.

3.3.6 Hepatic Effects

3.3.6.A Clomipramine Hydrochloride

Allergic hepatitis

Hepatotoxicity

3.3.6.A.1 Allergic hepatitis

a) A 41-year-old woman developed allergic hepatitis with extreme eosinophilia during the second month of treatment with clomipramine for suicidal depression. After 4 weeks of clomipramine treatment (dose incremented to 150 milligrams/day), she developed right-sided upper abdominal pain and had fever, which normalized after 2 days. Abdominal pain persisted. Liver enzymes were elevated, but there was no eosinophilia. By 6 weeks, eosinophils had increased to 65% of the differential white blood cell count. Allergic hepatitis was diagnosed and clomipramine was discontinued. Hematopoietic side-effects disappeared within 2 weeks. Liver function took longer to normalize. Her depression was then successfully treated with a chemically unrelated substance (moclobemide) (Wiersma et al, 2000).

3.3.6.A.2 Hepatotoxicity

a) Incidence: 1-3%
b) Clomipramine has induced elevated aspartate aminotransferase (AST or SGOT) and alanine aminotransferase (ALT or SGPT) in approximately 1% and 3% of patients, respectively, to levels 3 times the upper limit of normal (Prod Info Anafranil(R), 2001b). Caution is indicated in treating patients with known liver disease, and periodic monitoring of hepatic enzymes is recommended in such patients.
c) A 67-year-old man developed concurrent severe agranulocytosis with elevation of hepatic transaminases after treatment with clomipramine (CMI) for 1 month at 175 mg/day. The white count returned to normal 14 days after discontinuation of CMI (Alderman et al, 1993).

3.3.8 Musculoskeletal Effects

3.3.8.A Clomipramine Hydrochloride

Fracture of bone

Fracture of bone, Nonvertebral

3.3.8.A.1 Fracture of bone

a) In a case-control study including fracture cases (n=124,655) during the year 2000 and age- and gender-matched controls (n=373,962), there was an increased risk of any fracture in participants who

were using an average standard daily dose of clomipramine (adjusted odds ratio (OR), 1.49; 95% CI, 1.19 to 1.88) compared to those who were not exposed to clomipramine. Clomipramine use was associated with an increased risk of hip fracture (adjusted OR, 2.04; 95% CI, 1.11 to 3.75), but not forearm (adjusted OR, 1.61; 95% CI, 0.89 to 2.89) or spine fracture (adjusted OR, 2.79; CI, 0.88 to 8.8) (Vestergaard et al, 2008)

3.3.8.A.2 Fracture of bone, Nonvertebral

a) In a prospective, population-based, cohort study (n=7983) with a mean follow-up of 8.4 years, there was an increased risk of nonvertebral fracture in adult participants older than 55 years of age (mean age of 77.5 years) who were currently using an tricyclic antidepressant (TCA), including amitriptyline, clomipramine, dosulepine, doxepine, imipramine, maprotiline, nortriptyline, and opipramol, compared to those who were not exposed to antidepressants. Current TCA use was associated with an increased risk of nonvertebral fracture (hazard ratio (HR), 1.6; 95% confidence interval (CI), 1.08 to 2.38) compared with no antidepressant use. Current TCA use was also associated with an increased risk of nonvertebral fracture (HR, 1.6; 95% CI, 1.02 to 2.5) compared with past antidepressant use (n=1217). Duration of TCA use of greater than 6 months was not associated with an increased risk of fractures when compared with no antidepressant use and with past antidepressant use. Fractures of the hip (most frequent), wrist, humerus, and pelvis were reported (Ziere et al, 2008).

3.3.9 Neurologic Effects

Clomipramine

Clomipramine Hydrochloride

3.3.9.A Clomipramine

3.3.9.A.1 Seizure

See Drug Consult reference: COMPARATIVE INCIDENCE OF SEIZURES FROM ANTIDEPRESSANTS

3.3.9.B Clomipramine Hydrochloride

Central nervous system finding

Gilles de la Tourette's syndrome

Seizure

Serotonin syndrome

3.3.9.B.1 Central nervous system finding

a) Summary

1) Increased aggression, tremor and decreased cognitive function have been associated with clomipramine administration in obsessive-compulsive disorder (OCD) and depressed patients and in normal volunteers. It has also precipitated panic attacks in patients with panic disorder.

b) TREMOR is a commonly reported adverse effect with clomipramine 75 to 300 mg/day in both depressive and obsessive compulsive disorder patients (Flament et al, 1985; Stern et al, 1980; Larsen et al, 1984; Levin, 1982a). In one study, the tremor was rapid with low amplitude and was successfully treated within a few days with oral biperiden 6 mg/day (Klok et al, 1981a).

c) The effects of a 10-day regimen of clomipramine (CMI) 25 to 50 mg tid on psychomotor and cognitive function were assessed in 12 normal volunteer subjects. CMI had little effect on EEG but reaction speed was markedly slowed. Tolerance did not develop to acute MEMORY IMPAIRMENT on a verbal recall test and subjective ratings for mood and bodily symptoms were adversely affected by CMI (Allen et al, 1991).

d) Performance on tasks tapping automatic and voluntary aspects of memory, attention, and motor speed was examined in 14 patients with major depressive disorder, before and after 3 weeks of treatment with clomipramine 150 mg/day. Performance on tasks requiring frontal functions improved or did not change, whereas verbal learning and retention, where hippocampal functioning is critical, were impaired. The latter tasks were negatively related to cerebrospinal fluid (CSF) 5-HIAA levels and plasma concentration of clomipramine (Bartfai et al, 1991).

3.3.9.B.2 Gilles de la Tourette's syndrome

a) Vocal and motor tics (Tourettism) developed after administration of clomipramine to a young patient with obsessive compulsive disorder and schizoid personality disorder (Moshe et al, 1994).

3.3.9.B.3 Seizure

a) Summary

1) Seizures associated with clomipramine have been reported during therapy, upon withdrawal of therapy by patient or neonate, and with overdoses. The Medical Letter reports that 0.7% of approximately 3,000 patients in United States clinical trials with clomipramine have experienced seizures (Anon, 1988a).

b) Incidence: 0.7%

c) Several incidences of major motor SEIZURES and STATUS EPILEPTICUS have been reported during clinical trials. The patients had no history of epilepsy or seizures prior to clomipramine therapy. One patient who experienced 2 seizures while on oral clomipramine 150 mg/day had a slightly abnormal EEG before treatment began (Marshall, 1971). The other patient experiencing a seizure while on oral clomipramine 150 mg/day was withdrawn from the study (Anon, 1986). The patient who experienced status epilepticus was on oral clomipramine 50 mg 3 times a day. The seizures were controlled with anticonvulsants and he was withdrawn from the study (Klok et al, 1981a).

d) A 40-year-old man with no history of epileptic seizures or head trauma was admitted to an emergency room comatose with generalized tonic-clonic movements (Flechter et al, 1983). According to his wife, he had taken approximately 2.5 g (100 tablets each 25 mg) of clomipramine. Within 8 hours of admission he developed generalized myoclonic jerking. He was treated with diazepam, diuretics, and large volumes of intravenous fluids. Within 4 days the myoclonic attacks resolved and he became fully conscious.

e) Within 36 hours of stopping clomipramine 50 mg three times daily, a 67-year-old woman became unconscious and developed clonic contractions of her limbs (Robinson, 1978). Following her convulsion she was restarted on clomipramine and fully recovered in 6 weeks, at which time the drug was gradually reduced with no further problems. The patient had no history of epileptic seizures or head trauma.

f) Two cases of neonatal convulsions due to maternal withdrawal of clomipramine were reported (Cowe et al, 1982a). In the first case a 22-year-old mother had been receiving clomipramine at an unspecified dose for the last 7 weeks of pregnancy for depression. She delivered a normal term male infant which developed convulsions at 8 hours of age. Parenteral treatment with phenobarbital and paraldehyde did not control the convulsions, which occurred intermittently for 53 hours. In the second case a 38-year-old mother had been receiving clomipramine and flurazepam at unspecified doses throughout pregnancy. Convulsions in the infant began 7 hours after birth. Parenteral phenobarbital was started but the infant continued to have myoclonic jerks. After 24 hours parenteral clomipramine was started at 0.4 mg over 2 hours, which suppressed the convulsions for 11 hours. Twitching in all limbs returned at this time and the infant was started on a continuous infusion of clomipramine which was gradually decreased over 12 days. Oral clomipramine was started and also slowly decreased. The infant remained jittery but the convulsions were under control. The clomipramine was discontinued at day 17 with no ill effects.

g) During a 4-week comparative trial, 36 female patients received either oral clomipramine or oral fluvoxamine 50 mg 3 times daily. During the third treatment week, 1 patient on clomipramine developed status epilepticus that was controlled with anticonvulsants. The patient had no history of epilepsy and was withdrawn from the study (Klock et al, 1981).

h) Acute and chronic effects of clomipramine on the human EEG in patients treated for depression could not be differentiated (Ulrich et al, 1994).

3.3.9.B.4 Serotonin syndrome

a) A 60-year-old woman with depression and anxiety suffered a fatal case of serotonin syndrome secondary to her clomipramine treatment (Rosebush et al, 1999). The woman had been receiving clomipramine for 8 months and her dose had been increased to 250 mg daily. Other medication included lisinopril, glyburide, and clonazepam. She became ill over a period of hours and developed encephalopathy, myoclonus, hyperreflexia, tremulousness, diarrhea, and incoordination. Her creatine phosphokinase increased to 39,900 units/L. Liver function tests were elevated, platelet count was elevated, and her coagulation studies were consistent with disseminated intravascular coagulation. Her blood level of clomipramine plus the major metabolite was 2,230 nmol/L (normal range less than 1,900). She was treated with cooling blankets, intravenous fluids, lidocaine for ventricular tachycardia, and phenytoin for seizures. Rhabdomyolysis occurred resulting in acute renal failure and the need for dialysis. After 4 weeks, she developed opportunistic infections and died.

b) Sixteen of 38 inpatients with DSM-IIIR major depression treated with clomipramine alone developed at least one sympton of the serotonin syndrome in a prospective study (Lejoyeux et al, 1993). This syndrome includes confusion, agitation, myoclonus, diaphoresis, tremor, and diarrhea. In 14 cases, tremor and myoclonus occurred simultaneously and 10 patients presented tremor, myoclonus, diaphoresis, and shivering. With the exception of 2 patients, symptoms were transient, lasted less than 1 week, and resolved with treatment.

3.3.12 Psychiatric Effects

3.3.12.A Clomipramine Hydrochloride

Aggressive behavior

Delirium

Hallucinations

Mania

Panic attack

Suicidal thoughts

3.3.12.A.1 Aggressive behavior

a) Paranoid ideation and aggressive behavior developed in two adolescents with obsessive compulsive disorder during treatment with therapeutic doses of clomipramine. Possible pathogenetic factors involving serotonin and serotonin receptor abnormalities are discussed (Alarcon et al, 1991).

3.3.12.A.2 Delirium

a) Two women, 61 and 67 years old, whose DSM-IV major depression failed to respond to oral treatment with clomipramine 150 mg/day, developed delirium and HALLUCINATIONS when intravenous clomipramine 12.5 milligrams was added to the regimen. Delirium was diagnosed within 4 to 6 days after beginning intravenous administration. In both cases, discontinuation of intravenous administration resulted in gradual improvement, over days, of the delirious state. In both women, plasma levels of clomipramine and its metabolite, desmethylclomipramine, doubled with the introduction of intravenous dosing (Ueda et al, 2000).

3.3.12.A.3 Hallucinations

a) The onset of "music hallucinations" has been associated with the use of clomipramine 75 mg per day three weeks after it was initiated for the treatment of major depression in a 67-year-old widowed female patient (Valleda & Gentil, 1991).

3.3.12.A.4 Mania

a) MANIA developed in 6 of 25 patients being treated with clomipramine for unipolar depression (van Sheyen & van Kammen, 1979). The patients had been on oral clomipramine 150 to 225 mg/day in 3 divided doses for 6 to 13 weeks before the development of mania. Mania lasted from 15 to 49 days after clomipramine was stopped and perphenazine or haloperidol therapy was initiated. The duration of the mania strongly correlated with the duration of clomipramine therapy.

3.3.12.A.5 Panic attack

a) Low-dose (12.5 mg) intravenous clomipramine precipitated severe dysphoria/panic attacks in patients with diagnosed panic disorder (George et al, 1995).

3.3.12.A.6 Suicidal thoughts

a) Adult and pediatric patients being treated with antidepressants for major depressive disorder who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, or mania may be at risk of suicidal ideation and behavior (SUICIDALITY). This same concern applies to treating patients with other psychiatric and nonpsychiatric disorders. If these symptoms are observed, therapy should be reevaluated and it may be necessary to discontinue medications when symptoms are severe, sudden in onset, or were not part of the patient's initial symptoms. Patients and their caregivers should be provided with the Medication Guide that is available for this drug (Anon, 2004).

b) A causal role for antidepressants in inducing suicidality has been established in pediatric patients. Anyone considering the use of antidepressants in a child or adolescent must balance this risk with the clinical need. In pooled analyses of 24 short-term, placebo-controlled trials of nine antidepressants (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, bupropion, mirtazapine, nefazodone, and venlafaxine extended-release) including over 4400 pediatric patients with major depressive disorder, obsessive compulsive disorder, or other psychiatric disorders, a greater risk of suicidal behavior or ideation during the first few months of therapy was demonstrated in patients receiving antidepressants as compared with placebo (4% vs 2%, respectively). The risk of suicidality was most consistently observed in the trials that included patients with major depressive disorder, but there were signs of risk emerging from trials in other psychiatric indications, such as obsessive compulsive disorder and social anxiety disorder. No suicides occurred in these trials. The risk of suicidality during longer-term use (ie,

beyond several months) in pediatric patients is not known. It is also unknown whether this risk extends to adult patients (Anon, 2004).

3.3.13 Renal Effects

3.3.13.A Clomipramine Hydrochloride

3.3.13.A.1 Urinary retention

a) A 15-year-old male experienced 2 episodes of urinary retention while on oral clomipramine therapy for obsessive-compulsive disorder (Hermesh et al, 1987). The patient was on clomipramine 50 mg 3 times a day and first experienced urinary adverse effects 3 weeks from the initiation of therapy. Subcutaneous bethanechol 5 mg and oral phenoxybenzamine 40 mg/day for 3 days failed to improve his symptoms. Improvement in his obsessive-compulsive behavior was noted throughout clomipramine therapy and was maximal when the dose was increased to 200 mg/day. However during week 20 of therapy the patient experienced urinary retention for 16 hours and required catheterization to remove 1200 mL of urine. Within 8 days of clomipramine discontinuation all urinary symptoms had resolved.

3.3.14 Reproductive Effects

Clomipramine

Clomipramine Hydrochloride

3.3.14.A Clomipramine

3.3.14.A.1 Sexual dysfunction

See Drug Consult reference: DRUG-INDUCED SEXUAL DYSFUNCTION

3.3.14.B Clomipramine Hydrochloride

Sexual dysfunction

Sperm finding

3.3.14.B.1 Sexual dysfunction

a) DELAYED EJACULATION has been reported during several studies of patients with obsessive compulsive disorder at clomipramine doses of 50 to 300 mg/day (Yaryura-Tobias et al, 1976; Insel et al, 1983; Volavka et al, 1985a).

b) Partial or total ANORGASMIA was experienced by 92% (n=24; 17 men and 7 women) of patients with obsessive compulsive disorder during a double-blind, placebo-controlled study to assess changes in sexual function (Monteiro et al, 1987). None of the 9 placebo patients experienced any sexual dysfunction. Patients received clomipramine 25 to 200 mg/day. Most patients still had interest in sex but noticed difficulty in achieving orgasm within the first few days of clomipramine therapy. Normal sexual function returned within 3 days of stopping clomipramine in all but 1 man who improved without treatment in 3 months.

c) Orgasmic inhibition was reported in 1 male and 2 female patients who were depressed with obsessive-compulsive features (Quirk & Einarson, 1982). Orgasmic dysfunction occurred shortly after beginning clomipramine, despite a return of libido as the depression improved. Two patients were switched to desipramine; this resulted in resolution of sexual dysfunction while maintaining depression control. The third patient manipulated the dosing interval and reduced the intensity of the anorgasmia. Strong anticholinergic/antiadrenergic activity is felt to be the cause of anorgasmia from clomipramine.

d) There have been several interesting cases of patients experiencing ORGASM when yawning while receiving clomipramine therapy. Upon discontinuation of clomipramine these symptoms resolved. These side effects were discovered during routine questioning, and no placebo-replacement or rechallenge with clomipramine have been tried (McLean et al, 1983).

e) Three cases of painful ejaculation associated with clomipramine during the first 3 weeks of treatment were reported. Dosage was 100 mg/d in one case and 150 mg/d in 2 cases. The adverse effect resolved within several days of dosage reduction or discontinuation of the medication (Aizenberg et al, 1991).

3.3.14.B.2 Sperm finding

a) All spermiograms of 9 patients treated with clomipramine 75 mg/day for 3 months were pathological in terms of volume, motility, and morphology compared with 37% of control patients (same as healthy

population). Hormone levels associated with the hypothalamic hypophyseal-gonadal axis were not affected in either group (Maier & Koinig, 1994).

3.3.16 Other

3.3.16.A Clomipramine Hydrochloride

Summary

Withdrawal sign or symptom

3.3.16.A.1 Summary

a) GENERAL

1) Other than orthostatic hypotension, side effects from clomipramine treatment (dry mouth, tremor, sweating, constipation, accommodation disturbances, sedation) were no more frequent or severe in an older population (55 to 70 years of age, n=28) than in a younger one (less than 55 years of age, n=74) (Stage et al, 2002).

3.3.16.A.2 Withdrawal sign or symptom

a) A variety of withdrawal symptoms have been reported in association with abrupt discontinuation of clomipramine, including dizziness, nausea, vomiting, headache, malaise, sleep disturbance, hyperthermia, and irritability. In addition, such patients may experience a worsening of psychiatric status. The dosage of clomipramine should be gradually tapered and the patient monitored carefully during discontinuation (Prod Info Anafranil(R), 2001b; Diamond et al, 1989).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

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

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

2) Australian Drug Evaluation Committee's (ADEC) Category: C (Batagol, 1996)

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

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Yes

4) Clinical Management

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

5) Literature Reports

a) Clomipramine has not been associated with teratogenic effects in human case reports, however, other tricyclic antidepressants (imipramine, amitriptyline) have been associated with teratogenic effects. Neonatal withdrawal symptoms secondary to maternal use of clomipramine have been reported.

b) Two cases of neonatal convulsions due to maternal withdrawal of clomipramine have been reported (Cowe et al, 1982). In the first case a 22-year-old mother had been receiving clomipramine at an unspecified dose for the last 7 weeks of pregnancy for depression. She delivered a normal term male infant who developed convulsions at 8 hours of age. Parenteral treatment with phenobarbital and paraldehyde did not control the convulsions, which occurred intermittently for 53 hours. In the second case, a 38-year-old mother had been receiving clomipramine and flurazepam of unspecified doses throughout pregnancy. Convulsions in the infant began 7 hours after birth. Parenteral phenobarbital was started but the infant continued to have myoclonic jerks. After 24 hours parenteral clomipramine was started at 0.4 mg over 2 hours, which suppressed the convulsions for 11 hours. Twitching in all limbs returned at this time and the infant was started on a continuous infusion of clomipramine which was started and also slowly decreased. The infant remained jittery but the convulsions were under control. The clomipramine was discontinued at day 17 with no ill effects.

c) In a case report, a pregnant woman with endogenous depression had been taking oral clomipramine 200 mg daily throughout her pregnancy (Ostergaard & Pedersen, 1982). She delivered an infant who became cyanotic, lethargic, and tachypneic with moderate respiratory acidosis. Treatment with oxygen and incubation reversed these conditions. The infant developed twitches and tremors with an abnormal motor pattern within 24 hours of birth. Following treatment with phenobarbital, the symptoms gradually decreased and completely resolved in one week.

d) A mother treated with clomipramine during pregnancy delivered a normal infant at term (Schimmell et al, 1991). The newborn did show hypotonia and jitteriness at birth and both effects resolved spontaneously by 6 days of age. The infant was breast-fed while the mother took oral clomipramine in therapeutic dosage (150 mg/day), producing a clomipramine level in the infant of 0.4% of the material level. Four of five women who took clomipramine throughout their pregnancies delivered healthy babies with no evidence of congenital malformations. The fifth woman elected to terminate her pregnancy at 9 weeks. Thus, the authors concluded that clomipramine can be safely used in pregnant women and mothers who breast-feed their newborns without fear of clomipramine intoxication.

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

B) Breastfeeding

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

2) World Health Organization Rating: Compatible with breastfeeding. (Anon, 2002)

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

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

4) Clinical Management

a) According to the American Academy of Pediatrics, clomipramine is among those agents that may be of concern when used while breastfeeding (Anon, 2001). Although clomipramine appears in breast milk, the concentration is low and may not be pharmacologically significant.

5) Literature Reports

a) Clomipramine is excreted in breast milk. A mother treated with clomipramine during pregnancy delivered a normal infant at term (Schimmell et al, 1991a). The newborn did show hypotonia and jitteriness at birth and both effects resolved spontaneously by 6 days of age. The milk:plasma ratios on the 4th and 6th days were 1.62 and 1.04, respectively. The infant was started on breastfeeding at the 7th day of age while the mother took oral clomipramine in therapeutic dosage (150 mg/day), producing a clomipramine level in the infant of 0.4% of the maternal level. The milk:plasma ratios on the 10th, 14th, and 35th days were 0.76, 0.84, and 1.22, respectively.The infant remained asymptomatic.

b) A report describing four women maintained on clomipramine 75 mg to 125 mg per day who breastfed their infants demonstrated that infant serum concentrations of clomipramine metabolites (N-desmethylclomipramine, 8-hydroxyclomipramine and 8-hydroxydesmethylclomipramine) were below the assay sensitivity of 10 ng/mL. The measurements were taken after approximately 3 weeks of consistent maternal dosing, and all infants were noted to be developing normally (Wisner et al, 1995).

6) Drug Levels in Breastmilk

a) Parent Drug

1) Milk to Maternal Plasma Ratio

a) 0.76-1.62 (Schimmell et al, 1991a)

b) Active Metabolites

1) DESMETHYLCLOMIPRAMINE (Nagy & Johansson, 1977a)

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Food Combinations

3.5.1 Drug-Drug Combinations

Acenocoumarol

Amobarbital

Amphetamine

Amprenavir

Anisindione

Aprobarbital

Arbutamine

Arformoterol

Armodafinil

Atazanavir

Atomoxetine

Belladonna

Belladonna Alkaloids

Bepridil

Bethanidine

Butabarbital

Butalbital

Cannabis

Carbamazepine

Chlorotrianisene

Cimetidine

Cisapride

Clonidine

Clorgyline

Conjugated Estrogens

Dexfenfluramine

Dexmethylphenidate

Dextroamphetamine

Dicumarol

Dienestrol

Diethylpropion

Diethylstilbestrol

Diphenhydramine

Duloxetine

Enalaprilat

Enalapril Maleate

Epinephrine

Esterified Estrogens

Estradiol

Estriol

Estrone

Estropipate

Eterobarb

Ethinyl Estradiol

Etilefrine

Fenfluramine

Fluvoxamine

Formoterol

Fosamprenavir

Fosphenytoin

Gatifloxacin

Grepafloxacin

Guanadrel

Halofantrine

Heptabarbital

Hexobarbital

Iproniazid

Isocarboxazid

Linezolid

Lisdexamfetamine

Lumefantrine

Mazindol

Mephentermine

Mephobarbital

Mestranol

Methamphetamine

Methohexital

Methoxamine

Methylphenidate

Midodrine

Moclobemide

Modafinil

Moxifloxacin

Nefopam

Nialamide

Norepinephrine

Olanzapine

Oxilofrine

Oxybutynin

Pargyline

Paroxetine

Pemoline

Pentobarbital

Phendimetrazine

Phenelzine

Phenindione

Phenmetrazine

Phenobarbital

Phenprocoumon

Phentermine

Phenylephrine

Phenytoin

Primidone

Procarbazine

Propylhexedrine

Quinestrol

Quinidine

Rasagiline

S-Adenosylmethionine

Salmeterol

Secobarbital

Selegiline

Sertraline

St John's Wort

Tapentadol

Thiopental

Tibolone

Toloxatone

Tramadol

Tranylcypromine

Valproic Acid

Vasopressin

Venlafaxine

Warfarin

Yohimbine

3.5.1.A Acenocoumarol

1) Interaction Effect: increased risk of bleeding

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

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

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

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

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

3.5.1.D Amprenavir
1) Interaction Effect: increased tricyclic serum concentrations and potential toxicity (anticholinergic effects, sedation, confusion, cardiac arrhythmias)
2) Summary: Coadministered amprenavir may increase serum concentrations of tricyclic antidepressants, causing a potential risk of arrhythmias or other serious adverse effects. Currently no interaction study has been conducted. Amprenavir is metabolized by cytochrome P450 3A4 enzymes in addition to being a CYP3A4 inhibitor, and tricyclics may partially depend on this pathway for metabolism. Plasma concentrations of the tricyclic should be closely monitored and dose adjustments made accordingly in patients also receiving amprenavir (Prod Info Agenerase(R), 2000).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: If concomitant therapy with amprenavir and a tricyclic antidepressant is unavoidable, plasma concentrations of the tricyclic should be closely monitored and dose adjustments made accordingly. Also monitor patients for signs and symptoms of tricyclic toxicity (anticholinergic effects, sedation, confusion, cardiac arrhythmias).
7) Probable Mechanism: inhibition of cytochrome P450-mediated tricyclic metabolism

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

TCAs (Williams et al, 1976d). TCAs affected the stability of anticoagulant control leading to frequent changes in the doses of anticoagulants. Inhibition of coumarin metabolism was the postulated mechanism.

3.5.1.F Aprobarbital

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

3.5.1.G Arbutamine

1) Interaction Effect: unreliable arbutamine test results
2) Summary: Because tricyclic antidepressants may affect heart rate, arbutamine should not be administered to a patient receiving a tricyclic antidepressant, since arbutamine test results may be unreliable (Prod Info GenESA(R), 1997).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Arbutamine should not be administered to a patient receiving tricyclic antidepressant therapy.
7) Probable Mechanism: alteration of heart rate by the tricyclic antidepressant

3.5.1.H Arformoterol

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

3.5.1.I Armodafinil

1) Interaction Effect: increased clomipramine exposure
2) Summary: Administration of armodafinil (R-enantiomer of modafinil) may cause moderate inhibition of CYP2C19 isozyme activity. Although not studied with clomipramine, a CYP2C19 substrate, concurrent administration of a single 400-mg dose of armodafinil with a 40-mg dose of omeprazole, also a CYP2C19 substrate, led to an approximately 40% increase in systemic exposure of omeprazole. Additionally, increased levels of clomipramine and its active metabolite, desmethylclomipramine, were reported in a narcoleptic patient receiving concomitant therapy with modafinil. Therefore, use caution when armodafinil and clomipramine are used concurrently. Dose reductions of clomipramine may be necessary (Prod Info NUVIGIL(TM) oral tablets, 2007). Also, monitor patients for increased clomipramine adverse events (dry mouth, sedation, urinary retention).

3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the coadministration of armodafinil and clomipramine as this may result in increased clomipramine exposure. Dose reductions of clomipramine may be necessary (Prod Info NUVIGIL(TM) oral tablets, 2007). Monitor patients for increased clomipramine adverse events (dry mouth, sedation, urinary retention).
7) Probable Mechanism: inhibition of CYP2C19-mediated clomipramine metabolism

3.5.1.J Atazanavir
1) Interaction Effect: increased plasma concentrations of tricyclic antidepressants (drowsiness, hypotension, akathisia)
2) Summary: Coadministration of atazanavir and tricyclic antidepressants has not been studied. However, the coadministration of atazanavir and tricyclic antidepressants has the potential to produce serious and/or life-threatening adverse events (Prod Info 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 for clinical signs and symptoms of tricyclic antidepressant toxicity (hypotenstion, akathisia, anticholinergic effects, sedation, confusion, cardiac arrhythmias).
7) Probable Mechanism: unknown

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

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

3.5.1.M Belladonna Alkaloids
1) Interaction Effect: excessive anticholinergic activity (severe dry mouth, constipation, decreased urination, excessive sedation, blurred vision)
2) Summary: The anticholinergic activity of the active alkaloids present in belladonna may predispose the patient to excessive anticholinergic activity if taken with tricyclic antidepressants. Belladonna contains L-hyoscyamine, atropine, and scopolamine with a total alkaloid content of at least 0.3% in the leaves and 0.5% in the roots (Blumenthal et al, 1998). Because belladonna is typically available as a homeopathic preparation, the clinical severity of the interaction with tricyclic antidepressants is unknown. Caution is

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

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

3.5.1.O Bethanidine
1) Interaction Effect: decreased antihypertensive effectiveness
2) Summary: Antidepressants inhibit the uptake of bethanidine at its site of action in the adrenergic neuron. The antagonism may last for several days after discontinuation of the antidepressant (Skinner et al, 1969a; Avery, 1973a; Feagin et al, 1969).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The combination of bethanidine and clomipramine, as well as other tricyclic antidepressant agents, 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 received bethanidine or debrisoquine concurrently with a tricyclic antidepressant. In 24 control patients given the same drugs without antidepressants, blood pressure control was achieved in 18. Withdrawal of antidepressant therapy in several patients resulted in postural hypotension that necessitated a reduction in dosage of bethanidine or debrisoquine (Skinner et al, 1969).

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

3.5.1.Q Butalbital

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

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

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

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

7) Probable Mechanism: increased tricyclic antidepressant metabolism

8) Literature Reports

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

3.5.1.R Cannabis

1) Interaction Effect: tachycardia and delirium

2) Summary: Concomitant tetrahydrocannabinol and tricyclic antidepressant therapy has increased the heart rate and cause delirium beyond that expected with either drug alone (Wilens et al, 1997a; Hillard & Vieweg, 1983a).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Caution is advised if patients use cannabis with a tricyclic antidepressant. Monitor heart rate changes closely.

7) Probable Mechanism: possibly due to beta-adrenergic effect of cannabis coupled with the anticholinergic effect of tricyclic antidepressants

8) Literature Reports

a) A 21-year-old female receiving oral nortriptyline 30 milligrams at bedtime for 9 months developed marked sinus tachycardia (160 beats/minute) within 30 minutes of smoking a cannabis cigarette. The patient's heart rate was about 90 beats/minute before smoking the cannabis. She had used cannabis many times before starting the nortriptyline without ill effects (Hillard & Vieweg, 1983).

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

3.5.1.S Carbamazepine

1) Interaction Effect: decreased clomipramine effectiveness

2) Summary: The concomitant use of carbamazepine and antidepressants has been reported to decrease antidepressant levels (Leinonen et al, 1991; Brown et al, 1990). Although not reported for clomipramine, a similar interaction could occur.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical
6) Clinical Management: Monitor for clinical efficacy of the clomipramine therapy and for any signs of toxicity of carbamazepine. Serum levels of both agents should be considered when either agent is added or discontinued, with appropriate dosage adjustments made accordingly.
7) Probable Mechanism: increased clomipramine metabolism
8) Literature Reports
a) Concomitant administration of imipramine and carbamazepine to children with attention deficit disorder (ADD) has been reported to result in a 50% decrease in the total plasma concentration of imipramine plus desipramine (Brown et al, 1988). Carbamazepine enhances the hepatic microsomal metabolism of imipramine and other tricyclic antidepressants by inducing hepatic enzymes (Moody et al, 1977). Although not reported specifically for clomipramine, be aware that the potential for a similar interaction exists. Patients on chronic carbamazepine therapy may require increased doses of tricyclic antidepressants.

3.5.1.T Chlorotrianisene
1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973g), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972g). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972g) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984g).
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic
8) Literature Reports
a) The qualitative effects of concomitant administration of estrogen and TCAs was evaluated. In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received imipramine (150 milligrams/day) and placebo, 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (50 micrograms/day), while 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (25 micrograms/day). The 10 patients that received placebo did not improve over the 6 weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after 2 weeks, the 5 patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received imipramine 150 milligrams and ethinyl estradiol 50 micrograms daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972f).
b) A case reported demonstrated an interaction in a 32-year-old female taking conjugated estrogens 2.5 milligrams and imipramine 100 milligrams (Khurana, 1972f). The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side-effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973f).
c) A study in which women received clomipramine and oral contraceptives or clomipramine alone was reviewed. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973c).
d) The effects of oral contraceptives on clomipramine in 42 women between the ages of 18 and 40 was studied. Twenty-three women took clomipramine 25 milligrams at bedtime while 19 took clomipramine 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimental group (2 due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980c).

e) Akathisia in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently was reported. A 24-year-old patient receiving clomipramine 120 milligrams/day for anorexia nervosa and conjugated estrogens 1.25 milligrams/day for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogens 1.25 milligrams/day who was prescribed amitriptyline 50 milligrams/day for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. Positive rechallenge at one week with doxepin 100 milligrams, with resolution following discontinuation of doxepin. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogens 1.25 milligrams/day and amitriptyline 50 milligrams/day. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984f).
f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 micrograms or less of ethinyl estradiol) from 27 to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984c).
g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980c). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983c).

3.5.1.U Cimetidine

1) Interaction Effect: clomipramine toxicity (dry mouth, blurred vision, urinary retention)
2) Summary: Cimetidine impairs the metabolism of tricyclic antidepressants (Miller et al, 1983; Sutherland et al, 1987; Steiner & Spina, 1987). Although not reported for clomipramine, it is likely that a similar interaction would occur because of the mechanism involved.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Consider monitoring serum tricyclic antidepressant levels within the first few days of starting or discontinuing cimetidine. An H2 blocker that does not impair the metabolism of the tricyclic agents, such as ranitidine or famotidine, may be an alternative.
7) Probable Mechanism: decreased clomipramine metabolism

3.5.1.V Cisapride

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cisapride therapy has resulted in serious cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, torsades de pointes, and QT prolongation. Because tricyclic antidepressant agents also may prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of cisapride with a drug from this class is contraindicated (Prod Info Propulsid(R), 2000).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of cisapride and tricyclic antidepressants is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.W Clonidine

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

a) The interaction between clonidine and desipramine developed in five hypertensive patients. The results of this double-blind placebo controlled study showed that the introduction of the tricyclic antidepressant led to the loss of blood pressure control in four of the five subjects within two weeks. The rise in the arterial pressure was more prominent in the supine position than in the erect. The average

blood pressure increase in the desipramine period compared to the placebo period was 22/15 mm Hg in the lying position and 12/11 mm Hg standing (Briant et al, 1973).
b) Eleven drug-free patients who met the Research Diagnostic Criteria for Major Depressive Disorder enrolled in a study to determine the effects of desipramine on central adrenergic function. Patients were given a clonidine infusion after 0, 1 and 3 weeks of treatment with desipramine. Results showed that the sedative and hypotensive effects of clonidine were significantly inhibited after three weeks of treatment with desipramine. This interaction was also seen at one week, but did not reach clinical significance. The authors concluded that the effects that were observed during the study were due to an acute drug effect, rather than to a chronic adaptive change (Glass et al, 1982).
c) One case report describes a 65-year-old man who was experiencing perineal pain following the excision of a carcinoma. Pain management of amitriptyline 75 mg nightly and sodium valproate 500 mg three times daily was initiated after slow-release morphine only had a limited effect. A clonidine spinal intrathecal injection of 75 micrograms was given when it was felt that the patient had become tolerant to opioid treatment. Within five minutes, the patient was found to be in severe pain, which resolved within 30 minutes after diamorphine was given. Two mechanisms for this interaction were postulated. In the first, the pain could have been the result of a clonidine-cholinergic interaction. In the second, the tricyclic augmentation of serotoninergic transmission may have unmasked an effect of clonidine at central receptors to enhance nociception (Hardy & Wells, 1988).

3.5.1.X Clorgyline

1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982r; Spigset et al, 1993q; Brodribb et al, 1994p; Neuvonen et al, 1993i). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991j). Consequently, coadministration of TCAs and MAOIs is contraindicated in most cases. If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971u; White & Simpson, 1984p).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of clomipramine with a monoamine oxidase inhibitor (MAOI), such as clorgyline is contraindicated. If clomipramine is replacing treatment with clorgyline, a minimum of 14 days should elapse after clorgyline is discontinued before begin therapy with clomipramine. Similarly, if clomipramine is substituted by clorgyline, a minimum of 14 days should elapse after clomipramine is discontinued and begin therapy with clorgyline (Prod Info clomipramine hydrochloride oral capsule, 2002).
7) Probable Mechanism: altered catecholamine uptake and metabolism
8) Literature Reports
a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers (Prod Info clomipramine hydrochloride oral capsule, 2002). Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965j; Brachfeld et al, 1963f; Winston, 1971j; Schuckit et al, 1971t; Sargent, 1965f; Spiker & Pugh, 1976j). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965j).
b) Administration of a TCA after MAOI therapy may result in the development of serotonin syndrome. In a double-blind, crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-compulsive disorder, two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipramine therapy. After taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with clomipramine without adverse effects (Insel et al, 1982q).
c) A drug interaction was reported in a 76-year old woman who had been taking clomipramine 50 mg daily for several months prior to switching to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fever which then progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days later after discontinuing all antidepressant medications (Spigset et al, 1993p).
d) A 39-year old woman with bipolar disorder developed serotonin syndrome after imipramine was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when imipramine was started at 50 mg daily, followed by two dosage increases of imipramine to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in imipramine to 200 mg per day, the patient developed symptoms of serotonin syndrome, including sweating, shivering, confusion,

fever, and spasms in the extremities. The patient was treated with chlorpromazine and symptoms resolved over the next few days without further complications (Brodribb et al, 1994o).
e) Three patients with bipolar disorder developed manic symptoms while undergoing concurrent therapy with isocarboxazid and amitriptyline. In all three cases the patients had been given MAOIs and TCAs alone without complications. It was only when the drugs were used in combination that symptoms of mania emerged, suggesting a synergistic effect (de la Fuente et al, 1986d).
f) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a physically healthy 34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulation and eventual death (Tackley & Tregaskis, 1987i).
g) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 150 mg amitriptyline or its equivalent, 45 mg phenelzine, or 60 mg isocarboxazid) b) oral administration c) avoidance of clomipramine, imipramine, desipramine, and tranylcypromine in any combination, and d) close monitoring of patients (Kline, 1974e; Winston, 1971j; Schuckit et al, 1971t; White & Simpson, 1984o; Rom & Benner, 1972e). The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991i). Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some sources suggest that the combination of amitriptyline and isocarboxazid is preferred (Perry et al, 1991i). Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs (Ponto et al, 1977j; Schuckit et al, 1971t; Ashcroft, 1975i).

3.5.1.Y Conjugated Estrogens

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

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972h).
b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973h; Khurana, 1972h).
c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched

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

3.5.1.Z Dexfenfluramine

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

steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.AA Dexmethylphenidate

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

3.5.1.AB Dextroamphetamine

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

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

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

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

4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic
8) Literature Reports

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

b) A case report demonstrated an interaction in a 32-year-old female taking conjugated estrogens 2.5 milligrams and imipramine 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side-effects abated (Khurana, 1972). Some investigators have proposed that the side effects resulted from enhanced TCA 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 beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973).

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

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

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

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

3.5.1.AE Diethylpropion

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

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

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

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

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

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

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

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

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

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

3.5.1.AG Diphenhydramine

1) Interaction Effect: increased anticholinergic effects (dry mouth, urinary retention)

2) Summary: Concomitant antidepressants with strong anticholinergic effects (e.g., amitriptyline, amoxapine, clomipramine) and antihistamines may increase the possibility of adynamic ileus, urinary retention, or chronic glaucoma. This interaction may be more prominent in elderly patients (Blazer et al, 1983; Arnold et al, 1981).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Patients should be warned that taking antihistamines, including over-the-counter sleeping pills and cold and allergy preparations, may increase the side effects of clomipramine. Patients should be monitored for dry mouth, drowsiness, and problems with urination. Lower dose of diphenhydramine might be considered, particularly in elderly individuals.

7) Probable Mechanism: additive anticholinergic effects

3.5.1.AH Duloxetine

1) Interaction Effect: increased tricyclic antidepressant serum concentrations and potential toxicity

(anticholinergic effects, sedation, confusion, cardiac arrhythmias)
2) Summary: The coadministration of duloxetine with a tricyclic antidepressant is likely to increase bioavailability of the tricyclic agent, increasing the risk of adverse events. Duloxetine is a moderately potent inhibitor of CYP2D6. When a single dose of the CYP2D6 substrate desipramine 50 mg and duloxetine 60 mg twice daily were coadministered, the desipramine AUC increased 3-fold over baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the combined use of duloxetine with tricyclic antidepressants (TCAs). If concomitant therapy with duloxetine and a TCA is unavoidable, plasma concentrations of the tricyclic should be closely monitored and dose adjustments made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008). Also, monitor patients for signs and symptoms of TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrhythmias).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyclic agent metabolism

3.5.1.AI Enalaprilat
1) Interaction Effect: clomipramine toxicity (confusion, insomnia, irritability)
2) Summary: The addition of clomipramine to long-standing enalapril therapy resulted in high blood levels of clomipramine and signs of toxicity (confusion, insomnia, irritability, and mood changes) in 2 cases. Reduction of the clomipramine dose resulted in lower blood levels (Toutoungi, 1992).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for signs of clomipramine toxicity; lower doses may be required with concurrent therapy with enalapril.
7) Probable Mechanism: unknown

3.5.1.AJ Enalapril Maleate
1) Interaction Effect: clomipramine toxicity (confusion, insomnia, irritability)
2) Summary: The addition of clomipramine to long-standing enalapril therapy resulted in high blood levels of clomipramine and signs of toxicity (confusion, insomnia, irritability, and mood changes) in 2 cases. Reduction of the clomipramine dose resulted in lower blood levels (Toutoungi, 1992).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for signs of clomipramine toxicity; lower doses may be required with concurrent therapy with enalapril.
7) Probable Mechanism: unknown

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

(severe headaches, chest tightness, subarachnoid hemorrhage). The drug history was incomplete, but at least three had been taking a tricyclic antidepressant at the time (Anon, 1972).

3.5.1.AL Esterified Estrogens

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

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

3) Severity: minor

4) Onset: delayed

5) Substantiation: established

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

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

8) Literature Reports

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

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

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

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

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

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984d).
g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980d). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983d).

3.5.1.AM Estradiol

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

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972h).
b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973h; Khurana, 1972h).
c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973d).
d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980d).
e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed

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

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

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

3.5.1.AN Estriol

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

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

3) Severity: minor

4) Onset: delayed

5) Substantiation: established

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

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

8) Literature Reports

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

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

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

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

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984h).
f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984d).
g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980d). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983d).

3.5.1.AO Estrone

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

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972h).
b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973h; Khurana, 1972h).
c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973d).
d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of

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

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

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

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

3.5.1.AP Estropipate

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

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

3) Severity: minor

4) Onset: delayed

5) Substantiation: established

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

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

8) Literature Reports

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

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

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out.

The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973d).

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

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

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

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

3.5.1.AQ Eterobarb

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

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

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

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

7) Probable Mechanism: increased tricyclic antidepressant metabolism

8) Literature Reports

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

3.5.1.AR Ethinyl Estradiol

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

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

3) Severity: minor

4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic
8) Literature Reports
a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received imipramine (150 milligrams/day) and placebo, 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (50 micrograms/day), while 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (25 micrograms/day). The 10 patients that received placebo did not improve over the 6 weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after 2 weeks, the 5 patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received imipramine 150 milligrams and ethinyl estradiol 50 micrograms daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972b).
b) A case report demonstrated an interaction in a 32-year-old female taking conjugated estrogens 2.5 milligrams and imipramine 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side-effects abated (Khurana, 1972b). Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973b).
c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn (Beaumont, 1973a).
d) The effects of oral contraceptives on clomipramine were studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 milligrams at bedtime while 19 took clomipramine 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimental group (2 due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980a).
e) Akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 milligrams/day for anorexia nervosa and conjugated estrogens 1.25 milligrams/day for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogens 1.25 milligrams/day who was prescribed amitriptyline 50 milligrams/day for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. Positive rechallenge at one week with doxepin 100 milligrams, with resolution following discontinuation of doxepin. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogens 1.25 milligrams/day and amitriptyline 50 milligrams/day. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984b).
f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 micrograms or less of ethinyl estradiol) from 27 to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984a).
g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980a). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983a).

3.5.1.AS Etilefrine
1) Interaction Effect: hypertension, cardiac arrhythmias, and tachycardia

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

3.5.1.AT Fenfluramine

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

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

3.5.1.AU Fluvoxamine

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

3.5.1.AV Formoterol

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

3.5.1.AW Fosamprenavir

1) Interaction Effect: increased tricyclic agent serum concentrations and potential toxicity (anticholinergic effects, sedation, confusion, cardiac arrhythmias)
2) Summary: Coadministration of fosamprenavir with a tricyclic antidepressant may provoke increased serum concentrations of the tricyclic antidepressant, causing a potential risk of arrhythmias or other serious adverse effects. Fosamprenavir is a prodrug of amprenavir, an inhibitor of the CYP3A4 isoenzyme in addition to being a CYP3A4 substrate. Tricyclic agents may partially depend on the CYP3A4 pathway for metabolism. Plasma concentrations of the tricyclic agent should be closely monitored in patients also receiving fosamprenavir (Prod Info LEXIVA(R) oral solution, oral tablets, 2009).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: If concomitant therapy with fosamprenavir and a tricyclic antidepressant is unavoidable, plasma concentrations of the tricyclic agent should be closely monitored. Also monitor patients for signs and symptoms of tricyclic toxicity (anticholinergic effects, sedation, confusion, cardiac arrhythmias) (Prod Info LEXIVA(R) oral solution, oral tablets, 2009).
7) Probable Mechanism: inhibition of CYP3A4-mediated tricyclic agent metabolism

3.5.1.AX Fosphenytoin

1) Interaction Effect: an increased risk of phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremor)
2) Summary: Fosphenytoin is a prodrug of phenytoin and the same interactions that occur with phenytoin are expected to occur with fosphenytoin (Prod Info Cerebyx(R), 1999). A few case reports have indicated

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

3.5.1.AY Gatifloxacin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Gatifloxacin may prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Although pharmacokinetic studies between gatifloxacin and other drugs which prolong the QT interval have not been performed, an additive effect cannot be excluded. Therefore, the concurrent administration of gatifloxacin and a tricyclic antidepressant is not recommended (Prod Info Tequin(TM), 1999).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of gatifloxacin and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AZ Grepafloxacin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Healthy volunteers who received grepafloxacin during a Phase I study experienced prolongation of the QTc interval. On an outpatient basis, grepafloxacin is contraindicated with other drugs that are known to also prolong the QTc interval or cause torsades de pointes, including tricyclic antidepressants. When appropriate cardiac monitoring can be assured, such as in the hospitalized patient, these two agents should be coadministered with caution (Prod Info Raxar(R), 1999).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The concurrent use of grepafloxacin and tricyclic antidepressants is contraindicated unless appropriate cardiac monitoring can be assured, such as in the hospitalized patient.
7) Probable Mechanism: additive cardiac effects

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

3.5.1.BB Halofantrine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Halofantrine can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Because tricyclic antidepressants may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of halofantrine and tricyclic antidepressants is not recommended (Prod Info Halfan(R), 1998; Marshall & Forker, 1982b).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable

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

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

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

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

4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of a tricyclic antidepressant (TCA) and a monoamine oxidase inhibitor (MAOI) should be done only with close monitoring and where the clinical benefit outweighs the potential risk. Other antidepressant therapy should first be considered. Consider using a 14 day washout period between treatment with both medicines. If deemed clinically necessary, avoid large doses and use agents other than imipramine, clomipramine, desipramine, and tranylcypromine.
7) Probable Mechanism: altered catecholamine uptake and metabolism
8) Literature Reports

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

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

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

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

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

3.5.1.BF Isocarboxazid

1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: The concurrent administration of isocarboxazid and clomipramine is contraindicated (Prod Info Marplan(R), 1998). Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982g; Spigset et al, 1993h; Brodribb et al, 1994f; Neuvonen et al, 1993c). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991d). If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971i; White & Simpson, 1984f).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of clomipramine and isocarboxazid is contraindicated. In patients being transferred to isocarboxazid therapy from a dibenzazepine-related entity, allow at least a one-week medication-free interval and then initiate isocarboxazid at one-half of the normal dose for at least the first week of therapy. Also allow one week to elapse between the discontinuation of isocarboxazid and the administration of another MAO inhibitor or dibenzazepine-related entity.
7) Probable Mechanism: altered catecholamine uptake and metabolism
8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOI) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers. Reports of excitation, hyperpyrexia, convulsions, and possible death have been

attributed to the combination (Lockett & Milner, 1965d; Brachfeld et al, 1963b; Winston, 1971d; Schuckit et al, 1971h; Sargent, 1965b; Spiker & Pugh, 1976d). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965d).

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

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

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

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

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

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

3.5.1.BG Linezolid

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

2) Summary: Concomitant use of linezolid and a tricyclic antidepressant, such as clomipramine, is contraindicated in the absence of monitoring for serotonin syndrome. If symptoms occur, consider discontinuation of either one or both of the drugs. Linezolid is a reversible, nonselective inhibitor of monoamine oxidase and may therefore interact with tricyclic antidepressants. Spontaneous reports of serotonin syndrome associated with the co-administration of linezolid and serotonergic agents have been reported (Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension, 2008).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of linezolid and tricyclic antidepressants, such as clomipramine, is contraindicated unless patient is closely observed for signs and/or symptoms of serotonin syndrome. If concomitant use is clinically warranted, monitor for signs and symptoms of serotonin syndrome, such as neuromuscular abnormalities (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including tachycardia, mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and delirium). Serotonin syndrome can be life-threatening. If serotonin syndrome develops, discontinue the offending

agents and provide supportive care and other therapy as necessary (Boyer & Shannon, 2005; Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension, 2008).
7) Probable Mechanism: linezolid inhibition of monoamine oxidase resulting in an increased concentration of serotonin

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

3.5.1.BI 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 of artemether/lumefantrine and a CYP2D6 substrate (eg, amitriptyline, clomipramine, flecainide, and imipramine) can lead to elevated drug levels of the CYP2D6 substrate. As some CYP2D6 substrates can also prolong the QT interval, there is potential for additive QT prolongation. Therefore, artemether/lumefantrine should not be coadministered with CYP2D6 substrates that 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 substrates, such as amitriptyline, clomipramine, flecainide, and imipramine, due to the potential additive effect on QT interval prolongation (Prod Info COARTEM(R) oral tablets, 2009).
7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.BJ Mazindol

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

3.5.1.BK Mephentermine

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

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

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

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

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

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

3.5.1.BL Mephobarbital

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

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

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

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

7) Probable Mechanism: increased tricyclic antidepressant metabolism

8) Literature Reports

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

3.5.1.BM Mestranol

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

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

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

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

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

8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received imipramine (150 milligrams/day) and placebo, 5 patients received

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

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

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

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

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

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

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

3.5.1.BN Methamphetamine

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

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

3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports

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

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

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

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

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

3.5.1.BO Methohexital

1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977a; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports

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

3.5.1.BP Methoxamine

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

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

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

3.5.1.BR Midodrine

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

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

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

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

7) Probable Mechanism: inhibition of norepinephrine reuptake

8) Literature Reports

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

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

3.5.1.BS Moclobemide

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

2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982i; Spigset & Mjorndal, 1993a; Brodribb et al, 1994g; Neuvonen et al, 1993d). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991e). Consequently, coadministration of TCAs and MAOIs is contraindicated in most cases. If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971k; White & Simpson, 1984h). An 18-year-old woman suffered irritability, twitching, agitation, myoclonus, and hypertonicity after changing from clomipramine to moclobemide with no washout period (Chan et al, 1998).

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concomitant use of moclobemide and a tricyclic antidepressant, such as clomipramine, is contraindicated. If clomipramine is replacing treatment with moclobemide, a minimum of two days should elapse after moclobemide is discontinued and clomipramine therapy is begun (Prod Info Manerix(R), 2001). However, the manufacturer of clomipramine recommends that the monoamine oxidase inhibitor (MAOI) be discontinued for at least 14 days before treatment with doxepin is initiated. If moclobemide is replacing treatment with clomipramine, a minimum of 14 days should elapse after clomipramine is discontinued and moclobemide therapy is begun (Prod Info clomipramine hydrochloride oral capsule, 2002).

7) Probable Mechanism: altered catecholamine uptake and metabolism

8) Literature Reports

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

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

Manerix(R), 2001).
c) A drug interaction occurred in which a 76-year old woman who had been taking clomipramine 50 mg daily for several months prior to switching to moclobemide 300 mg daily. The patient experienced somnolence, confusion, and fever which then progressed to further mental impairment, muscle stiffness, myoclonus, and convulsive attacks. The patient's symptoms were described as fulfilling the diagnostic criteria for serotonin syndrome and were resolved a few days later after discontinuing all antidepressant medications (Spigset & Mjorndal, 1993).
d) Administration of a TCA after MAOI therapy may result in the development of serotonin syndrome. In a double-blind, crossover study examining the effects of clorgyline and clomipramine for the treatment of obsessive-compulsive disorder, two subjects developed severe reactions characteristic of serotonin syndrome. During the study, patients had received clorgyline therapy, followed by a washout period of approximately four weeks and subsequent clomipramine therapy. After taking the first 100 mg dose of clomipramine, one patient developed coarse myoclonic jerking in both legs, hyperreflexia, diaphoresis, and arrhythmia. Another patient developed a similar reaction after the first dose, with upper motor neuron symptoms, myoclonic movements, and cardiac irritability. Both patient's symptoms resolved several hours later, and both patients were later treated successfully with clomipramine without adverse effects (Insel et al, 1982h).
e) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a physically healthy 34-year old man. After taking several doses, the patients developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulation and eventual death (Tackley & Tregaskis, 1987e).
f) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 150 mg amitriptyline or its equivalent, 45 mg phenelzine, or 60 mg isocarboxazid) b) oral administration c) avoidance of clomipramine, imipramine, desipramine, and tranylcypromine in any combination, and d) close monitoring of patients (Kline, 1974b; Winston, 1971e; Schuckit et al, 1971j; White & Simpson, 1984g; Rom & Benner, 1972b). The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991d). Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some sources suggest that the combination of amitriptyline and isocarboxazid is preferred (Perry et al, 1991d). Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs (Ponto et al, 1977e; Schuckit et al, 1971j; Ashcroft, 1975d).
g) A 29-year-old male presented to the emergency department of a hospital one hour after ingesting moclobemide 7.5 g, clomipramine 1 g, and clorazepate 450 mg. He was treated with gastric lavage, charcoal 30 g, and flumazenil, and was admitted to the hospital for observation. One hour later, he began to experience severe tremor, increased body temperature, and tonic-clonic seizures. He died of a cardiorespiratory arrest approximately 145 minutes after his arrival to the hospital. Moclobemide overdoses of 7 g to 8 g produce fatigue, agitation, increased blood pressure, and tachycardia with few other complications. However, in this case, the addition of clomipramine produced a fatal serotonin syndrome (Ferrer-Dufol et al, 1998).
h) A 25-year-old female with recurrent depressive disorder was stabilized on clomipramine 150 mg daily and alprazolam 1.5 to 3 mg daily for seven months when her depressive disorder again reappeared. Clomipramine therapy was discontinued, and moclobemide 300 mg daily was initiated 24 hours later. Moclobemide was rapidly increased to 600 mg daily, and the alprazolam dose remained the same. One week after the start of moclobemide, the patient presented with confusion, mild euphoria, and disinhibition. She reported that within a few hours of starting moclobemide therapy, she experienced an elevation of her mood, nausea, shivering, and flushing. Moclobemide was discontinued, with complete recovery from the drug interaction-induced symptoms eight days later. Because clomipramine has a half-life of 22 to 84 hours, significant amounts of the drug may still have been present when moclobemide therapy was instituted, causing serotonin syndrome (Dardennes et al, 1998).

3.5.1.BT Modafinil
1) Interaction Effect: increased plasma levels of clomipramine and desmethylclomipramine
2) Summary: A narcoleptic patient experienced an increase in her clomipramine levels when modafinil was added to her therapeutic regimen. Hepatic enzymes also increased from 2- to 7-fold, requiring that clomipramine be discontinued (Grozinger et al, 1998a). However, in healthy volunteers, the coadministration of a single dose of clomipramine 50 mg during the first day of a 3-day regimen of modafinil 200 mg daily did not result in an alteration in the pharmacokinetics of either drug (Prod Info Provigil(R), 1998).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients receiving modafinil and clomipramine concurrently for signs and symptoms of tricyclic intoxication. Liver enzymes should also be closely followed for marked increases.
7) Probable Mechanism: unknown
8) Literature Reports

a) A 60-year-old narcoleptic female was being treated with clomipramine without complete resolve of her symptoms. At a clomipramine dose of 75 mg under steady-state conditions, her clomipramine (CI) and desmethylclomipramine (DMCI) blood levels were 109 ng/mL and 212 ng/mL, respectively. These levels increased to 129 ng/mL and 208 ng/mL, respectively, when the clomipramine dose was increased to 100 mg. When modafinil 200 mg was instituted, the clomipramine dose was decreased to 75 mg, and the CI/DMCI levels increased to 158/238 ng/mL. With modafinil 400 mg and clomipramine 75 mg, the CI/DMCI levels further rose to 210/449 ng/mL. Hepatic enzymes (GOT, GLDH, GGT, GPT) increased from 2- to 7-fold, necessitating the discontinuation of clomipramine. Three weeks later, the DMCI level was 63 ng/mL, while clomipramine was no longer detectable. Hepatic enzymes also returned to baseline. The patient was determined to be a poor metabolizer with regard to cytochrome P450 2D6 (CYP2D6) isoenzymes, indicating that CYP2D6 was not a factor in this drug interaction (Grozinger et al, 1998).

3.5.1.BU Moxifloxacin

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

3.5.1.BV Nefopam

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

3.5.1.BW Nialamide

1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982c; Spigset et al, 1993d; Brodribb et al, 1994b; Neuvonen et al, 1993a). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991b). If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971c; White & Simpson, 1984a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of a tricyclic antidepressant (TCA) and a monoamine oxidase inhibitor (MAOI) should be done only with close monitoring and where the clinical benefit outweighs the potential risk. Other antidepressant therapy should first be considered. If deemed clinically necessary, avoid large doses and use agents other than imipramine, clomipramine, desipramine, and tranylcypromine.
7) Probable Mechanism: altered catecholamine uptake and metabolism
8) Literature Reports
a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past. Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965a; Winston, 1971a; Schuckit et al, 1971b; Spiker & Pugh, 1976a). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965a).
b) In a double-blind, crossover study examining the effects of clorgyline and clomipramine for the

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

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

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

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

3.5.1.BX Norepinephrine

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

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

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

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

7) Probable Mechanism: inhibition of norepinephrine reuptake

8) Literature Reports

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

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

3.5.1.BY Olanzapine

1) Interaction Effect: an increased risk of seizures

2) Summary: Psychotropic drugs have been shown to reduce the seizure threshold. A case report describes a patient without an underlying seizure disorder who received treatment with olanzapine and clomipramine concomitantly. This combination resulted in seizures which were repeated upon rechallenge with olanzapine and clomipramine. It is advised to use caution when administering olanzapine concomitantly with clomipramine, or any agent known to reduce seizure threshold (Deshauer et al, 2000a).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: It is advised to use caution when administering olanzapine concomitantly with

clomipramine, or other agents known to lower the seizure threshold.
7) Probable Mechanism: unknown
8) Literature Reports
a) A 34-year-old male with schizophrenia and obsessive-compulsive disorder (OCD) without any underlying seizure disorder, presented for treatment following long-term noncompliance. Inpatient olanzapine treatment (20 mg/day) was initiated and positive psychotic symptoms subsequently resolved. Patient was discharged and readmitted because of inability to control symptoms. Clomipramine 250 mg per day was initiated. Within a week, dizziness and myoclonic jerks were reported which quickly progressed to general motor seizures and postictal somnolence (without incontinence). Spike waves and paroxysmal slowing on the EEG was consistent with seizure activity. Clomipramine and olanzapine were subsequently withheld, and the seizures were controlled with diazepam 30 mg per day for three days. This pattern repeated upon re-challenge with the combination of olanzapine and clomipramine. Presumably from the temporal relationship between clomipramine and olanzapine administration and seizure manifestation, it can be suspected that this adverse event is due to an interaction between these two drugs. Clomipramine and olanzapine are both metabolized by the cytochrome P450 isoenzymes 1A2 and 2D6. One theory is that coadministration may result in elevated levels of both compounds. Although the mechanism by which this interaction occurs is not yet known, it is advised to use caution when administering olanzapine concomitantly with clomipramine, or other agents known to lower the seizure threshold (Deshauer et al, 2000).

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

3.5.1.CA Oxybutynin
1) Interaction Effect: decreased clomipramine efficacy
2) Summary: Oxybutynin was suspected of inducing the metabolism of clomipramine in an elderly female patient. Subsequent dextromethorphan testing of the patient showed that she was an extensive metabolizer (EM) of cytochrome P450 2D6 (CYP2D6). A pilot study exploring the long- and short-term effects of oxybutynin on the activity of CYP2D6 and another isoenzyme, probably of the CYP3A family, showed that oxybutynin caused a disproportionate increase of hydroxymorphinan compared with dextrorphan. Because the formation of hydroxymorphinan is mainly dependent on the activity of CYP2D6 and CYP3A4, but only the latter is known to be inducible, the authors suggest that oxybutynin is an inducer of a CYP3A subfamily (Grozinger et al, 1999a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Patients receiving concurrent therapy with clomipramine and oxybutynin should be monitored for loss of clomipramine efficacy, including worsening of symptoms. Plasma levels of clomipramine may be helpful in determining if efficacy is being compromised.
7) Probable Mechanism: induction by oxybutynin of cytochrome P450 3A-mediated clomipramine

metabolism
8) Literature Reports
a) A 72-year-old female was receiving clomipramine 150 mg daily for depression with a clomipramine and desmethylclomipramine blood level of 230 ng/mL and 348 ng/mL, respectively. Clomipramine was decreased to 25 mg daily, and fluvoxamine 100 mg daily was added to therapy. Eighteen days later, her clomipramine and desmethylclomipramine levels were 405 ng/mL and 50 ng/mL, respectively. Oxybutynin 5 mg daily was initiated for urinary incontinence, and within one week the clomipramine and desmethylclomipramine levels had decreased to 133 ng/mL and less than 25 ng/mL. They remained low one week later. The patient refused to discontinue oxybutynin to determine if her clomipramine blood levels would again increase (Grozinger et al, 1999).

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

3.5.1.CC Paroxetine
1) Interaction Effect: clomipramine toxicity (dry mouth, sedation, urinary retention)
2) Summary: Concurrent use of paroxetine with drugs that are metabolized by cytochrome P450 2D6, such

as clomipramine, should be approached with caution (Prod Info Paxil(R), 2003).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When paroxetine is coadministered with clomipramine, monitor patients for signs and symptoms of clomipramine toxicity (dry mouth, sedation, urinary retention, blurred vision). Clomipramine doses may need to be reduced.
7) Probable Mechanism: decreased cytochrome P450 2D6-mediated clomipramine metabolism

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

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

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

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

3.5.1.CG Phenelzine
1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982e; Spigset et al, 1993f; Brodribb et al, 1994d; Neuvonen et al, 1993b). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991c). Consequently, coadministration of TCAs and MAOIs is contraindicated in most cases. If TCAs and MAOIs must be used

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

3.5.1.CH Phenindione
1) Interaction Effect: increased risk of bleeding

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

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

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

3.5.1.CJ Phenobarbital

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

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

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

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

7) Probable Mechanism: increased tricyclic antidepressant metabolism

8) Literature Reports

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

3.5.1.CK Phenprocoumon

1) Interaction Effect: increased risk of bleeding

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

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

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

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

8) Literature Reports

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

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

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

3.5.1.CL Phentermine

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

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

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

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

3.5.1.CN 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

increased serum phenytoin concentration (Petti & Campbell, 1975a; Perucca & Richens, 1977a). Tricyclic antidepressants (TCAs) may lower the seizure threshold in epileptic patients stabilized on anticonvulsants. Theoretically, because phenytoin is an enzyme inducer, the metabolism of antidepressants may be increased resulting in reduced TCA serum levels.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Consider phenytoin serum levels if a tricyclic antidepressant is added to therapy or if the patient begins to exhibit signs of toxicity; lower doses of phenytoin may be required. If phenytoin is added to tricyclic antidepressant therapy, monitor for clinical efficacy of the tricyclic agent.
7) Probable Mechanism: inhibition of phenytoin metabolism

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

3.5.1.CP Procarbazine
1) Interaction Effect: neurotoxicity, seizures
2) Summary: Concomitant tricyclic antidepressant and more potent MAOI use has resulted in hyperpyrexia, convulsions, and death. Procarbazine has relatively weak MAOI actions, so while the potential for drug interactions between tricyclic antidepressants and procarbazine exists, clinical data are lacking at this time (Schuckit et al, 1971g; White & Simpson, 1984d). Concurrent use is not recommended (Prod Info Matulane (R), 1997).
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use is not recommended and should probably be initiated only under close medical supervision, and then only if other antidepressant class agents have proven unsuccessful. With more potent MAOIs, recommendations for concurrent use of TCAs have included avoiding large doses of the TCA, using only oral tricyclics, and avoiding imipramine, clomipramine, and desipramine. Procarbazine therapy should not begin until seven days following discontinuation of tricyclic antidepressants and 14 days following the discontinuation of other MAO inhibitors.
7) Probable Mechanism: altered catecholamine uptake and metabolism
8) Literature Reports
a) Procarbazine is primarily used as an antineoplastic agent, but was originally investigated as a monoamine oxidase inhibitor (Gilman et al, 1985). Animal studies have indicated that procarbazine is a monoamine oxidase inhibitor (MAOI) (DeVita et al, 1965) but appears to be a relatively weak MAOI in man (Gilman et al, 1985). Hypertensive reactions may still result from concomitant administration of tricyclic antidepressants, sympathomimetics, and tyramine-containing foods (Gilman et al, 1985; Ponto et al, 1977c). Concomitant administration of monoamine oxidase (MAO) inhibitors with tricyclic antidepressants has been considered an absolute contraindication in the past and still is listed as such by the manufacturers. Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965c; Brachfeld et al, 1963a; Winston, 1971c; Schuckit et al, 1971f; Sargent, 1965a; Spiker & Pugh, 1976c). Careful examination of such reports indicate unusual circumstances in most cases such as parenteral administration of a tricyclic. The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and

inhibition of catecholamine metabolism (Sjoqvist, 1965c).
b) Procarbazine therapy should not begin until 7 days following discontinuation of tricyclic antidepressants and 14 days following the discontinuation of other MAO inhibitors (AMA Department of Drugs, 1992; Gilman et al, 1985).

3.5.1.CQ Propylhexedrine

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

3.5.1.CR Quinestrol

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

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

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

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

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

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

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

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

3.5.1.CS Quinidine

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

2) Summary: The concomitant use of quinidine and clomipramine is not recommended. Two studies have demonstrated that concomitant use of quinidine and imipramine or desipramine results in increased serum concentrations of these antidepressants (Brosen & Gram, 1989a; Steiner et al, 1987). A similar interaction may occur with other tricyclic antidepressants including clomipramine.

3) Severity: major

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Monitor for increased antidepressant side effects with concomitant therapy with

quinidine; lower doses of the tricyclic agent may be required. Conversely, if quinidine is discontinued from therapy, monitor for antidepressant efficacy. Tricyclic antidepressant serum levels might be considered in some clinical situations.
7) Probable Mechanism: decreased clomipramine metabolism
8) Literature Reports
a) Quinidine is an inhibitor of the cytochrome P450 2D6 isoenzyme responsible for the 2-hydroxylation of imipramine and desipramine (Brosen & Gram, 1989). Inhibition of this enzyme system can result in a 35% decrease in imipramine clearance and 85% decrease in desipramine clearance. Demethylation of imipramine by the cytochrome P450 3A3/4 isoenzyme is unaffected by this interaction. Until more information is available all patients having quinidine added to drug regimen containing imipramine or desipramine should be monitored for increased antidepressant serum concentrations and potential toxicity.
b) In a placebo controlled study, imipramine 3.5 mg/kg was administered daily for seven patients with severe depression and doses were titrated to obtain therapeutic plasma concentrations. Two patients displayed premature atrial depolarizations and premature ventricular depolarizations before therapy. On patient had 33 premature atrial depolarizations (PAD) and 30 premature ventricular depolarizations (PVD) per hour, which decreased to 0.4 PAC and zero PVC per hour on imipramine. The other patient had 12 PAD and 169 PVD per hour before treatment and 1.8 PAD and 28.1 PVD per hour on imipramine. The authors also cautioned that the incidence of cardiotoxicity may increase if tricyclic antidepressants are administered with Type I antiarrhythmics. It was also recommended that quinidine and procainamide not be used to treat the arrhythmias of a tricyclic overdose. The similarities between these agents may exacerbate the cardiotoxicity (Kantor et al, 1978).

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

3.5.1.CU S-Adenosylmethionine
1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: A single case has been reported of serotonin syndrome likely resulting from the combination of S-adenosylmethionine (SAMe) and clomipramine (Iruela et al, 1993a). SAMe was shown to hasten the onset of therapeutic response of imipramine in a clinical trial involving 40 patients, without serotonergic side effects (Berlanga et al, 1992). If therapy is initiated with SAMe and a tricyclic antidepressant, the patient should be monitored closely for early signs of serotonin syndrome. Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result (Sternbach, 1991).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: S-adenosylmethionine (SAMe) used concomitantly with imipramine was found to decrease depressive symptoms sooner than imipramine alone (Berlanga et al, 1992). One case has been reported of serotonin syndrome likely resulting from concomitant use of SAMe and clomipramine (Iruela et al, 1993). If SAMe and a tricyclic antidepressant are used together, use low doses of each and titrate upward slowly, while monitoring closely for early signs of serotonin syndrome such as increasing anxiety, confusion, and disorientation.
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) A 71 year-old female was hospitalized with anxiety, agitation, confusion, and symptoms of serotonin syndrome. She had been taking S-adenosylmethionine 100 milligrams (mg) intramuscularly daily and clomipramine 25 mg daily for 10 days, which was then increased to 75 mg/day. Within 48-72 hours of the increased clomipramine dosage, she became progressively anxious, agitated, and confused. On admission she was verbally unresponsive and stuporous, with heart rate 130 beats/minute, respiratory

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

3.5.1.CV Salmeterol

1) Interaction Effect: an increased risk of cardiovascular excitation
2) Summary: Salmeterol should be administered with extreme caution to patients who are being treated with a tricyclic antidepressant, or within two weeks of the discontinuation of a tricyclic antidepressant (Prod Info SEREVENT(R) DISKUS(R) inhalation powder, 2006). Clinically significant changes in systolic and diastolic blood pressure, pulse rate, and electrocardiograms have been seen with the use of salmeterol, and these changes may be exacerbated by the use of a tricyclic antidepressant.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Close observation for adverse cardiovascular effects is warranted when these agents are administered concurrently or if salmeterol is given within two weeks of discontinuation of a tricyclic antidepressant.
7) Probable Mechanism: potentiation of vascular effects

3.5.1.CW Secobarbital

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

3.5.1.CX Selegiline

1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982n; Spigset et al, 1993m; Brodribb et al, 1994l; Neuvonen et al, 1993g). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991h). Consequently, coadministration of TCAs and MAOIs is contraindicated in most cases. If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971q; White & Simpson, 1984l).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of clomipramine with a monoamine oxidase inhibitor (MAOI), such as selegiline is contraindicated. A minimum of 14 days should elapse after selegiline is discontinued

before therapy with clomipramine is begun. Similarly, a minimum of 14 days should elapse after clomipramine is discontinued and therapy with selegiline is begun (Prod Info clomipramine hydrochloride oral capsule, 2002).

7) Probable Mechanism: altered catecholamine uptake and metabolism

8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers (Prod Info clomipramine hydrochloride oral capsule, 2002). Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965h; Brachfeld et al, 1963d; Winston, 1971h; Schuckit et al, 1971p; Sargent, 1965d; Spiker & Pugh, 1976h). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965h).

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

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

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

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

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

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

3.5.1.CY Sertraline

1) Interaction Effect: modest elevations of clomipramine serum levels or possible serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: There is limited evidence suggesting that sertraline may inhibit tricyclic antidepressant (TCA) metabolism resulting in higher TCA serum concentrations. Sertraline inhibits cytochrome P450 2D6 enzyme activity and may increase the plasma concentrations of coadministered drugs that are metabolized by this pathway, including the tricyclic antidepressants (Prod Info Zoloft(R), 2002; Preskorn et al, 1994a; Lydiard et al, 1993). Effects of the interaction may have little or no clinical impact, however. Increases in TCA serum levels associated with sertraline coadministration were modest compared with those found when fluoxetine (another selective serotonin reuptake inhibitor) was combined with desipramine (von Moltke et al, 1994). Monitor patients on clomipramine-sertraline therapy for TCA toxicity (dry mouth, urinary retention, CNS

depression). Clomipramine doses may need to be reduced.
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The combined use of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) may result in the inhibition of the TCA metabolism. A few cases of serotonin syndrome have also been reported with concurrent TCA and SSRI therapy. Caution should be observed when drugs in these two classes are used together.
7) Probable Mechanism: inhibition of clomipramine metabolism
8) Literature Reports
a) The pharmacokinetics of desipramine were studied in 18 healthy male volunteers. Study subjects received only desipramine (50 mg daily) for seven days followed by desipramine with sertraline (50 mg daily) for 21 days. When sertraline was added to desipramine therapy, the mean maximum concentration of desipramine increased by 34% and the area under the concentration-time curve increased by 26%. Trough concentrations of desipramine were close to baseline one week after sertraline was discontinued. The changes in desipramine concentrations were modest and the interaction may not be clinically significant (Preskorn et al, 1994).

3.5.1.CZ St John's Wort
1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Theoretically, since St. John's Wort is thought to inhibit serotonin reuptake and may have mild monoamine oxidase inhibitory activity (Singer et al, 1999; Thiede & Walper, 1994), serotonin syndrome could result when St. John's Wort is taken along with a tricyclic antidepressant. This theoretical risk of serotonin syndrome is also based on case reports of serotonin syndrome resulting from concomitant use of selective serotonin reuptake inhibitors with tricyclic antidepressants (Alderman & Lee, 1996), as well as concomitant use of monoamine oxidase inhibitors with tricyclic antidepressants (Brodribb et al, 1994a; Spigset et al, 1993b; Tackley & Tregaskis, 1987a). Coadministration of amitriptyline and St. John's Wort decreased the area under the concentration-time curve of amitriptyline and its metabolite nortriptyline (Roots et al, 2000); if other tricyclic antidepressants are similarly affected by St. John's Wort, the risk of serotonin syndrome may be reduced, yet effectiveness of the tricyclic antidepressant may also be reduced. To maintain maximal effectiveness of the tricyclic antidepressant, as well as avoid any potential risk of serotonin syndrome, avoid concomitant use of St. John's Wort and tricyclic antidepressants.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of St. John's Wort with tricyclic antidepressants.
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.DA Tapentadol
1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent use of tapentadol and a tricyclic antidepressant may result in serotonin syndrome, which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea (Prod Info tapentadol immediate release oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of tapentadol and a tricyclic antidepressant may result in a life-threatening condition called serotonin syndrome. If these agents are used together, monitor the patient closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination), especially during treatment initiation and dose increases (Prod Info tapentadol immediate release oral tablets, 2008).
7) Probable Mechanism: additive serotonergic effect

3.5.1.DB Thiopental
1) Interaction Effect: possible decreased tricyclic antidepressant serum concentrations and possible additive adverse effects
2) Summary: Concomitant barbiturate and tricyclic antidepressant (TCA) therapy may result in increased metabolism of the TCA. There have been scattered reports of individuals with decreased serum levels of TCAs in the presence of a barbiturate (Moody et al, 1977a; Silverman & Braithwaite, 1972; Burrows & Davies, 1971). In addition, TCAs can worsen seizure control by reducing the seizure threshold (Brodie, 1992). These drugs also have additive CNS and respiratory depressant effects.
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable

6) Clinical Management: Monitor for efficacy of antidepressant effect. Increases in tricyclic antidepressant dosages may be required. Additionally, monitor for toxicity when either drug is added to or withdrawn from therapy. Serum concentrations may be of value in determining appropriate dosage.
7) Probable Mechanism: increased tricyclic antidepressant metabolism
8) Literature Reports
a) The pharmacokinetics of a single oral dose of desipramine (100 mg) were studied in eight epileptic patients chronically treated with phenobarbital and in eight drug-free healthy controls (Spina et al, 1996). All subjects were extensive metabolizers with respect to the genetically determined CYP2D6-related metabolic polymorphism. Compared with controls, epileptic patients exhibited lower peak plasma desipramine concentrations (74 nmol/L vs. 107 nmol/L), smaller desipramine area under the concentration-time curve values (1943 nmol/L/h vs. 3234 nmol/L/h), and shorter desipramine elimination half-lives (15.1 h vs. 20.6 h). All barbiturates are believed to have similar effects leading to induction of hepatic enzymes and the 2D6 isozyme is believed to be important in the metabolism of most or all TCAs. Thus, similar effects should be expected with any combination of TCA and barbiturate.

3.5.1.DC Tibolone
1) Interaction Effect: attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens (Somani & Khurana, 1973e), with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously (Prange, 1972e). The effects of the interaction appear to be estrogen dose-related (Khurana, 1972e) and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy (Krishnan et al, 1984e).
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible estrogen-enhanced hepatic metabolism of the tricyclic
8) Literature Reports
a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to 4 treatment groups. Ten patients received placebo, 10 received imipramine (150 milligrams/day) and placebo, 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (50 micrograms/day), while 5 patients received imipramine (150 milligrams/day) and ethinyl estradiol (25 micrograms/day). The 10 patients that received placebo did not improve over the 6 weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after 2 weeks, the 5 patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of 2 weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, 5 women received imipramine 150 milligrams and ethinyl estradiol 50 micrograms daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension (Prange, 1972d).
b) A case report demonstrated an interaction in a 32-year-old female taking conjugated estrogens 2.5 milligrams and imipramine 100 milligrams. The patient developed lethargy, tremors, and signs of depersonalization. After 2 years of therapy, the patient increased her estrogen dose to 5 milligrams and then 7.5 milligrams daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side-effects abated (Khurana, 1972d). Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes (Somani & Khurana, 1973d).
c) A study in which women received clomipramine and oral contraceptives or clomipramine alone was reviewed (Beaumont, 1973b). At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn.
d) The effects of oral contraceptives on clomipramine were studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 milligrams at bedtime while 19 took clomipramine 25 milligrams at bedtime with oral contraceptives. Over the 4-week study, 3 control patients (2 due to side-effects) and 5 in the experimental group (2 due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given (Luscombe & John, 1980b).

e) Akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 milligrams/day for anorexia nervosa and conjugated estrogens 1.25 milligrams/day for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 milligrams was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 milligrams/day who was prescribed amitriptyline 50 milligrams/day for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. Positive rechallenge at one week with doxepin 100 milligrams, with resolution following discontinuation of doxepin. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 milligrams/day and amitriptyline 50 milligrams/day. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant (Krishnan et al, 1984d).
f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 micrograms or less of ethinyl estradiol) from 27 to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve (Abernethy et al, 1984b).
g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes (John et al, 1980b). Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect (Oppenheim, 1983b).

3.5.1.DD Toloxatone

1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982l; Spigset et al, 1993k; Brodribb et al, 1994j; Neuvonen et al, 1993f). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991g). If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971o; White & Simpson, 1984j).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of a tricyclic antidepressant (TCA) and a monoamine oxidase inhibitor (MAOI) should be done only with close monitoring and where the clinical benefit outweighs the potential risk. Other antidepressant therapy should first be considered. If deemed clinically necessary, avoid large doses and use agents other than imipramine, clomipramine, desipramine, and tranylcypromine.
7) Probable Mechanism: altered catecholamine uptake and metabolism
8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past. Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965g; Winston, 1971g; Schuckit et al, 1971n; Spiker & Pugh, 1976g). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965g).
b) There is minimal risk of a clinically significant pharmacokinetic interaction between amitriptyline and toloxatone, a MAOI-A (Vandel et al, 1993). Seventeen inpatients being treated for major depressive illness were administered amitriptyline 125 mg once daily for two weeks, and the following two weeks they received amitriptyline 125 mg daily and toloxatone 600 mg daily. With combined therapy there was a small, nonsignificant increase in amitriptyline plasma levels. The availability and urinary excretion of amitriptyline and its metabolites were not significantly affected.
c) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991f). Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs (Ponto et al, 1977g; Schuckit et al, 1971n; Ashcroft, 1975f).
d) Serotonin syndrome has been reported with the use of moclobemide, a reversible inhibitor of monoamine oxidase, and a TCA. A 39-year old woman with bipolar disorder developed serotonin syndrome after imipramine was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when imipramine was started at 50 mg daily, followed by two dosage increases of imipramine to 200 mg and a reduction of moclobemide dosage to 150 mg twice daily. Five days after the increase in imipramine to 200 mg per day, the patient developed symptoms of serotonin syndrome, including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated

with chlorpromazine and symptoms resolved over the next few days without further complications (Brodribb et al, 1994i).

3.5.1.DE Tramadol

1) Interaction Effect: an increased risk of seizures
2) Summary: Seizures have been reported in patients using tramadol. Some medications, including tricyclic antidepressants (TCAs), are known to reduce the seizure threshold. The risk of seizures may be enhanced when clomipramine and tramadol therapy are combined (Prod Info Ultram(R), 1998).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Caution should be used if tramadol is to be administered to patients receiving concomitant TCA therapy. If possible, avoid this combination, especially in patients with underlying conditions that might predispose to seizures.
7) Probable Mechanism: unknown

3.5.1.DF Tranylcypromine

1) Interaction Effect: neurotoxicity, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concomitant TCA and MAOI use has resulted in hyperpyrexia, convulsions, and death. Concurrent use of MAOIs and TCAs has also been reported to result in a condition termed serotonin syndrome (Insel et al, 1982p; Spigset et al, 1993o; Brodribb et al, 1994n; Neuvonen et al, 1993h). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus, and changes in mental status (Sternbach, 1991i). Consequently, coadministration of TCAs and MAOIs is contraindicated in most cases. If TCAs and MAOIs must be used concurrently, avoid large doses, use only oral TCAs, avoid imipramine, clomipramine, desipramine, and tranylcypromine, and monitor patients closely (Schuckit et al, 1971s; White & Simpson, 1984n).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of clomipramine with a monoamine oxidase inhibitor (MAOI), such as tranylcypromine is contraindicated. If clomipramine is replacing treatment with tranylcypromine, a minimum of 14 days should elapse after tranylcypromine is discontinued and therapy with clomipramine begins. If clomipramine is substituted by tranylcypromine, a minimum of 14 days should elapse after clomipramine is discontinued and tranylcypromine treatment begins (Prod Info clomipramine hydrochloride oral capsule, 2002). However, the manufacturer of tranylcypromine recommends that at least 7 days should elapse before tranylcypromine therapy is replaced by clomipramine. Similarly, if clomipramine therapy is substituted by tranylcypromine, there should be a 7 day washout period. Tranylcypromine should then be given using half the normal starting dosage for, minimally, the first week of therapy (Prod Info Parnate(R), 2001).
7) Probable Mechanism: altered catecholamine uptake and metabolism
8) Literature Reports

a) Concomitant administration of monoamine oxidase inhibitors (MAOIs) with tricyclic antidepressants (TCAs) has been considered an absolute contraindication in the past and still is listed as such by the manufacturers (Prod Info clomipramine hydrochloride oral capsule, 2002). Reports of excitation, hyperpyrexia, convulsions, and possible death have been attributed to the combination (Lockett & Milner, 1965i; Brachfeld et al, 1963e; Winston, 1971i; Schuckit et al, 1971r; Sargent, 1965e; Spiker & Pugh, 1976i). The mechanism may relate to the combined inhibition of catecholamine reuptake into the central nervous system and inhibition of catecholamine metabolism (Sjoqvist, 1965i).

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

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

d) A 39-year old woman with bipolar disorder developed serotonin syndrome after imipramine was added to moclobemide. The patient was taking moclobemide 300 mg twice daily when imipramine was started at 50 mg daily, followed by two dosage increases of imipramine to 200 mg and a reduction of

moclobemide dosage to 150 mg twice daily. Five days after the increase in imipramine to 200 mg per day, the patient developed symptoms of serotonin syndrome, including sweating, shivering, confusion, fever, and spasms in the extremities. The patient was treated with chlorpromazine and symptoms resolved over the next few days without further complications (Brodribb et al, 1994m).
e) Three patients with bipolar disorder developed manic symptoms while undergoing concurrent therapy with isocarboxazid and amitriptyline. In all three cases the patients had been given MAOIs and TCAs alone without complications. It was only when the drugs were used in combination that symptoms of mania emerged, suggesting a synergistic effect (de la Fuente et al, 1986c).
f) In one case, clomipramine 10 mg twice daily was added to a stable regimen of tranylcypromine in a physically healthy 34-year old man. After taking several doses, the patient developed symptoms of nausea and profuse sweating, followed by pyrexia, dyspnea, and agitation. The hyperpyrexical state led to disseminated intravascular coagulation and eventual death (Tackley & Tregaskis, 1987h).
g) There is evidence that MAOIs and TCAs can be given concomitantly in patients previously unresponsive to the MAOI or TCA alone. A few precautions must be followed including: a) avoidance of large doses (no more than 150 mg amitriptyline or its equivalent, 45 mg phenelzine, or 60 mg isocarboxazid) b) oral administration c) avoidance of clomipramine, imipramine, desipramine, and tranylcypromine in any combination, and d) close monitoring of patients (Kline, 1974d; Winston, 1971i; Schuckit et al, 1971r; White & Simpson, 1984m; Rom & Benner, 1972d). The combination may be utilized in one of two ways. Most frequently, the recommendation is to stop all previous antidepressants (five to ten days for TCAs and 14 days for MAOIs); the combination is then simultaneously started (Perry et al, 1991h). Alternatively, in a patient previously receiving a TCA, small doses of the MAOI may be slowly added (Schoonover, 1983). Some sources suggest that the combination of amitriptyline and isocarboxazid is preferred (Perry et al, 1991h). Numerous studies in patients with refractory depression or phobic anxiety states have successfully used the combination of MAOIs and TCAs (Ponto et al, 1977i; Schuckit et al, 1971r; Ashcroft, 1975h).

3.5.1.DG Valproic Acid

1) Interaction Effect: an increased risk of clomipramine toxicity (agitation, confusion, hallucinations, urinary retention, tachycardia, seizures, coma)
2) Summary: Comedication with clomipramine and valproic acid may increase serum levels of clomipramine resulting in increased side effects. Clomipramine toxicity developed in a patient twelve days after valproic acid therapy was initiated. Metabolism of clomipramine is mediated through N-demethylation, hydroxylation, and glucuronidation, and valproic acid appears to inhibit the enzymes responsible for this mode of metabolism (Fehr et al, 2000a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor serum clomipramine levels to avoid overdosing as a result of elevated concentrations of clomipramine when comedicating with valproic acid. The clomipramine dose may need to be reduced when valproic acid is added to therapy.
7) Probable Mechanism: inhibition of cytochrome P450 2C-mediated metabolism of clomipramine
8) Literature Reports
a) A case report describes a 46-year-old female with personality disorder whose serum clomipramine concentrations became elevated after she began concomitant therapy with valproic acid. Antidepressant therapy with clomipramine and lorazepam was initiated while being hospitalized for treatment of her psychiatric disorder. These two agents were chosen to reduce the frequency of panic attacks and to improve symptoms of suicidal and self-destructive behavior. A target dose of clomipramine 150 mg/day resulted in serum clomipramine levels in the normal range. Lorazepam was initiated at a dose of 2 mg/day After two weeks of therapy valproate was initiated at 1000 mg/day because emotional instability and self-destructive behavior remained unimproved. After five days of therapy the serum levels of clomipramine and desmethylclomipramine increased to 447 ng/mL and 85 ng/mL, respectively. Valproate serum concentration was 63.2 mcg/mL. The valproate dose was subsequently adjusted to 1400 mg/day. Seven days after the increase in valproate dose, clomipramine and desmethylclomipramine serum concentrations were 479 ng/mL and 269 ng/mL respectively. Conversely, the valproate serum level was 55 mcg/mL. The patient noted a feeling of numbness and exaggerated sleep disturbances. After the clomipramine dose was reduced to 75 mg/day, these symptoms resolved. The author concludes that the increase in serum clomipramine concentrations was primarily due to comedication with valproate (Fehr et al, 2000).

3.5.1.DH Vasopressin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants and vasopressin have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Vivactil(R), 1999; McCue et al, 1989; Munger & Effron, 1988; Mauro et al, 1988; Marshall & Forker, 1982c; Goldstein & Claghorn, 1980; Buckhardt et al, 1978; Pinder et al, 1977; Thorstrand, 1976; Singh, 1972). Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.
3) Severity: major

4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of drugs that prolong the QT interval, such as tricyclic antidepressants and vasopressin, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.DI Venlafaxine

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

3.5.1.DJ Warfarin

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

3.5.1.DK Yohimbine

1) Interaction Effect: increased risk of hypertension
2) Summary: Yohimbine increased blood pressure and decreased orthostatic hypotension experienced by depressed patients treated with clomipramine on a short-term basis (less than 2 weeks of clomipramine treatment, with 4 days of concomitant yohimbine treatment) (Lacomblez et al, 1989a). The effect of yohimbine on orthostatic hypotension induced by clomipramine beyond this time frame is unknown. Levels of yohimbine may continue to increase during the period when clomipramine is accumulating (i.e. at the start of therapy and following any dosage changes). Demethylclomipramine may decrease first pass hepatic metabolism of yohimbine, increasing yohimbine levels and thereby increasing the hypertensive effect of

yohimbine. It was also proposed that patients with depression may have increased sensitivity to the effect of yohimbine on alpha2-receptors (Lacomblez et al, 1989a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Monitor orthostatic and sitting blood pressure in patients taking clomipramine who initiate therapy with yohimbine, as yohimbine may increase blood pressure.
7) Probable Mechanism: inhibition of hepatic metabolism of yohimbine
8) Literature Reports
a) Yohimbine 12 milligrams daily significantly increased blood pressure in a randomized, double-blind, placebo-controlled, crossover study of 12 patients with depression. Patients had been treated with clomipramine 150 mg for a minimum of 48 hours to 1 week maximum and experienced a fall in systolic blood pressure of at least 20 mmHg after 2 and 5 minutes of standing up. Patients received yohimbine 4 mg three times daily for 3 days, and 4 mg once on day 4. Supine blood pressure was significantly increased on day 1 (p between 0.001 and 0.05) and on day 4 (p between 0.01 and 0.05). Standing blood pressure was significantly increased on day 1 (p between 0.01 and 0.05), and on day 4 (p between 0.001 and 0.05). Hypertensive effects lasted 17 to 24 hours after yohimbine administration and were accompanied by an increase in heart rate (Lacomblez et al, 1989).
b) Since yohimbine concentrations are undetectable after 17 to 24 hours, the interaction with clomipramine was suggested to involve more than pharmacokinetic alterations. The hypertensive effect of yohimbine was significantly correlated with plasma yohimbine levels (p equals 0.0025). Plasma levels of yohimbine were significantly correlated with plasma levels of demethylclomipramine, the main metabolite of clomipramine (p less than 0.006), but not with clomipramine levels. The low dose of yohimbine used in this study had no effect on blood pressure in healthy (non-depressed, normotensive) subjects. Demethylclomipramine may decrease first pass hepatic metabolism of yohimbine, increasing yohimbine levels and thereby increasing the hypertensive effect of yohimbine. It was proposed that patients with depression may have increased sensitivity to the effect of yohimbine on alpha2-receptors (Lacomblez et al, 1989).

3.5.2 Drug-Food Combinations

Ethanol

Grapefruit Juice

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

3.5.2.B Grapefruit Juice

1) Interaction Effect: an increased risk of clomipramine toxicity

2) Summary: Clomipramine is metabolized by several different cytochrome P450 pathways, including CYP1A2, 3A4, and 2D6. Grapefruit juice has been shown to inhibit CYP3A4, causing an increase in the concentrations of drugs which require CYP3A4 for metabolism. Two case reports demonstrated that the addition of grapefruit juice to a clomipramine regimen increased the trough plasma concentrations of clomipramine. Whether the inhibition of clomipramine metabolism by grapefruit juice would be sustained over time is not known (Oesterheld & Kallepalli, 1997a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor clomipramine and desmethylclomipramine trough levels in patients receiving grapefruit juice. Also monitor the patient for signs of clomipramine toxicity.

7) Probable Mechanism: inhibition of clomipramine metabolism by grapefruit juice

8) Literature Reports

a) An 8-year-old male patient was being treated with clomipramine 25 mg three times daily for obsessive-compulsive disorder. Trough plasma levels of clomipramine (CMI) and desmethylclomipramine (DMCI) were 73 ng/mL and 144 ng/mL, respectively. When 250 mL of grapefruit juice was administered with each dose of clomipramine, the trough levels of CMI and DMCI increased to 198 ng/mL and 233 ng/mL, respectively, after three days. In another case, a 13-year-old female being treated with clomipramine 125 mg daily had a CMI trough blood level of 48 ng/mL and a DMCI trough blood level of 195 ng/mL. Grapefruit juice 250 mL was administered with each clomipramine dose for three days, and the CMI trough level increased to 69 ng/mL while the DMCI trough level decreased to 170 ng/mL (Oesterheld & Kallepalli, 1997).

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) Clomipramine Hydrochloride

1) Therapeutic

a) Physical Findings

1) DEPRESSION

a) Improvement in mood, affect, and behavior.

b) Improvement in vegetative signs including appetite, sleep pattern, interest in work/recreation, and improvement in weight (if abnormal).

2) OBSESSIVE COMPULSIVE DISORDER (OCD)

a) Reduction in frequency and severity of obsessions and compulsions characteristic of the patient.

b) Improvement in work function, and reduction in amount of time spent with obsessions/compulsions.

2) Toxic

a) Laboratory Parameters

1) Liver function tests

b) Physical Findings

1) Signs of central and peripheral hyperactivity: tremor, seizures, manic- like behavior, increased aggression.

2) Constipation, urinary retention, dry mouth, or blurred vision.

3) Orthostatic hypotension, tachycardia.

4) Sexual dysfunction of both genders: impotence, ejaculation problems, anorgasmia.

5) Monitor patients receiving antidepressants for worsening of depression, suicidality, or unusual changes in behavior, especially at the initiation of therapy or when the dose increases or decreases. Such monitoring should include at least weekly face-to-face contact with patients or their family

members or caregivers during the initial 4 weeks of treatment, then visits every other week for the next 4 weeks, then at 12 weeks, and then as clinically indicated beyond 12 weeks. Families and caregivers should be advised of the need for close observation (ie, daily observation) of patients and communication with the prescriber (Anon, 2004).

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

4.2 Patient Instructions

A) Clomipramine (By mouth)

Clomipramine

Treats obsessive-compulsive disorder, depression, chronic pain, bulimia, sleep disorders, and panic disorder. This medicine is a tricyclic antidepressant (TCA).

When This Medicine Should Not Be Used:

You should not use this medicine if you have had an allergic reaction to clomipramine or to related medicine such as Elavil® or nortriptyline. You should not use this medicine if you have had a recent heart attack or have used an MAO inhibitor (MAOI) such as Eldepryl®, Marplan®, Nardil®, or Parnate® within 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 several times in order to find out what works best for you. Do not use more medicine or use it more often than your doctor tells you to.

Your doctor may tell you to take the medicine at bedtime, because clomipramine can make you sleepy.

You may take the tablet with or without food. It is best to take the oral capsules with food to decrease stomach upset.

Do not break or chew the capsules. You may open the capsule and mix the medicine beads with soft food (applesauce, pudding). Swallow the mixture without chewing.

It may be 2 to 3 weeks after you start clomipramine before you notice an improvement in your symptoms.

Do not stop taking clomipramine suddenly without asking your doctor.

This medicine should come with a Medication Guide. Read and follow these instructions carefully. Ask your doctor or pharmacist if you have any questions. Ask your pharmacist for the Medication Guide if you do not have one. Your doctor might ask you to sign some forms to show that you understand this information.

If a Dose is Missed:

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

If you take one dose a day at bedtime, you should not use the missed dose the next morning without asking your doctor.

How to Store and Dispose of This Medicine:

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

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

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

Drugs and Foods to Avoid:

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

Make sure your doctor knows if you are using cimetidine (Tagamet®), clonidine (Catapres®), digoxin (Lanoxin®), guanethidine (Ismelin®), haloperidol (Haldol®), methylphenidate (Ritalin®), or phenothiazine medicine (such as prochlorperazine, Compazine®, Mellaril®, Phenergan®, Thorazine®, or Trilafon®). Tell your doctor if you are also using other medicines to treat depression (such as fluoxetine, sertraline, paroxetine, fluvoxamine, Prozac®, Zoloft®, Paxil®, or Luvox®), medicine to treat seizures (such as phenytoin, phenobarbital, Dilantin®, or Luminal®), certain medicine for heart rhythm problem (such as quinidine, flecainide, propafenone, Quinaglute®, Tambocor®, or Rythmol®), or a blood thinner (such as warfarin or Coumadin®).

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

Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:

Make sure your doctor knows if you are pregnant or breastfeeding, or if you have kidney disease, liver disease, thyroid problems, glaucoma, high blood pressure, heart problems, trouble going to the bathroom (urinating), adrenal gland tumor (such as pheochromocytoma or neuroblastoma), or a history of seizure disorder.
For some children, teenagers, and young adults, this medicine can increase thoughts of suicide. Tell your doctor or your child's doctor right away if you or your child start to feel more depressed and have thoughts about hurting yourselves. Report any unusual thoughts or behaviors that trouble you or your child, especially if they are new or are getting worse quickly. Make sure the doctor knows if you or your child have trouble sleeping, get upset easily, have a big increase in energy, or start to act reckless. Also tell the doctor if you or your child have sudden or strong feelings, such as feeling nervous, angry, restless, violent, or scared. Let the doctor know if you, your child, or anyone in your family has bipolar disorder (manic-depressive) or has tried to commit suicide.
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert.
Make sure any doctor or dentist who treats you knows that you are using this medicine. You may need to stop using this medicine several days before having surgery or medical tests.
This medicine may make your skin more sensitive to sunlight. Use a sunscreen when you are outdoors. Avoid sunlamps and tanning beds.
Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to keep all appointments.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing.
Change in how much or how often you urinate, or painful or difficult urination.
Changes in behavior, or thoughts of hurting yourself or others.
Chest pain.
Ear pain or discharge, or ringing in the ears.
Fast, pounding heartbeat.
Fever, chills, cough, sore throat, runny or stuffy nose, and body aches.
Lightheadedness or dizziness when getting up suddenly from a lying or sitting position.
Memory problems, confusion, or depression.
Nervousness, anxiety, agitation, or irritability.
Numbness, tingling, or burning pain in your hands, arms, legs, or feet.
Tremors, or muscle twitching or stiffness.
Trouble sleeping, unusual dreams.
Trouble swallowing.
Unusual bleeding, bruising, or weakness.

If you notice these less serious side effects, talk with your doctor:
Changes in appetite.
Changes in taste.
Changes in vision.
Dry mouth or tooth problems.
Headache or drowsiness.
Menstrual cramps or change in monthly periods.
Muscle, joint, or back pain.
Nausea, vomiting, diarrhea, constipation, or stomach pain or upset.
Problems with sex.
Skin rash or itching.
Sweating.
Tiredness.
Warmth or redness in your face, neck, arms, or upper chest.
Weight changes.

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

4.3 Place In Therapy

A) Clomipramine is indicated for the treatment of obsessive compulsive disorder. It is recommended as first-line therapy along with behavioral therapy (Park et al, 1997). Other first-line agents include fluvoxamine, fluoxetine, sertraline, and paroxetine. However, clomipramine may be selected for patients with concomitant insomnia, akathisia, or nausea/diarrhea (Anon, 1997).

B) Clomipramine is not superior to tricyclic antidepressants, including imipramine and amitriptyline, for treating major depression. The drug has been effective for obsessive compulsive behavior associated with depression, although imipramine seems to be equally suited for treating this disorder. Clomipramine appears to be more effective than amitriptyline for relieving chronic pain caused by trigeminal neuralgia and tension headaches, but not post-herpetic neuralgia.

C) Clomipramine should be considered for hospital formulary inclusion for the treatment of obsessive compulsive disorder, with or without major depression (Kelly & Myers, 1990). Clomipramine cannot be recommended for first-line treatment of chronic pain induced by trigeminal neuralgia or tension headaches until additional controlled studies are conducted, but may be considered for those patients refractory to amitriptyline.

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) The exact mechanism of action of clomipramine is not known. The drug is classified as a tertiary amine tricyclic antidepressant with very potent inhibition of serotonin uptake (Bertilsson et al, 1974; Asberg et al, 1977). The active metabolite, desmethylclomipramine, is a potent norepinephrine uptake inhibitor and may retain some serotonin uptake inhibition (Benfield et al, 1980; Ross & Renyi, 1975). Several researchers feel that the effect of clomipramine's serotonin uptake may be essential to the anti-obsessive compulsive activity observed (Flament et al, 1987); (Thoren et al, 1980)(Zohar et al, 1988). Obsessive-compulsive patients with initially high cerebrospinal fluid levels of the serotonin metabolite, 5-hydroxyindole-acetic acid (5-HIAA), demonstrated a positive correlation with the improvement of obsessive-compulsive behavior and the reduction of the cerebrospinal fluid levels of 5-HIAA during clomipramine therapy (Thoren et al, 1980). High pretreatment levels of platelet serotonin were a strong predictor of clomipramine treatment response (Flament et al, 1987). During clomipramine therapy clinical improvement in obsessive-compulsive symptoms was positively correlated with a reduction in platelet serotonin levels.

2) The therapeutic effects of clomipramine in obsessive compulsive disorder are mediated via serotonergic mechanisms (Benkelfat et al, 1989). The plasma ratio of tryptophan (TRP) to other large neutral amino acids (LNAA) were studied in 44 patients with major depression (Moller et al, 1990). The LNAA selected were thought to reflect brain serotonin formation. The patients were subsequently treated with paroxetine (N=27) or clomipramine (N=17) in double-blind fashion on fixed dosage schedules for 4 weeks. Endogenous and nonendogenous patients were comparable with respect to the ratio of TRP/LNAA. The clomipramine group showed a significant inverse correlation between the TRP/LNAA ratio and clinical improvement. Patients with a TRP/LNAA ratio below the mean showed a trend towards greater improvement than patients with a higher ratio, but with comparable serum drug levels. These findings suggest that it may be possible to increase the efficacy of antidepressant treatment in populations of depressed patients by prior selection based on plasma amino acid patterns. The published evidence that supports a link between depression and obsessive-compulsive disorder from a biochemical basis was reviewed (Asberg et al, 1982).

3) The effect of clomipramine (CMI) treatment on serum prolactin (PRL) levels was studied in 18 children and adolescents with obsessive compulsive disorder. PRL was measured at baseline and after 4 and 8 weeks of CMI treatment. Baseline PRL was higher in patients with tics and OCD than in patients with OCD alone. CMI administration significantly increased basal PRL levels. A slight decline in PRL during the last 4 weeks of CMI treatment was positively correlated with a favorable response and negatively correlated with duration of illness. If these PRL changes are related to changes in serotonergic neurotransmission, the results suggest that CMI treatment of OCD produces an adaptive decrease in the responsiveness of serotonergic receptors (Hanna et al, 1991).

4) Cytokine production by peripheral blood mononuclear cells (PBMC) was assessed in 10 patients with major depression (5 male, 5 female) before and after 4 weeks of clomipramine (CMI) treatment and in age- and gender-matched controls (Weizman et al, 1994). A significant reduction in interleukin-1B (IL-1B), interleukin-2 (IL-2) and interleukin-3-like activity (IL-3-LA) was observed in untreated depressed patients when compared to controls. IL-1B and IL-3-LA synthesis was significantly increased after treatment with CMI. The suppression of cytokine production by PBMC in depressed patients may be associated with the depression per se, or may be related to depression-related hyperactivity of the hypothalamic-pituitary-adrenal axis. The authors did not discuss the role of serotonergic drugs (clomipramine) in possible reversal of cytokine suppression.

B) REVIEW ARTICLES

1) Treatment guidelines for obsessive compulsive disorders including the use of clomipramine have been published (Goodman, 1999; Ellingrod, 1998; Anon, 1997a; Park et al, 1997a; Flament & Bisserbe, 1997; Rasmussen & Eisen, 1997; Jackson et al, 1994; Jenike, 1992).

2) Comprehensive review articles on CLOMIPRAMINE have been prepared (Peters et al, 1990; McTavish & Benfield, 1990).

3) The worldwide use of CLOMIPRAMINE was summarized (Trimble, 1990).

4) The pharmacokinetics of CLOMIPRAMINE are summarized in a review (Balant-Gorgia et al, 1991).

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

4.5 Therapeutic Uses

Clomipramine

Clomipramine Hydrochloride

4.5.A Clomipramine

Anorexia nervosa

Cataplexy - Narcolepsy

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.B Clomipramine Hydrochloride

Anorexia nervosa

Autistic disorder

Chronic pain

Delusional disorder

Depression

Disorder of ejaculation

Obsessive-compulsive disorder

Obsessive-compulsive disorder, Intravenous therapy

Panic disorder

Pervasive developmental disorder

Premenstrual syndrome

Self-injurious behavior

Steinert myotonic dystrophy syndrome

Trichotillomania

4.5.B.1 Anorexia nervosa

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Found to be no more effective than placebo in producing weight gain in patients with anorexia nervosa

c) Adult:

1) In a double-blind, placebo-controlled trial of 16 female ANOREXIA NERVOSA patients, CLOMIPRAMINE 50 milligrams/day was found no more effective than placebo in producing weight gain (Lacey & Crisp, 1980). Placebo or oral CLOMIPRAMINE 50 milligrams was administered once daily to anorexic patients until their predetermined target weight was attained. Patients on CLOMIPRAMINE had increased appetite, hunger and calorie consumption during the early part of the study; however, this had no impact on the final outcome. Patients on placebo took a mean of 72 days to attain their target weight, while those on CLOMIPRAMINE took a mean of 76 days. Two patients on CLOMIPRAMINE and 1 patient on placebo did not complete the study. At a 4-year follow-up, measurement outcomes of

nutritional status, sexual adjustment, socioeconomic adjustment and mental state showed no significant differences between the 2 groups (Crisp et al, 1987a). Patients treated with CLOMIPRAMINE and placebo- treated patients were at a mean of 94% and 93% of target weight, respectively.

4.5.B.2 Autistic disorder

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Effective in one study

c) Adult:

1) CLOMIPRAMINE (CMI) was superior to placebo and desipramine (DMI) on ratings of autistic symptoms such as anger, and compulsive, ritualized behaviors in a 10-week, double-blind crossover comparison of CMI and placebo and CMI and DMI (Gordon et al, 1993a).

4.5.B.3 Chronic pain

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:

Possibly effective for chronic low back pain in selected patients

c) Adult:

1) In an open study, 23 out of 30 patients with chronic low back pain responded to clomipramine treatment. Clomipramine 25 milligrams (mg) was increased to 150 mg/day intravenously during a 10-day hospital stay. After discharge, clomipramine 150 mg/day orally was used for 20 days. Patients with lower initial mean scores on the Minnesota Multiphasic Personality Inventory (MMPI) for hypochondria, depression, and hysteria were more likely to respond to treatment (p less than 0.02, p less than 0.05, p less than 0.02, respectively). These study findings may assist in proper patient selection for beneficial clomipramine therapy, however further placebo-controlled studies are recommended (Fouquet et al, 1997).

2) In 2 case reports, patients with schizophrenia and obsessive-compulsive symptoms had their chronic back pain alleviated by clomipramine (Kurokawa & Tanino, 1997). Doses used ranged from 30 to 75 milligrams. The authors believe that the back pain was related to serotonin dysfunction.

4.5.B.4 Delusional 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:

Appears effective in the treatment of some types of delusional disorders including DELUSIONAL DISORDER, SOMATIC TYPE and BODY DYSMORPHIC DISORDER

c) Adult:

1) In a double-blind, cross-over trial clomipramine was more effective than desipramine in patients with body dysmorphic disorder (BDD)(Hollander et al, 1999). Patients (n=29) with distress or impairment in functioning due to BDD were randomized to receive first either clomipramine, a selective serotonin reuptake inhibitor, or desipramine, a selective norepinephrine reuptake inhibitor (specifically an active placebo), for 8 weeks each. Patients initially received 25 milligrams (mg)/day and were increased to a maximum of 250 mg/day or the highest tolerated dose. Mean dosages attained were 138 mg/day for clomipramine and 147 mg/day for desipramine. Assessments were done using a BDD modified version of the Yale-Brown Obsessive Compulsive Scale (BDD-YBOCS), a modified National Institute of Mental Health Global Obsessive-Compulsive Scale (BDD-NIMH), and the Clinical Global Impression Scale specific to BDD symptoms (BDD-CGI). Clomipramine was superior to desipramine on all 3 of the outcome measures. On the BDD-YBOCS there was a 65% improvement rate with clomipramine and a 35% rate with desipramine (p=0.09). On the BDD-NIMH the response rate was 70% with clomipramine and 30% with desipramine (p=0.02). For the BDD-CGI, clomipramine was also significantly better than desipramine (p=0.01). Also of significance was that patients who were more delusional appeared to improve more with clomipramine therapy (BDD-CGI, p=0.007). Adverse effects were similar for both drugs. This is the first study demonstrating the effectiveness of clomipramine for BDD.

2) Four patients with delusional disorder of the somatic type showed clinical improvement with

clomipramine therapy (Wada et al, 1999). All patients persistently complained that something was moving inside their bodies although nothing was found after extensive evaluations. All repeatedly visited physicians complaining of symptoms with 1 patient receiving a possibly unnecessary surgery. Another patient was unresponsive to multiple therapies including sulpiride, nemonapride, mosapramine, levomepromazine, risperidone, fluphenazine, pimozide, and clocapramine. The dosage of clomipramine ranged from 60 to 120 milligrams daily and the time to improvement ranged from 27 to 52 days. Further studies including comparisons with pimozide are needed.

4.5.B.5 Depression

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Oral and intravenous clomipramine have been successfully used to treat dysthymia and major depression (Faravelli & Pallanti, 1987)
Intravenous therapy has had no advantage over oral therapy (Faravelli & Pallanti, 1987)
Early improvement in severe depressive symptoms may be achieved by using loading doses of oral or intravenous CLOMIPRAMINE

c) Adult:

1) Five days after pulse-therapy with oral or intravenous clomipramine, symptoms of depression significantly improved in 22 inpatients. Patients were given either an evening infusion of 150 milligrams of clomipramine and placebo tablets or 150 milligrams of oral clomipramine and an isotonic saline infusion. Twenty-four hours later, this was repeated using 200 milligrams of clomipramine. Pulse-therapy with oral and intravenous clomipramine showed no difference in efficacy or side effects in treating depression. In this double-blind randomized trial results were based on the Hamilton Depression, Raskin, and Beck scales (Pollock et al, 1989).

2) Clomipramine was significantly (p equals 0.02) more effective than placebo in improving mood in 21 depressed patients with probable Alzheimer's disease. Results were based on the Hamilton Depression scores. Clomipramine- treated patients showed a significantly (p less than 0.01) lower Mini-Mental State score than placebo; no significant drug effects were seen on the Independence measure scores. Patients received 6 weeks of clomipramine or placebo in a double-blind crossover design. During the first 6 week period, 9 of 11 clomipramine-treated patients experienced a complete remission while the same effect occurred in only 3 of 10 placebo-treated patients. Clomipramine was administered at 25 mg for 1 week, 50 mg for week 2, 75 mg for week 3, and 100 mg for weeks 4 to 6 (Petracca et al, 1996).

d) Pediatric:

1) A single pulse dose of clomipramine 200 milligrams intravenously was administered in a double-blind, placebo-controlled trial of 16 depressed adolescents, (14-to 18-years-old), demonstrating dramatic and rapid reduction in depressive symptoms at day 6 post-clomipramine infusion, based upon decreases in Hamilton Depression Rating Scale score ($p = 0.04$) and Clinical Global Impression severity score ($p = 0.003$). The clomipramine effect (88% study response rate) may persist for up to 8 weeks in some patients. The authors suggest that gradually administered clomipramine is less effective than pulse intravenous clomipramine due to the pulse regimen's rapid enhancement of serotonergic transmission (Sallee et al, 1997).

4.5.B.6 Disorder of ejaculation

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:

Useful in the treatment of ejaculatory disorders

c) Adult:

1) Daily dosing with clomipramine was successful in treating premature ejaculation in men who were unresponsive to clomipramine 25 milligrams (mg) on an "as needed" basis. Four men who, in an earlier study, were nonresponders to clomipramine 25 mg "as needed" participated in a 12 week study in which they took clomipramine 0, 10, 20, and 30 mg daily, each dose for 3 weeks. Latencies were significantly longer with the 30-mg per day dose than with the previous 25-mg regimen. Ejaculatory control, sexual arousal, and penile rigidity were not significantly affected by treatment. All subjects reported satisfaction with the treatment. Side-effects were mild and generally transient. Of the 3 men who opted to continue clomipramine treatment, 1 chose 30 mg as needed, and 2 chose 20 mg daily (Rowland et al, 2001).

2) Clomipramine 25 milligrams, as needed, effectively increased ejaculatory latency in men with primary premature ejaculation. In a prospective, double-blind, placebo controlled, crossover study,

patients with primary premature ejaculation (n=8), premature ejaculation and erectile dysfunction (n=6), and controls (n=8) were randomly given clomipramine for a 3 week period and placebo for 3 a week period. Each was to be used 12 to 24 hours before sexual activity. Patients with ejaculatory latency increased their time to ejaculation from approximately 2 to 8 minutes (p=0.035). No significant effects occurred in controls and men with premature ejaculation and erectile dysfunction (Haensel et al, 1996).
3) CLOMIPRAMINE (CMI) was useful in the treatment of PREMATURE EJACULATION (Segraves et al, 1993). Twenty patients with premature ejaculation were randomly allocated to treatment with CLOMIPRAMINE or placebo in a double-blind study. Mean estimated time to ejaculation after vaginal penetration increased to 6.1 minutes on CMI 25 mg and to 8.4 minutes on CMI 50 mg. These estimated times were significantly different from estimated time to ejaculation while on placebo. The results suggest that low-dose CMI may be useful in the treatment of premature ejaculation.
4) Two of 3 cases of RETROGRADE EJACULATION were successfully treated with oral CLOMIPRAMINE 25 milligrams twice a day. Two of the 3 patients responded with normal ejaculation within 5 days and subsequent conception, while the third patient only partially improved (Eppel & Berzin, 1984).

4.5.B.7 Obsessive-compulsive disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (10 years and older)
Efficacy: Adult, Effective; Pediatric, Effective
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indicated for the treatment of obsessions and compulsions associated with obsessive compulsive disorder

c) Adult:

1) Double-blind, placebo-controlled trials have demonstrated the efficacy of CLOMIPRAMINE in relieving some obsessive compulsive symptoms (Greist et al, 1990; DeVeaugh-Geiss et al, 1989; Pato et al, 1988; Flament et al, 1985a; Marks et al, 1980a). Some researchers feel that patients with a depressive component will do better with CLOMIPRAMINE. Other researchers believe that behavioral therapy is also required to alleviate ritualistic behavior. Large long-term studies have been difficult to conduct because of the apparent low incidence of this disorder. In a meta-analysis, it was concluded that the most common treatments for obsessive-compulsive disorder include CLOMIPRAMINE, FLUOXETINE, and exposure-based behavior therapy (Cox et al, 1993). Results from 25 appropriate treatment studies from 1975 to 1991 revealed that all three treatments were significantly effective for most of the outcome variables (overall severity, anxiety, depression). Exposure was not significantly effective for reducing depressed mood.
2) A 24-year-old female with a 3-year history of obsessive compulsive disorder (OCD) experienced a 90% resolution of symptoms in 4 weeks following inpatient behavior therapy and treatment with clomipramine 50 milligrams (mg) gradually increased to 150 mg daily. Patient symptoms included fear of contamination from touching various items she considered dirty and excessive hand washing (30-50 times per contact with a dirty object). The symptoms began to adversely affect her social and academic life, and depression developed. She failed an outpatient behavior program and treatment with fluoxetine 40 mg to 60 mg daily prior to being admitted to an inpatient behavior program. Clomipramine therapy was started at 50 mg daily and was gradually increased to 150 mg daily; therapy was well tolerated with the exception of periodic sedation. Upon discharge, her compulsive rituals were 90% improved and she was maintained on clomipramine 25 mg daily. No relapses of OCD or severe depression occurred during a 5-year follow-up period (Al-Sughayir, 2000).
3) A 93-year-old woman with a long-standing history of obsessive-compulsive disorder that worsened after developing Alzheimer's disease was helped by clomipramine therapy (Trappler, 1999). Her obsessions consisted of needing to know and remember trivial events with a compulsion of making excessive lists of these events. She had previously failed trials of fluoxetine and buspirone. She began clomipramine 25 milligrams (mg) daily and was increased over 10 days to 50 mg. After 9 weeks her score on the Yale-Brown Obsessive-Compulsive Scale dropped from 29 to 3. The author notes that clomipramine was effective and well-tolerated in this very old patient.
4) A combination of CLOMIPRAMINE and FLUOXETINE was effective in 4 cases of OCD where either drug used alone was ineffective. No increased side effects resulted (Browne et al, 1993).
5) There was no significant difference in treatment outcome with CLOMIPRAMINE between those patients with at least one personality disorder and those with no personality disorders. The effect of Axis II diagnosis on the outcome of treatment with CLOMIPRAMINE was determined in 55 patients with obsessive-compulsive disorder (Baer et al, 1992). Patients with paranoid, schizoid, or schizotypal personality disorders (DSM-III) had significantly higher obsessive-compulsive disorder severity scores at baseline, and the number of personality disorders was strongly related to baseline severity of obsessive compulsive symptoms. At the conclusion of this 12-week study, the presence of schizotypal, borderline, and avoidant personality disorders, along with the total number of personality disorders, did predict poorer treatment outcome.

6) Using standard OCD assessment tools, it was shown that CLOMIPRAMINE (CMI) was significantly more effective than placebo (38 to 44% response vs 3 to 5% response). Two double-blind studies at 21 centers evaluated the efficacy and safety of up to 300 mg/d of CMI vs placebo in 520 patients with OCD. TCA-like side effects were reported for CMI. Although uncommon, seizures and elevated aminotransferase values are potentially serious side effects of CMI (Anon, 1991).
7) Ten patients with DSM-III-R obsessive compulsive disorder (OCD) who were being treated chronically with CLOMIPRAMINE (CMI) in a mean dosage of 270 milligrams/day, were studied to determine the minimum dose of CMI needed to maintain therapeutic benefit. Gradual, open dosage reduction resulted in a mean dosage of 165 milligrams/day, a reduction of 105 milligrams/day (approximately 40%). This decrease in dosage was accompanied by no significant change in three OC measures, as determined by the paired t-test. These results suggest that even though OCD patients were not able to discontinue medication completely, they were able to do well at lower doses than those used initially in the treatment of the disorder (Pato et al, 1990).

d) Pediatric:
1) Continued CLOMIPRAMINE (CMI) treatment seems necessary for children and adolescents. The need for continued CLOMIPRAMINE (CMI) treatment in children and adolescents with obsessive compulsive disorder (OCD) was evaluated in a double-blind DESIPRAMINE substitution study. Twenty-six children and adolescents with severe primary OCD receiving long-term CMI maintenance treatment (mean 17 months) entered an 8-month study. All patients received CMI for the first 3 months, then half received CMI and half were given DESIPRAMINE (DMI) for the next 2 months, then all subjects were given CMI for the last 3 months. Eighty-nine percent of the substituted versus 18% of the non-substituted group relapsed during the 2-month comparison period. However, even subjects who continued uninterrupted CMI treatment experienced OC symptoms which varied in severity over time (Leonard et al, 1991a).
2) In a case series, 7 children and adolescents (9-to 23-years-old) with obsessive compulsive disorder, benefited from combination therapy of clomipramine and a selective, serotonin reuptake inhibitor (Figueroa et al, 1998). The combination therapy appeared to augment the effectiveness of monotherapy. Clomipramine was used in doses of 25 to 100 milligrams. The serotonin reuptake inhibitors used included: fluoxetine, sertraline, paroxetine, and fluvoxamine. In 2 cases, once the combination was effective, one of the drugs was successfully discontinued. Two cases of QTc interval prolongation occurred.

4.5.B.8 Obsessive-compulsive disorder, Intravenous therapy

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:
Appears effective in the treatment of obsessive-compulsive disorder even in some patients refractory to oral clomipramine
Intravenous clomipramine is not FDA approved

c) Adult:
1) Intravenous clomipramine was more effective than placebo in the treatment of obsessive-compulsive disorder (OCD) in patients refractory to oral clomipramine (Fallon et al, 1998). In a double-blind 4-week study, OCD patients refractory to oral clomipramine were randomized to receive 1-hour infusions of 500 milliliters of 0.9% isotonic sodium chloride solution containing either clomipramine (n=28) or placebo (n=23). Clomipramine was titrated over 14 infusions from 25 milligrams (mg) daily to 250 mg daily. Oral clomipramine was started in all patients after the infusions. Patients were evaluated using the Clinical Global Impression (CGI) scale. After the seventh infusion, no patients showed improvement. After infusion 14, 6 (20.7%) clomipramine patients were responders on the CGI versus none in the placebo group (p less than 0.02). At 1 week after the infusions, 9 out of 21 (43%) clomipramine patients were responders according to the CGI (not all patients were evaluated at this time point). Again there were no responders in the placebo group. At 1 month after the infusion, 9 out of 16 patients were rated as overall intravenous clomipramine responders. Further study is needed comparing the intravenous route to the oral route of therapy.
2) Intravenous pulse loading of clomipramine was beneficial in 6 out of 7 patients with obsessive compulsive disorder. Patients were randomized to receive either oral loading of clomipramine (n=8) or intravenous loading (n=7). The intravenous loading consisted of clomipramine 150 milligrams (mg) given intravenously over 90 minutes, followed by clomipramine 200 mg intravenously, 24 hours later. Trimethobenzamide hydrochloride 250 mg was given before each dose to reduce nausea. The oral loading consisted of clomipramine 150 mg on day 1 and 200 mg given on day 2. Oral clomipramine 150 mg was started in all patients 4.5 days after the second dose and increased by 25 mg every fourth day to 250 mg/day. Using the Yale-Brown scale, 6 out of 7 patients in the intravenous group had responded before the oral dosing was started while only 1 in the oral dose group had responded (p=0.009). After 8 weeks, there was no difference in the 2 groups, both had 4 responders (p=0.38). Pulse intravenous loading may be an effective method for quickly testing patient responsiveness to clomipramine therapy

(Koran et al, 1997).
3) A 25-year-old woman with schizophrenia and ego-dystonic checking and cleaning rituals benefited from intravenous clomipramine (Poyurovsky & Weizman, 1998). Her schizophrenia was stabilized with perphenazine 8 milligrams (mg) daily. She had failed trials of fluvoxamine and fluoxetine for her obsessive-compulsive disorder (OCD). Further deterioration of her OCD led to hospitalization where a course of intravenous clomipramine 75 mg was added to her perphenazine. The infusion was repeated the next day. Five days later her Yale-Brown Obsessive Compulsive score had dropped from 19 to 4. She was maintained on clomipramine 150 mg daily and has had no recurrence of her OCD symptoms over the last 6 months.

4.5.B.9 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:
Reported to be effective in the treatment of panic attacks and AGORAPHOBIA

c) Adult:
1) Low-dose clomipramine 60 mg/day was as effective as high-dose clomipramine 150 mg/day in the treatment of phobias, anxiety, and panic attacks in a multi-center study (Caillard et al, 1999). In an 8-week study, patients were randomized to clomipramine 150 milligrams (mg)/day (n=56), clomipramine 60 mg/day (n=51), or placebo (n=51). Doses were titrated over 2 weeks. At the end of 8 weeks, phobias as evaluated on the Cottraux Scale were significantly improved in both clomipramine groups as compared to placebo (p=0.002). For anxiety, both clomipramine groups were significantly better than the placebo group as measured on the anxiety subscale of the Cottraux Anxiety Scale (p=0.002). For panic attacks, the average number of attacks during the previous week was not significantly different in either of the clomipramine groups or for placebo. However, the number of DSM-III-R symptoms of panic attacks was decreased in both clomipramine groups but not in the placebo group (p=0.03). There was no difference seen between the 2 clomipramine therapies in these 3 areas. The author notes that differences may have become evident if a longer treatment period had been used.
2) In a randomized, placebo-controlled, 10-week study, exercise was found to be effective for the treatment of panic disorder, however, clomipramine was even more effective. Forty-six patients with panic disorder were assigned to either regular aerobic exercise (running), clomipramine (increasing doses over three weeks up to 112.5 milligrams/day), or placebo capsules. The dropout rate was 31% for the exercise group, 27% for the placebo group, and 0% for the clomipramine group. On the Bandelow Panic and Agoraphobia Scale, Observer-Rated, clomipramine and exercise improved anxiety symptoms more effectively than placebo (p less than 0.001, p less than 0.05, respectively). Improvements in the clomipramine group were seen as early as 4 weeks while exercise improvements were not seen until the 8th week. Patients receiving clomipramine or placebo experienced more side effects (dry mouth, sweating, mild tremor, dizziness, tachycardia, nausea, constipation, diarrhea) than those in the exercise group. Additional studies are warranted to investigate exercise in the treatment of anxiety disorders, perhaps in combination with drug treatment (Broocks et al, 1998).
3) Despite lowering the initial starting dose of clomipramine to 10 milligrams (mg)/day to maximize compliance, a study involving 58 patients with panic disorder (with or without agoraphobia) resulted in a 45% dropout rate due to adverse reactions occurring mostly during the first two weeks of treatment. Of those completing the study, 84% were markedly or moderately improved. The initial dose was clomipramine 10 mg at bedtime and increased slowly to 20 mg/day after 4 days, then by 10 mg at 1-to 2-week intervals up to 80 mg after 8 weeks. Patients could receive up to 250 mg daily if the drug was tolerated, with the mean daily dosage being 96.9 mg after 13 weeks of treatment. The primary adverse reactions reported were increased nervousness and agitation (Papp et al, 1997).
4) Clomipramine (10 milligrams (mg) for three days and 20 mg for four days) and fluvoxamine (50 mg/day for seven days) were both effective in decreasing the hypersensitivity to 35% carbon dioxide, supporting the serotonergic effect of these drugs to decrease panic attacks through modification of carbon dioxide sensitivity. Thirty-nine panic disorder patients were enrolled in a double-blind, randomized, placebo-controlled study, where each patient was given the 35% carbon dioxide challenge on days 0, 3, and 7. Patients on clomipramine and fluvoxamine showed significant reduction in sensitivity over placebo after seven days as seen by the percent change on a visual analogue for anxiety scale (p=0.027) (Perna et al, 1997a).
5) Clinical improvement was modest on agoraphobia in panic disorder patients who failed to respond to exposure-based behavioral treatment and were treated then with CLOMIPRAMINE (CMI) (Hoffart et al, 1993). Eighteen patients with panic disorder with agoraphobia who had not responded to previous inpatient behavioral treatment entered a 12-week, placebo- controlled, double-blind crossover study of CLOMIPRAMINE at maximum doses of 150 milligrams/kilogram for 3 weeks. Patient outcome was assessed on measures of phobic avoidance, agoraphobic cognitions, panic, state and trait anxiety, subjective anxiety, and depression. Seventeen of 18 patients completed the study. One patient (placebo group) dropped out after 6 weeks after developing acute gastric pain. On most outcome measures,

patients had significantly lower symptom scores at posttest in the active drug period than at posttest in the placebo period. However, while this study showed short-term efficacy of CLOMIPRAMINE for agoraphobic patients who did not respond to behavioral treatment, its ability to produce lasting benefits remains to be proven.
6) CLOMIPRAMINE in low doses (25 to 75 milligrams daily) was reported effective in the treatment of panic ANXIETY and agoraphobia in outpatients in an uncontrolled 8-week clinical trial (Gloger et al, 1989). Of 17 patients treated, panic attacks were abolished completely in 13, and markedly decreased in 4 others. In 7 agoraphobic patients, avoidance behavior disappeared in 5. Overall mean doses were 45 milligrams daily, with 8 patients (6 panic and 2 agoraphobic) receiving 25 milligrams daily or less (mean, 18.76 milligrams). There was a trend towards the need for higher doses in agoraphobia (mean, 56 milligrams) as opposed to panic disorder (mean, 40 milligrams). Well-controlled clinical trials are required to confirm these findings and determine the optimal dose of CLOMIPRAMINE in panic disorder and agoraphobia.
7) Oral CLOMIPRAMINE was significantly superior to placebo on measures of DEPRESSION, DYSPHORIA, and on several indexes of PHOBIC SYMPTOMS in an 8-week double-blind, placebo-controlled study of 94 agoraphobic women as diagnosed by DSM-III guidelines (Johnston et al, 1988a). CLOMIPRAMINE was started at 25 milligrams/day which was slowly increased up to a maximum of 300 milligrams/day as tolerated. At the end of the study the mean daily dose of CLOMIPRAMINE was 83 milligrams. Adverse effects associated with CLOMIPRAMINE use included dry mouth, high energy levels, constipation, and increased sweating.

4.5.B.10 Pervasive developmental 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:
May be effective in adults with pervasive developmental disorders (PDDs)

c) Adult:
1) Clomipramine was found to be effective in 18 of 35 adult patients (55%) with pervasive developmental disorders (PDDs) (18 patients with autistic disorder, 6 with Asperger's disorder, 11 with PDD not otherwise specified). In an open-label study, clomipramine was started at 50 milligrams (mg) at bedtime and increased by 50 mg every 3 or 4 days to a maximum dosage of 250 mg daily within 3 weeks and continued for a minimum of 9 additional weeks. Based on the Clinical Global Impression scale, 18 patients were "much" or "very much" improved (p less than 0.001). In those 18 patients, clomipramine significantly reduced total repetitive thoughts and behavior (p less than 0.001), aggression (p less than 0.001), and some aspects of social relatedness such as eye contact and verbal responsiveness (p less than 0.001). Improvements were not related to a specific subtype of PDD. Three patients had seizures during treatment (two having a prior seizure history), prompting the authors to recommend a selective serotonin uptake inhibitor in these patients (Brodkin et al, 1997).

4.5.B.11 Premenstrual syndrome

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

b) Summary:
Effective in reducing the symptoms of Premenstrual Syndrome in small studies

c) Adult:
1) Intermittent administration of low-dose CLOMIPRAMINE (25 to 75 milligrams/day) during the luteal phase only for the treatment of premenstrual syndrome was effective (N=29), and the onset of clinical effect was shorter than when clomipramine was used to treat depression, panic disorder, or obsessive-compulsive disorder (Sunblad et al, 1993).
2) CLOMIPRAMINE (CMI) was effective in reducing symptoms of Premenstrual Syndrome (PMS) in a placebo-controlled trial. Forty non-depressed women with severe premenstrual irritability and/or dysphoria and fulfilling DSM-IIIR diagnostic criteria for late luteal phase dysphoric disorder were treated daily for 3 menstrual cycles with either CMI (25 to 75 milligrams/d) or placebo. Both groups had 20 patients. The response rate in the placebo group was 40% compared with 80% for the CMI group. The possible role of serotonin in the pathophysiology of PMS is discussed (Sundblad et al, 1992).
3) Subjects reported a dramatic reduction in premenstrual complaints with clomipramine therapy. CLOMIPRAMINE was administered orally as 25 to 50 milligrams/day for 5 consecutive menstrual cycles to 5 non-depressed women with severe premenstrual irritability and sadness (Eriksson et al, 1990).

4.5.B.12 Self-injurious behavior

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:
Useful in certain types of self-injurious behaviors such as severe NAIL BITING

c) Adult:
1) In an open clinical trial, CLOMIPRAMINE was useful for chronic stereotypic and self-injurious behaviors in 11 consecutive patients with concomitant development disorders (Garber et al, 1992). Patients received CLOMIPRAMINE in a mean dosage of 70 milligrams/d (range 25 to 125 mg/d). Ten patients (91%) had marked decreases in rates of target behaviors as early as 2 days after starting treatment and as late as 1 month. No seizures occurred despite the inclusion of six patients with previous histories of epileptic events, and improvement was evident regardless of level of mental retardation. These findings support the use of serotonergic medications in this population and the need for further research.
2) CLOMIPRAMINE has been helpful in reducing SELF-MUTILATING BEHAVIOR in a 25-year-old female patient with obsessive compulsive disorder. Excessive nail-biting and arm-burning with cigarettes was successfully curtailed after 4 months of treatment with CMI at doses of 250 milligrams per day (Lipinski, 1991).
3) CLOMIPRAMINE (CMI) was significantly more effective than DESIPRAMINE (DMI) in decreasing severe nail-biting in 25 adult subjects with severe morbid ONYCHOPHAGIA. During a 10-week double-blind, crossover trial CMI at 120 milligrams/day was superior to DMI at 135 mg/d as determined by nail-biting rating scale assessments. It is hypothesized that similar biological systems mediate a spectrum of "grooming" behaviors, including onychophagia, trichotillomania, and obsessive compulsive disorder (Leonard et al, 1991a).

4.5.B.13 Steinert myotonic dystrophy syndrome

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 improved some symptoms associated with myotonic dystrophy

c) Adult:
1) CLOMIPRAMINE (CMI) has improved grip myotonia in patients with myotonic dystrophy in a placebo-controlled double-blind, crossover study. Fifteen of 17 patients completed the two 33-day treatment periods separated by a 30-day washout period. Grip myotonia was determined by a standardized test and was video-taped for later analysis. Results showed that mean relaxation time after CLOMIPRAMINE was significantly shorter than after placebo (Antonini et al, 1990).

4.5.B.14 Trichotillomania

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

b) Summary:
Effective for short-term treatment of trichotillomania

c) Adult:
1) In a 9-week study comparing cognitive-behavioral therapy (CBT), clomipramine, and placebo in the treatment of trichotillomania, CBT significantly reduced symptoms from pretreatment to posttreatment, whereas clomipramine and placebo did not. Twenty-three patients were randomized to receive either CBT, clomipramine (50 mg at bedtime titrated as tolerated to 250 mg at bedtime), or placebo and were evaluated on a weekly basis by either a psychiatrist (clomipramine and placebo patients) or a behavioral psychologist (CBT patients). Of the 16 patients that completed the trial, severity and impairment of trichotillomania were significantly reduced ($p=0.002$ and $p=0.006$, respectively) in the CBT group (n=5); however, significant differences were not noted in the clomipramine (n=6) or the placebo (n=5) groups. Clomipramine did produce more changes in pretreatment and posttreatment evaluations ($p=0.061$) than placebo; however, given the low power of the study conventional levels of significance were not achieved. Documented side effects of moderate or severe intensity included tremor, sedation, dry mouth, constipation, memory difficulty, and nausea (Ninan, 2000).
2) Four consecutive patients treated for trichotillomania (hair-pulling) with CLOMIPRAMINE reported initial dramatic reductions in symptoms. However, three of the four patients had relapsed completely at

3-month follow-up, although all four were taking previously effective dosages of the drug. The fourth patient relapsed for about 2 weeks but regained initial treatment benefits. Daily dosage used was 150 milligrams (1), 100 milligrams (2), and 50 milligrams (1) (Pollard et al, 1991).

4.6 Comparative Efficacy / Evaluation With Other Therapies

Albuterol

Amineptine

Amitriptyline

Buspirone

Citalopram

Desipramine

Diazepam

Dixyrazine

Dothiepin

Doxepin

Fluoxetine

Fluvoxamine

Haloperidol

Imipramine

Lithium

Lofepramine

Maprotiline

Metoprolol

Mianserin

Milnacipran

Moclobemide

Nortriptyline

Oxaprotiline

Paroxetine

Pentazocine

Phenelzine

Sildenafil

Venlafaxine

4.6.A Albuterol

4.6.A.1 Depression

a) In depression, albuterol 6 milligram/day was superior to clomipramine 150 milligram/day, both given by intravenous infusion. Ten patients received each drug; symptoms were evaluated by 2 blind observers at days 0, 5, and 15, using the Hamilton rating scale. With albuterol, global improvement on day 5 was significantly superior to clomipramine. This improvement included mood retardation, anxiety, and insomnia. On day 15, the improvement in the albuterol group was only slightly increased over the clomipramine group. Eight of 10 patients in the albuterol group, and 5 of 10 patients in the clomipramine group demonstrated a clear improvement. An additional 2 patients responded to clomipramine 1 week later (Lecrubier et al, 1980).

4.6.B Amineptine

4.6.B.1 Depression

a) Amineptine and clomipramine were found to have similar antidepressant activity in 62 depressed patients during a 6-week, randomized, double-blind study (Lemoine et al, 1981). Patients were diagnosed with psychotic, non-psychotic, or melancholic depression by the investigators; however, the diagnostic criteria were not described. The Hamilton Rating Scale for Depression was used to evaluate therapeutic effects. Oral daily doses of amineptine 100 to 300 milligrams (mean 180 mg) or clomipramine 50 to 150 milligrams (mean 84 mg) were administered during the trial. Improvement in depression symptoms were seen in both groups and no apparent differences in antidepressant activity could be determined. Fifteen patients did not complete the study: 4 on amineptine and 11 on clomipramine.

4.6.C Amitriptyline

Chronic pain

Obsessive-compulsive disorder

4.6.C.1 Chronic pain

a) Clomipramine appeared to be better than amitriptyline in treating chronic trigeminal neuralgia and tension headache pain; however, amitriptyline was more effective in treating postherpetic neuralgia during a 3-month, randomized, single-blind study with 67 chronic pain sufferers (Carasso et al, 1979). Oral clomipramine was dosed between 20 and 75 milligrams daily in 3 divided doses, while oral amitriptyline was dosed between 30 and 110 milligrams daily in 3 divided doses. Severe sedation was the most commonly reported adverse effect with amitriptyline. The most severe adverse effect with clomipramine was motor agitation, which was experienced by 4 of 35 (10%) patients. Anticholinergic effects were experienced with both drugs.

4.6.C.2 Obsessive-compulsive disorder

a) Oral clomipramine produced a statistically significant reduction in the number or severity of obsessive-compulsive symptoms over amitriptyline on the Psychiatric Questionnaire for Obsessive-Compulsive Disorder (Ananth et al, 1981). Twenty patients with chronic obsessive-compulsive disorder were randomized to receive either clomipramine or amitriptyline in a 4-week, double-blind study. Both drugs were started at 75 milligrams/day and increased up to 300 mg/day as tolerated. The clomipramine-treated group demonstrated improvement over amitriptyline on depression and anxiety scales. The most common adverse effects experienced by both groups included dizziness, drowsiness, and dry mouth. Three patients failed to complete the study: 1 from each group due to syncope and 1 from amitriptyline due to an inadequate response.

4.6.D Buspirone

4.6.D.1 Obsessive-compulsive disorder

a) A double-blind study comparing buspirone and clomipramine in the tretment of obsessive-compulsive disorder (OCD) was performed (Pato et al, 1991). Eighteen of 20 study entrants completed the trial, which included an initial 2-week placebo washout period, a 2-week titration phase (in which doses were increased as tolerated to a daily maximum of 60 mg buspirone or 250 mg clomipramine), and a 4-week dose maintenance phase; subjects then received half the maximum tolerated dose for 4 days, followed by 3-1/2 weeks of placebo. Although the study was conducted in a crossover fashion, with the alternate treatment

given after the 3-1/2 week placebo washout, the trial results were analyzed as a parallel design because subjects did not return to baseline status by the beginning of the second active treatment period. The authors reported similar efficacy of the 2 active treatments, with at least half of the patients in each group evidencing a minimum of 20% improvement in several measures of OCD and one of depression. However, the small sample size may have obscured differences in efficacy. The authors noted that response was not correlated with dose of clomipramine (mean 225 +/- 49 mg/day) or of buspirone (mean 58 +/- 7 mg/day), or with previous use of benzodiazepines. Buspirone warrants further study as a possible treatment for OCD.

4.6.E Citalopram

4.6.E.1 Depression

a) Clomipramine (a tricyclic antidepressant with potent 5-HT reuptake inhibiting properties) 150 milligrams once daily was statistically superior to citalopram 40 milligrams once daily in the treatment of endogenously depressed patients in a 5-week double-blind study (n=75). Clomipramine appeared to have a faster onset and was particularly more effective in improving sleep disturbances, although other depressive symptoms were also improved to a greater degree with this agent compared to citalopram. In the subgroup of patients with nonendogenous depression in this study (n=27), a similar trend was observed in favor of clomipramine; however, the number of patients treated was too small to enable an effective comparison. Orthostatic symptoms, dry mouth, and perspiration were seen only with clomipramine, whereas nausea, vomiting, and headache were more common with citalopram (Anon, 1986). Flaws in this study were that fixed doses of each agent were employed and the duration of 5 weeks may have been too short. The onset of full antidepressant effects of citalopram may take 5 to 6 weeks. Titrating the dose of each agent based on clinical response would enable a more effective comparison in that optimal doses for specific patients could be achieved. A further comparison of these agents with flexible dosing regimens is warranted.

4.6.E.2 Efficacy

a) A small, 5-week, double-blind study reported significant orthostatic hypotensive effects (systolic pressure) in depressed patients treated with clomipramine 150 milligrams once daily but not citalopram 40 milligrams once daily. Diastolic blood pressure was also significantly reduced, although to a lesser extent, with clomipramine, whereas this change did not occur in citalopram-treated patients (Christensen et al, 1985).

b) Similar findings were reported in a clinical efficacy comparison of clomipramine and citalopram (Anon, 1986), and these results are consistent with other clinical data suggesting the lower propensity of citalopram to induce cardiovascular effects compared to tricyclic antidepressants (Milne & Goa, 1991).

4.6.F Desipramine

Autistic disorder

Diabetic neuropathy

Nail biting

Obsessive-compulsive disorder

Paraphilia

Trichotillomania

4.6.F.1 Autistic disorder

a) Clomipramine was superior to both desipramine and placebo for treatment of autistic behavior such as stereotypies, anger, and compulsive, ritualized behavior. Clomipramine and desipramine were both superior to placebo, and had equivalent effects in reducing hyperactivity of patients with autistic disorder (Gordon et al, 1993).

4.6.F.2 Diabetic neuropathy

a) Clomipramine and desipramine both significantly reduced symptoms of diabetic neuropathy as determined by investigators and self-rating compared to placebo (Sindrup et al, 1990). In this double-blind, placebo-controlled, 3-way crossover study, 19 patients were randomized to 2 weeks of treatment with oral desipramine 50 or 200 milligrams/day, clomipramine 50 or 75 milligrams/day, or placebo. Washout between treatment periods was not mentioned. Both agents significantly reduced neuropathy symptoms (pain, paresthesia, dysesthesia, numbness, nightly deterioration, and sleep disturbances) compared to placebo. No significant difference between active treatments was observed. The most common adverse events, which occurred with equal frequency in each active treatment group, included dry mouth, sweating, orthostatic dizziness, and fatigue.

4.6.F.3 Nail biting

a) Clomipramine was superior to desipramine in the treatment of onychophagia in a 10-week, double-blind, crosover study. Of the 25 patients enrolled, only 14 complete the study perhaps due to lack of other psychiatric disturbance (Leonard et al, 1991a).

4.6.F.4 Obsessive-compulsive disorder

a) Clomipramine was significantly more effective than desipramine for treating obsessive compulsive disorder. In a 10-week, double-blind, crossover study forty-eight children and adolescents (ages 6 to 18 years) received clomipramine (mean dose 150 milligrams/day) then desipramine (153 milligrams/day). Sixty-four percent of the patients who received clomipramine for the first time demonstrated a relapse during desipramine therapy. None of the subjects studied exhibited a greater than 20% improvement as measured by the Global OCD Scale during a 2-week, single-blind trial before receiving active treatment. Unlike desipramine, clomipramine decreased obsessive compulsive ratings and depression ratings measured on the Hamilton and NIMH Depression scales (Leonard et al, 1989).
b) Oral clomipramine was superior to desipramine in a comparative, crossover, double-blind study in childhood obsessive-compulsive disorder (Leonard et al, 1989). Twenty-one adolescents were treated for 5 weeks with each drug in increasing doses to a maximum of 3 mg/kg. The results showed a striking superiority of clomipramine over desipramine and the clinical effects were not attributed to a nonspecific antidepressant effect. In a group of 26 obsessive compulsive patients on clomipramine who entered a double-blind drug substitution study using desipramine, clomipramine was superior to desipramine (Leonard et al, 1991).

4.6.F.5 Paraphilia

a) Clomipramine and desipramine had similar efficacy in the treatment of paraphilias in a small, double-blind, crossover study. Eight of 15 patients completed the study in which each patient received a mean maximal daily dose of clomipramine 162.5 milligrams (range 75 to 250 mg) and desipramine 212.5 milligrams (range 100 to 250 mg) for 5 weeks after a 2-week placebo phase. Four of the 8 were also clinically depressed, and there was a great deal of variety in the paraphilias demonstrated by this patient population. As measured by the Schedule for Affective Disorders and Schizophrenia, Lifetime Version, severity of paraphilic symptoms were significantly decreased by both clomipramine (p less than or = 0.005) and desipramine (p less than or = 0.002) as compared with placebo (Kruesi et al, 1992).

4.6.F.6 Trichotillomania

a) Clomipramine was superior to desipramine in the treatment of trichotillomania (hair pulling) during a 10-week, double-blind, crossover study involving 13 women (Swedo et al, 1989). In this study, capsules containing 50 mg of either clomipramine or desipramine were administered; initial doses were 50 milligrams daily, increasing over 3 weeks to a maximum dose of 3 milligrams/kilogram/day (250 mg daily). Mean maximal doses were 180 mg daily for clomipramine and 173 mg daily for desipramine. Clomipramine was superior to desipramine by a physician's rating scale and a trichotillomania-impairment scale. Symptom severity was reduced more with clomipramine as compared to desipramine and clomipramine patients were better able to resist the urge to pull hair as opposed to desipramine patients. Clomipramine appears to be a specific antitrichotillomanic agent; this disorder may be related to an obsessive-compulsive disorder.

4.6.G Diazepam

4.6.G.1 Agoraphobia

a) Clomipramine was significantly superior to diazepam in the treatment of 33 agoraphobic patients during a 12-week, multicentered, randomized, double-blind study (Allsopp et al, 1984). The patients were diagnosed with agoraphobia or social phobia of at least a 1-month duration. Both drugs were administered orally in low doses initially; the doses were then increased to 25 to 150 milligrams in 3 divided daily doses for clomipramine and to 10 to 30 milligrams in 3 divided daily doses of diazepam. Headaches were experienced more in the diazepam group, while dry mouth and drowsiness were more prevalent in the clomipramine group. By the end of the study, clomipramine demonstrated significant improvement over diazepam in total scores for situational anxiety, interference in life-style, and accompanied travel distance on an agoraphobia inventory.

4.6.H Dixyrazine

4.6.H.1 Panic disorder

a) Dixyrazine plus clomipramine was more effective than clomipramine alone in reducing the number of panic attacks. In a 12-week study, 45 patients with panic attacks (with or without agoraphobia) were treated with clomipramine titrated up to 250 milligrams (mg) per day plus either dixyrazine 50 mg per day or placebo. Patients treated with dixyrazine plus clomipramine showed a larger reduction in the Hamilton Anxiety Rating Scale (HARS-P) scores for panic attacks from week 6 to week 12 than the patients in the placebo group (p less than 0.05). The reduction of the number of panic attacks and the increase in patients daily functioning were also significantly greater in the dixyrazine- clomipramine group (p less than 0.05) (Feet & Gotestam, 1994).

4.6.I Dothiepin

4.6.I.1 Depression

a) Although dothiepin and clomipramine were equally capable of diminishing depressive symptoms in a randomized, double-blind, parallel-group comparison of the two tricyclic antidepressants over 6 weeks, adverse events affected 50% more patients in the clomipramine group (n=45) than in the dothiepin group (n=47), and overall more than one-quarter of patients in the clomipramine group withdrew because of such adverse effects as dry mouth, dizziness, and somnolence (Welch et al, 1997).

4.6.J Doxepin

4.6.J.1 Dysthymia

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

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

4.6.K Fluoxetine

4.6.K.1 Obsessive-compulsive disorder

a) Treatment with fluoxetine (FLX) was compared with treatment with clomipramine (CMI) in two groups of patients with obsessive compulsive disorder (OCD) using two different experimental designs. In the first group of 11 patients with OCD studied using a randomized, double-blind, crossover design, treatment with FLX (20 to 80 milligrams/d) for 10 weeks was found to produce therapeutic effects similar to that obtained with CMI (50 to 250 milligrams/d) for 10 weeks. There were significantly fewer total side effects reported during FLX than CMI treatment. Drug tapering and placebo substitution in the 4-week crossover interval phase led to substantial relapses in OCD symptoms and depression. In addition, response to the second drug took as long as response to the first drug, despite a putative common mechanism of action of serotonin uptake inhibition. A second group of 21 patients with OCD that had been previously stabilized on CMI with at least partial benefit were crossed over to FLX in double blind fashion. After 10 weeks of FLX, most patients manifested behavioral rating scores of OCD and depressive symptoms that were comparable with pre-crossover ratings completed during CMI treatment. A significant exacerbation in OCD and depression ratings as well as a similar lag in therapeutic efficacy were also noted in this second cohort of patients with OCD. Platelet serotonin concentrations were reduced 95% during both CMI and FLX treatment periods. These results suggest that FLX may represent a viable alternative to CMI in the treatment of OCD, although more studies with larger sample sizes are needed (Pigott et al, 1990).

b) Clomipramine (CMI) and fluoxetine (FLX) were shown to be equally effective in the treatment of 120 patients with DSM-III major unipolar depressive disorder over a 6-week period. Adverse effects were more frequent with CMI. Those that did occur with FLX tended to disappear during the course of the study (Noguera et al, 1991).

4.6.L Fluvoxamine

Anxiety

Cataplexy

Depression

Obsessive-compulsive disorder

Panic disorder

4.6.L.1 Anxiety

a) Fluvoxamine and clomipramine were comparable in reducing anxiety symptoms in patients with agoraphobia with panic attacks (APA), generalized anxiety disorders (GAD), and obsessive-compulsive

disorders (OCD) as classified by DSM-III during a randomized, double-blind study (Westenberg et al, 1987). Of the 50 patients in this study, 39 diagnosed with APA, 5 with GAD, and 6 with OCD. Patients were randomly assigned to receive either clomipramine, up to 150 milligrams/day, or fluvoxamine, up to 100 milligrams/day, for the 6-week study. Both drugs demonstrated significant improvement in anxiety symptoms after drug therapy when compared to pretreatment.

4.6.L.2 Cataplexy

a) Both fluvoxamine and clomipramine improved cataplexy, but not narcolepsy, in 18 patients with these diseases during a cross-over study (Schachter & Parkes, 1980). It was not revealed if either the patients or researchers were blinded to drug therapy. It should be noted that 15 of the 18 patients were receiving clomipramine 25 to 100 milligrams/daily at the start of the trial, and may have been accustomed to the adverse effects of clomipramine. Also, if the patients were not blinded to drug therapy, some patients may have associated more adverse effects with a new drug, fluvoxamine. Patients were randomly allocated to receive fluvoxamine or clomipramine for a 3-week interval. After a 1-week drug-free period, the patients crossed over to the other drug. The daily dosing range for both drugs ranged from 25 to 200 milligrams/day. All patients were clinically assessed by observers on 5 occasions. The observers' impression was that fluvoxamine caused a moderate reduction in the frequency of attacks of cataplexy and sleep paralysis in most subjects. Fluvoxamine abolished cataplexy in 4 patients and sleep paralysis in 2 patients; only 12 of the 18 patients completed the fluvoxamine-treatment period. The observers felt that clomipramine was more effective than fluvoxamine in preventing both cataplexy and sleep paralysis. Clomipramine abolished cataplexy in 4 patients and sleep paralysis in 5 patients.

4.6.L.3 Depression

a) SUMMARY: Several double-blind, short-term studies have demonstrated fluvoxamine to be as effective as clomipramine in the treatment of depression (De Wilde et al, 1983; Klok et al, 1981). Anticholinergic adverse effects appear to be less common with fluvoxamine therapy.

b) Fluvoxamine and clomipramine were compared for antidepressant activity in a 6-week, randomized, double-blind study of 43 outpatients with major depression (De Wilde et al, 1983). Oral fluvoxamine 100 to 300 milligrams or oral clomipramine 50 to 150 milligrams was administered once daily in the evening. Assessments of the HAM-D (Hamilton Rating Scale for Depression) during the study and at the end failed to demonstrate any significant differences in antidepressant activity between the 2 drugs. The incidence of anticholinergic adverse effects were slightly more significant in the clomipramine-treated group.

c) Clomipramine and fluvoxamine appeared to be equally effective in the treatment of depression for 36 female inpatients during a 4-week, randomized, double-blind study (Klok et al, 1981). Patients were randomized to receive either oral clomipramine or oral fluvoxamine 50 milligrams 3 times daily. Diazepam 10 to 30 mg/day for severe agitation and/or anxiety was the only other psychotropic agent administered. Significant improvements in the Hamilton Rating Scale for Depression, the Clinical Global Impression, and the Zung Self-Rating Depression scale were seen in both treatment groups. Anticholinergic adverse effects appeared more frequently in the clomipramine-treated patients, while gastrointestinal effects were more prevalent in the fluvoxamine group.

d) Fluvoxamine and clomipramine appeared to have similar clinical efficacy in the treatment of endogenous depression for 30 unipolar and bipolar inpatients during a 4-week, randomized, double-blind study (De Wilde et al, 1983). Both drugs were administered orally in doses of 150 to 300 milligrams/day in 3 divided doses. At the end of the study, the fluvoxamine-treated patients demonstrated a 73% improvement on the Hamilton Rating Scale for Depression, while the clomipramine-treated patients had a 62% improvement. In the bipolar patients, 3 of 4 on fluvoxamine responded, while only 1 of 5 on clomipramine demonstrated a good response on the CGI Global Change Scale. Overall, the differences in efficacy between the 2 drugs were not statistically significant. Adverse anticholinergic effects were significantly more prevalent in the clomipramine-treated group.

e) Both clomipramine and fluvoxamine produced significant improvements on the Hamilton Rating Scale for Depression (HAM-D) in 32 patients with mixed depression during a 4-week, randomized, double-blind study (Dick & Ferrero, 1983). The average daily dosage was 130 milligrams and 132.8 milligrams for fluvoxamine and clomipramine, respectively. The mean percentage improvement on the HAM-D for the fluvoxamine-treated patients was 63.8%, and for the clomipramine-treated patients it was 66.3%.

4.6.L.4 Obsessive-compulsive disorder

a) Fluvoxamine (150 to 125 milligrams/day) and clomipramine (100 to 250 milligrams/day were equally effective in the treatment (10 weeks) of 66 outpatients with obsessive compulsive disorder. Both treatments were well-tolerated. Fluvoxamine produced fewer anticholinergic adverse effects and caused less sexual dysfunction than clomipramine, but caused more headache and insomnia (Freeman et al, 1994). under OBSESSIVE COMPULSIVE DISORDER add:

b) In a randomized, double-blind study of 26 patients with obsessive compulsive disorder without comorbid diseases, fluvoxamine and clomipramine, each titrated from an initial dose of 50 milligrams (mg) in the evening up to a maximum of 300 mg daily within two weeks, were equally effective (38% improvement over baseline with fluvoxamine versus 40% for clomipramine). Efficacy was assessed according to the Yale-Brown Obsessive Compulsive Scale and Clinical Global Impression Scale. Fluvoxamine was better tolerated, with less anticholinergic adverse effects while clomipramine had a quicker onset of action. Further studies are needed to demonstrate a time-related effect that might differentiate these drugs (Milanfranchi et

al, 1997).

4.6.L.5 Panic disorder

a) Clomipramine (10 milligrams (mg) for three days and 20 mg for four days) and fluvoxamine (50 mg/day for seven days) were both effective in decreasing the hypersensitivity to 35% carbon dioxide, supporting the serotonergic effect of these drugs to decrease panic attacks through modification of carbon dioxide sensitivity. Thirty-nine panic disorder patients were enrolled in a double-blind, randomized, placebo-controlled study, where each patient was given the 35% carbon dioxide challenge on days 0, 3, and 7. Patients on clomipramine and fluvoxamine showed significant reduction in sensitivity over placebo after seven days as seen by the percent change on a visual analogue for anxiety scale (p=0.027) (Perna et al, 1997).

4.6.M Haloperidol

4.6.M.1 Autistic disorder

a) Among subjects who completed full therapeutic trials of haloperidol and clomipramine for treatment of autistic disorder, the two drugs were comparable; however, haloperidol was superior to clomipramine on an intent-to-treat basis, because of the large proportion of patients who were unable to complete clomipramine treatment due to side effects and behavior problems. In a double- blind, placebo-controlled crossover study, 36 subjects with a DSM- IV diagnosis of autism were given placebo, haloperidol, and clomipramine for periods of 7 weeks each. Clomipramine was begun at 25 milligrams (mg) at bedtime for 2 days and increased to 25 mg twice a day for 2 days, 25 mg 3 times a day for 2 days, and finally 50 mg twice a day. Haloperidol was begun at 0.25 mg at bedtime for 2 days and increased to 0.25 mg twice a day for 2 days, 0.25 mg 3 times a day for 2 days, and finally 0.5 mg twice a day. For both drugs, adjustments of the final dose could be made as clinically indicated. During week 7 of each period, drug dosages were tapered in preparation for the next treatment. Percentages of subjects completing each trial were 70% for haloperidol, 38% for clomipramine, and 66% for placebo. In the haloperidol trials, 7 of 10 discontinuations were for side effects (fatigue or lethargy, dystonia, depression) and the remainder for behavior problems. With clomipramine, 12 of 20 discontinuations were for side effects (fatigue or lethargy, tremors, tachycardia, insomnia, diaphoresis, nausea or vomiting, and decreased appetite) and the remainder for behavior problems. In the placebo trials, 10 of 11 discontinuations were for behavior problems. On an intent-to-treat basis, significant improvement in irritability (p less than 0.05) and hyperactivity (p less than 0.05) was seen with haloperidol only (versus baseline). No differences among treatments were observed for stereotypic behavior, lethargy, or inappropriate speech. When data only from patients completing full therapeutic trials were assessed, both haloperidol and clomipramine were superior to baseline with regard to irritability and stereotypy (Remington et al, 2001).

4.6.N Imipramine

Depression

Obsessive-compulsive disorder

4.6.N.1 Depression

a) Clomipramine was as effective as imipramine in treating depression in 24 patients during a 44-day, randomized, double-blind study (McClure et al, 1973). The patients were diagnosed with psychotic depression independently by 2 psychiatrists. Oral imipramine or oral clomipramine was administered 3 times daily in 50 milligrams doses. Throughout the study periodic assessments using the Hamilton Depression Rating Scale and the Beck Depression Inventory demonstrated a significant reduction in depression from baseline for both drugs; however, a significant difference in antidepressant effects between drugs could not be seen. Minor and transient anticholinergic adverse effects were noted in all patients and included blurred vision, dry mouth, increased sweating, hand tremor, and dizziness. Three patients dropped out of the study, but none of these was due to adverse effects.

4.6.N.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-compulsive disorder (Volavka et al, 1985). A 12-week, double-blind study of 23 patients according to DSM-III with secondary depression diagnosed was conducted to compare the 2 drugs. Both drugs were started at 50 milligrams/day; this was gradually increased to 300 mg/day as tolerated. Seven patients did not complete the study: 4 because of adverse effects (2 from each group), 2 because of unsatisfactory therapeutic response with imipramine, and 1 for no apparent reason. Both drugs produced improvement in depressive symptoms; however, only clomipramine demonstrated improvement in obsessive symptoms when compared to baseline. Typical anticholinergic adverse effects were experienced by both treatment groups with no significant differences between the two. It is difficult to accurately evaluate the clinical response in this study

because of the small number of patients and the methods used for statistical analysis.
c) Both oral clomipramine and oral imipramine were effective in improving symptoms in obsessive-compulsive disorder patients who met DSM-III criteria (Mavissakalian et al, 1985). The study was a 12-week, double-blind trial that compared the efficacy of clomipramine and imipramine in treating obsessive-compulsive disorders. Both drugs were begun at 25 to 50 milligrams/day; this was increased to 300 mg/day as tolerated. At the end of the trial, the mean daily dose of both drugs was 220 mg. Two of 3 clomipramine-treated patients and 2 of 5 imipramine-treated patients were classified as responders. For both drugs, maximal improvement in depression was evident at 4 weeks, while maximal improvement in obsessive-compulsive symptoms was not seen until 8 weeks. The responders also had higher pretreatment depression scores than did nonresponders, which corresponded with the results of another study (Marks et al, 1980). Because of the small sample size, differences (n=8) in efficacy between clomipramine and imipramine could not be determined.
d) The relationship between the antiobsessional and antidepressant effects of tricyclic drugs was studied in primary obsessive-compulsive disorder. Study 1 consisted of a controlled 12-week trial with clomipramine (n=7) and placebo (n=5); study 2 analyzed the pooled data from 15 uniformly selected patients who were treated with either clomipramine or imipramine. Although the antiobsessional and antidepressant effects of the drugs covaried, antidepressant action was not a prerequisite for antiobsessional effects. Clomipramine, and probably imipramine, possess specific antiobsessive effects that are at least partially independent of the antidepressant effects (Mavissakalian et al, 1985).

4.6.O Lithium

4.6.O.1 Depression
a) The effects of lithium and clomipramine (CMI) on signs and symptoms were compared in 22 patients with major depression (Linder et al, 1989). They also compared effects of the two drugs on serum calcium and magnesium. Evaluation of response using the Comprehensive Psychopathological Rating Scale (CPRS) and side effects was made after a 5 to 7 day placebo period, at 2 weeks and at 4 weeks of treatment. After 2 weeks of treatment, the rated scores dropped for more than half of the CPRS items. After 4 weeks, the scores for all but one item were reduced in both groups and after 4 weeks global scores were also reduced. There was no significant difference between lithium patients and CMI patients in response at 2 and 4 weeks. Lithium treatment was associated with fluctuations in calcium and magnesium levels in plasma but there were no changes in CMI patients. Serum prolactin increased during CMI treatment but was unaffected by lithium treatment. There was no correlation between rating scores and drug blood levels, serum prolactin, calcium or magnesium.

4.6.P Lofepramine

4.6.P.1 Depression
a) A meta-analysis of 4 studies comparing lofepramine (n=79) with clomipramine (n=79) concluded that lofepramine was superior to clomipramine in efficacy and tolerance (Kerihuel & Dreyfus, 1991). Overall, there was a significant difference between the number of lofepramine-treated patients (62%) and clomipramine-treated patients (37%) who improved during the 6-week trials. Fewer patients reported side effects with lofepramine than clomipramine (54% vs 65%; p less than 0.15). Lofepramine doses ranged from 70 to 210 milligrams/d, and clomipramine doses ranged from 50 to 150 milligrams/d.
b) Oral lofepramine 70 milligrams twice daily was slightly superior to oral clomipramine 50 milligrams twice daily in a 6-week, randomized, double-blind study involving 60 depressed patients. Lofepramine-treated patients demonstrated a significantly greater improvement on the Hamilton Depression Scale than clomipramine by the end of the study. Statistical significance between the 2 drugs could not be determined in the Self-Rating Depression Scale. Typical mild anticholinergic effects were experienced by both groups, with no significant differences between the drugs (Dimitriou et al, 1984).

4.6.Q Maprotiline

Depression

Pain, Idiopathic

4.6.Q.1 Depression
a) Maprotiline and clomipramine were equally effective in a 4-week, randomized, double-blind study in 12 depressed patients (Ridges, 1977). All patients were endogenously depressed; however, diagnosis criteria was not discussed. Both drugs were started orally at 75 milligrams/day; this was increased to 225 mg/day after 2 weeks if 150 mg/day was inadequate. The Hamilton Depression Rating Scale was used to assess therapeutic efficacy. At the end of the study, both drugs improved depression symptoms to a similar degree and no difference in efficacy could be distinguished. The clomipramine-treated patients appeared to improve sooner than the maprotiline-treated patients. Adverse effects were generally mild and similar for both drugs:

dry mouth, constipation, and tremor. Because of the small number of patients and short duration of the study, further studies are required to adequately compare the 2 drugs in the treatment of depression.

4.6.Q.2 Pain, Idiopathic

a) Oral clomipramine (mean 97 milligrams/day) was more effective in reducing the overall idiopathic pain syndrome symptoms than oral maprotiline (mean 100 milligrams/day) during a 6-week, randomized, double-blind study of 52 patients (Eberhard et al, 1988). An overall improvement was seen in 63% of the clomipramine-treated patients and in only 36% of the maprotiline-treated patients. Clomipramine produced improvements in pain, memory disturbances, concentration difficulties, inner tension, sadness, and bodily discomfort. The most common adverse effect for both drugs was dry mouth, while sweating was more prevalent with clomipramine. Eight clomipramine patients withdrew from the study because of adverse effects compared to only 1 maprotiline-treated patient.

4.6.R Metoprolol

4.6.R.1 Migraine

a) Metoprolol, in oral doses up to 100 milligrams/day, was superior to oral clomipramine (up to 100 milligrams/day) and placebo in 63 migraine headache sufferers during a 16-week, randomized, double-blind, crossover study (Langohr et al, 1985). All patients were diagnosed with common or classic migraines according to the Ad Hoc Committee on Classification of Headache. The drugs were administered at 4-week intervals, with 4-week washout periods before crossover. Metoprolol was the only agent that significantly reduced both the frequency and duration of migraine attacks. When compared to placebo, clomipramine had no influence on migraine attacks. Adverse effects from clomipramine caused 18 patients to discontinue treatment. The most commonly reported adverse effects with clomipramine included insomnia, sweating, tiredness, and constipation.

4.6.S Mianserin

Depression

Headache

Pain

4.6.S.1 Depression

a) SUMMARY: Comparative clinical trials with mianserin and clomipramine fail to demonstrate any significant differences in antidepressant activity. Clomipramine may produce more adverse effects than mianserin.

b) Oral mianserin 60 mg daily and oral clomipramine 150 mg daily were compared for antidepressant activity during a 4-week, multicenter, randomized, double-blind study of 145 depressed patients (Pinder et al, 1980). At the end of the trial, both drugs produced significant but indistinguishable improvement in depression. The clomipramine patients demonstrated a slightly significant increase in adverse effects that were mild and included dry mouth, hypotension, and tremor. Ten patients, 4 on mianserin and 6 on clomipramine, did not complete the study because of drug-related problems; these included adverse effects, clinical deterioration, and increased suicidal risk.

c) A 5-week, randomized, double-blind study compared the safety and efficacy of mianserin and clomipramine in 42 patients with primary unipolar depression according to the International Classification of Diseases (Anon, 1968; Levin, 1982). Patients were started on either oral mianserin 30 milligrams or oral clomipramine 75 milligrams once daily; both doses were doubled beginning in the second week. Both groups demonstrated significant improvement in depression symptoms; however, the mianserin group demonstrated slightly more improvement after 5 weeks of therapy. Adverse effects were similar in both groups, but more prevalent in the clomipramine group, and included dry mouth, tremor, tachycardia, dizziness, excitement, and nasal congestion. Tachycardia and excitement were only present in the clomipramine group. One mianserin patient and 5 clomipramine patients withdrew from the study because of adverse effects.

d) The antidepressant activity of oral mianserin 30 to 60 milligrams daily and oral clomipramine 75 to 150 milligrams daily was compared in 62 mildly depressed patients during a 4-week, randomized, double-blind study (Dunbar et al, 1985). No significant difference in antidepressant activity could be demonstrated between the 2 drugs. Similar anticholinergic adverse effects were experienced by both groups; however, clomipramine patients reported more tremor, dry mouth, tachycardia, and dizziness and 2 withdrew from the study because of adverse effects.

4.6.S.2 Headache

a) Mianserin, clomipramine, and placebo were studied in a double-blind, parallel group comparison involving 82 patients with chronic tension headaches. Both mianserin and clomipramine produced

improvements in pain scores in light of a significant placebo response after 6 weeks of therapy with either oral clomipramine 75 to 150 milligrams/day or mianserin 30 to 60 milligrams/day (Langemark et al, 1990).

4.6.S.3 Pain

a) No significant difference was found among oral clomipramine (75 to 150 milligrams/day), mianserin (30 to 60 milligrams/day), and placebo in a study of 253 patients with chronic idiopathic pain syndrome. Improvement rate was about 40% after 6 weeks when using a 50% or better reduction in pain level. In patients who fulfilled checklist criteria for minor-to-major depression (30% of patients), clomipramine was superior to mianserin and placebo, with an improvement rate of 75% after 7 weeks. Both mianserin and clomipramine were superior to placebo in patients with low back pain. No difference among the 3 treatments was found in patients with burning mouth syndrome or abdominal pain (Loldrup et al, 1989).

4.6.T Milnacipran

4.6.T.1 Depression

a) Milnacipran offers no efficacy advantage over tricyclic antidepressants. Milnacipran 50 to 100 mg twice daily has been comparable to or less effective than imipramine 100 to 150 mg daily, amitriptyline 150 mg daily, and clomipramine 75 to 150 mg daily in the treatment of major depressive disorders; primary endpoints were improvements on the Hamilton and Montgomery-Asberg scales (Tignol et al, 1998; Leinonen et al, 1997; Kasper et al, 1996; Anon, 1997b; Von Frenckell et al, 1990; Ansseau et al, 1989). A more rapid onset of action has been observed with clomipramine and amitriptyline (Leinonen et al, 1997; Ansseau et al, 1989).

b) Greater improvement of CGI-3 scores (therapeutic index, incorporating efficacy and tolerance) was reported with milnacipran in a manufacturer-prepared meta analysis of tricyclic antidepressant comparative trials (Anon, 1997b; Kasper et al, 1996), and this appears in manufacturer product information. However, statistical significance between treatments was not demonstrated (Anon, 1997b).

4.6.U Moclobemide

4.6.U.1 Depression

a) SUMMARY: Clomipramine and moclobemide have been similarly effective in the treatment of depression; a faster onset of action and lower incidence of adverse effects have been reported with moclobemide in some studies. Drop-out rates due to clinical worsening and suicidality were more likely with moclobemide than clomipramine in one study.

b) Clomipramine in doses of 75 to 200 milligrams daily has been as effective as moclobemide 300 to 600 milligrams daily in treating endogenous and non-endogenous depression in most controlled studies (Dierick et al, 1990; Civeira et al, 1990; Lecrubier & Guelfi, 1990). One study (Larsen et al, 1989) reported that moclobemide, imipramine, and placebo were all associated with similar clinical improvement in patients with non-endogenous depression. Lack of statistical superiority of these agents over placebo in this report may have been a reflection of the small number of patients treated (20 in each group). In a larger controlled trial (n=191), moclobemide and clomipramine produced similar and significant improvement in non-endogenously depressed patients; however, placebo was not incorporated into this study (Stabl et al, 1989).

c) An advantage for moclobemide with regard to tolerability (particularly its lesser anticholinergic effects) was reported in some of these studies. However, a similar adverse effect profile for moclobemide and clomipramine emerged in others (Civeira et al, 1990).

d) The onset of antidepressant effect was quicker with moclobemide (10 days) as compared to clomipramine (13 days) in some studies (Lecrubier & Guelfi, 1990).

e) Antidepressant and adverse effects of moclobemide (MCB) (400 milligrams/day) and clomipramine (CMI) (150 milligrams/day) were compared in a double-blind, randomized, inpatient, fixed-dose study with weekly ratings and drug level measurements. After 1 week on single-blind treatment, 115 patients with major depression who met inclusion criteria were begun on active treatment for 6 weeks. MCB drop-outs (N=20) were primarily due to clinical worsening and suicidality (N=9) whereas CMI drop-outs were related primarily to adverse effects (N=6) with none due to clinical worsening. End-point analysis using the Hamilton Depression Scale showed a significant difference favoring CMI over MCB (Anon, 1993).

4.6.V Nortriptyline

4.6.V.1 Pain

a) Twenty-four patients with central pain completed a randomized, crossover, placebo-controlled study of the efficacy and tolerability of clomipramine and nortriptyline. Results showed strong predominance of active drugs over placebo and a significantly more effective analgesic effect of clomipramine over nortriptyline. The analgesic effect of both tricyclic compounds is independent of any antidepressant effect (Panerai et al, 1990).

4.6.W Oxaprotiline

4.6.W.1 Depression

a) Oral oxaprotiline 150 milligrams/day and oral clomipramine 150 milligrams/day were compared for

efficacy in the treatment of 38 depressed patients during a 4-week, randomized, double-blind study (Wolfersdorf et al, 1987). All patients were diagnosed as having either endogenous or psychogenous (psychotic) depression according to ICD (International Classification of Diseases) criteria and were divided equally between the 2 drug therapy groups. After 2 weeks of therapy, both drugs demonstrated equal improvement in depression as assessed by a trained therapist; however, after 4 weeks, the clomipramine group was slightly more improved as determined by the Hamilton Depression Rating Scale and the Self-Rating Scale of Depression. Adverse effects were generally mild and similar for both drugs; they included tremor, sweating, agitation, headaches, and dizziness. Three patients withdrew from the study: 1 from each group due to perceived lack of efficacy and the third due to a venous thrombosis that was not felt to be drug-related.

4.6.X Paroxetine

Depression

Obsessive-compulsive disorder

4.6.X.1 Depression

a) In a large (n=1002) clinical trial, treatment with paroxetine or clomipramine produced similar decreases in anxiety and depression scores; however, adverse effects occurred in significantly (p=0.025) more patients treated with clomipramine than paroxetine (Ravindran et al, 1997). Statistically significant differences between treatments were NOT found on the Montgomery-Asberg Depresssion Rating Scale (MADRS) or Clinical Anxiety Scale (CAS), but a trend in favor of paroxetine was observed for the Clinical Global Impressions (CGI) score at 6 and 12 weeks (p=0.015). Patients entered into this trial had depression with anxiety which was treated in a primary care setting. Paroxetine 20 milligrams (mg) daily was used initially but the protocol permitted an increase to 40 mg daily, if needed, after 4 weeks. Clomipramine titration proceeded as follows: (1) 25 mg in the evening for 3 days; (2) 50 mg in the evening for 4 days; (3) 75 mg daily (25 mg in the morning and 50 mg in the evening); and (4) after 4 weeks, the dose could be increased to 150 mg/day. Based on this study, paroxetine and clomipramine have comparable efficacy but the incidence of adverse effects (AE) including serious AE is lower in patients treated with paroxetine.
b) Paroxetine 30 milligrams once daily was as effective as clomipramine 25 milligrams three times daily in the treatment of major depressive disorder in a 6-week, double-blind study involving 79 elderly patients (60 years of age or older) (Guillibert et al, 1989). Anticholinergic effects and somnolence occurred to a greater degree with clomipramine, whereas nausea and vomiting were observed more frequently with paroxetine.
c) Clomipramine demonstrated a significantly better therapeutic effect than paroxetine using categorical response measures and group averages of rating scores during a double-blind, randomized, inpatient study of 120 depressed patients (Anon, 1990). Patients were randomized to receive either paroxetine 30 milligrams/day or clomipramine 150 milligrams/day for this 6-week study. At the end of week 4, 27 patients were rated as nonresponders and were terminated from the study. Of thses 27 patients, 23 were in the paroxetine group.

4.6.X.2 Obsessive-compulsive disorder

a) In a 12-week, comparative study, paroxetine was as effective as clomipramine for treating obsessive compulsive disorder. Patients were randomly assigned to receive placebo (n=99), paroxetine 10 milligrams (mg) (n=201), or clomipramine 25 mg daily (n=99); the dose of active treatments was titrated to a maximum of 60 mg and 250 mg for paroxetine and clomipramine, respectively. No statistically significant differences were found in the primary efficacy measures, the Yale-Brown Obsessive-Compulsive Scale or the National Institute of Mental Health Obsessive-Compulsive Scale, between paroxetine or clomipramine; however, both drugs were significantly better than placebo. Adverse effects requiring treatment withdrawal occurred in fewer patients treated with paroxetine (9%; p=0.033) than clomipramine (17%). Limitations of the study are the relatively short duration, and the potential loss of blinding due to differences in adverse effects (Zohar et al, 1996).

4.6.Y Pentazocine

4.6.Y.1 Postoperative pain

a) Clomipramine was as effective as pentazocine for relieving postoperative pain. Forty patients (30 to 50 years old) received either intramuscular clomipramine 50 mg or pentazocine 30 mg a half an hour after the end of anesthesia for hysterectomies or laparotomies. No significant difference was observed between either agent for analgesia (Tiengo et al, 1987).

4.6.Z Phenelzine

4.6.Z.1 Obsessive-compulsive disorder

a) Clomipramine and phenelzine had similar efficacy in a double-blind clinical trial conducted in 30 patients

suffering from DSM-III obsessive-compulsive disorder. The study period was 12 weeks and the maximum doses used (from the fifth week on) were 225 milligrams/d for clomipramine (14 patients) and 75 milligrams/d for phenelzine (12 patients); four patients dropped out. Obsessive symptoms improved significantly in both drug groups, but there was no significant difference between groups. Depressive symptoms responded faster than obsessive symptoms (Vallejo et al, 1992).

4.6.AA Sildenafil

4.6.AA.1 Premature ejaculation

a) According to a double-blind, randomized, cross-over study (n=31), as-needed SILDENAFIL was superior in the treatment of premature ejaculation compared with CLOMIPRAMINE, PAROXETINE, SERTRALINE, and PAUSE-SQUEEZE technique. Clomipramine, paroxetine, and sertraline had generally similar efficacy and safety. Paroxetine exhibited improved efficacy and satisfaction over pause-squeeze, while efficacy and satisfaction were similar to pause-squeeze for clomipramine and sertraline. Median intravaginal ejaculation latency time (IVELT) increased significantly to 4 minutes (min), 4 min, 3 min, 15 min, and 3 min from baseline 1 min for clomipramine, paroxetine, sertraline, sildenafil, and pause-squeeze, respectively (all p less than 0.0001). Paroxetine was superior to pause-squeeze with respect to IVELT (p=0.04) and sexual satisfaction (p=0.025). A significant positive correlation occurred between ejaculation latency and sexual satisfaction. No significant differences in adverse effects were found among the 4 drugs. Three patients dropped out due to side effects, including sildenafil (2) and clomipramine (1; also lack of efficacy in this patient). Three additional patients dropped out due to lack of efficacy related to clomipramine, paroxetine, sertraline, and/or pause-squeeze. Medications were administered as needed 3 to 5 hours before planned intercourse and not more than twice a week. Doses were clomipramine 25 milligrams (mg), paroxetine 20 mg, sertraline 50 mg, and sildenafil 50 mg (Abdel-Hamid et al, 2001).

4.6.AB Venlafaxine

4.6.AB.1 Depression

a) Venlafaxine 105 milligrams/day (average dose) tended to be more effective than clomipramine 105 milligrams/day (average dose) for the treatment of depression in a 6-week study with 102 patients; however, the difference was not statistically significant (Holliday & Benfield, 1995). Patients were assessed using the Hamilton Depression Rating Scale, Montgomery-Asberg Depression Rating Scale, and the Clinical Global Impressions scale. Venlafaxine was associated with fewer anticholinergic side effects and a greater incidence of headache/nausea than clomipramine.

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