DRUGDEX® Evaluations

TRAZODONE

0.0 Overview

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

2) Dosing Information
- **a)** Trazodone Hydrochloride
  - **1)** Adult
    - **a)** Depression
      - **1)** outpatients, 150 mg/day ORALLY in divided doses; may increase
      days; MAX dosage 400 mg/day (Prod Info trazodone hcl tablets, 200
      - **2)** inpatients, 150 mg/day ORALLY in divided doses; may increase d
      days; MAX dosage 600 mg/day (Prod Info trazodone hcl tablets, 200
  - **2)** Pediatric
    - **a)** Safety and effectiveness in pediatric patients have not been establishe

3) Contraindications
- **a)** Trazodone Hydrochloride
  - **1)** Hypersensitivity to trazodone

4) Serious Adverse Effects
- **a)** Trazodone Hydrochloride
  - **1)** Cardiac dysrhythmia
  - **2)** Depression, worsening
  - **3)** Hemolytic anemia
  - **4)** Hypertension
  - **5)** Hypotension
  - **6)** Leukocytosis
  - **7)** Methemoglobinemia
  - **8)** Priapism
  - **9)** Seizure
  - **10)** Suicidal thoughts
  - **11)** Suicide

5) Clinical Applications
- **a)** Trazodone Hydrochloride
  - **1)** FDA Approved Indications
    - **a)** Depression

1.0 Dosing Information

Drug Properties

Adult Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring Index)

B) Synonyms
Trazodone
Trazodone HCl

Trazodone Hydrochloride
C) Physicochemical Properties
1) Molecular Weight
a) 408.33
2) Systemic: Trazodone is not chemically related to tricyclic, tetracyclic, or oth
Info Desyrel, 88) (Prod Info Trazodone Hydrochloride (generic), 88) (Prod Info
(generic), 86) (Prod Info Trazodone Hydrochloride (generic), 86a).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Geriatric Patients

1.3.1 Normal Dosage

Trazodone

Trazodone Hydrochloride

1.3.1.A Trazodone

1.3.1.A.1 Electroconvulsive therapy
See Drug Consult reference: DRUGS FOR SEIZURE PROLONGATI

1.3.1.B Trazodone Hydrochloride

1.3.1.B.1 Oral route
a) The therapeutic dose ranges from 50 to 600 milligrams daily. Mos
100 to 300 milligrams/day in single or divided daily doses (Anon, 197
200 milligrams/day have been well tolerated (Rawls, 1982c).
b) The manufacturer recommends that therapy be initiated with 150
and increased gradually, as needed, every 3 to 4 days in increments
doses should not exceed 400 milligrams/day in divided doses. Inpatie
milligrams/day in divided doses, but this dose should not be exceede
on the lowest effective dose (Prod Info Desyrel(R), 1998c).
c) Gradual increases in dosage by 25 to 50 milligrams every 2 week
reduce drowsiness and dizziness with large doses on initiation of ther
1.3.1.B.2 DEPENDENCE
a) After a 60-day study of 50 patients, no drug dependence was obs
25 milligrams three times daily therapy (Piccione & Laguardia, 1975).
1.3.1.B.3 OBESITY
a) The clearance of trazodone appeared unchanged in obese individ
kilograms). It was suggested that the dose of the drug during chronic
rather than total body weight in this patient population (Greenblatt et

1.3.2 Dosage in Renal Failure
A) Trazodone Hydrochloride
1) Dosage adjustments are not required in renal insufficiency (Catanese

1.3.4 Dosage in Geriatric Patients
A) Trazodone Hydrochloride
1) Geriatric patients may not tolerate a single daily dose of trazodone and
considered (Anon, 1979). In one controlled study involving 20 geriatric inp
optimal dose of trazodone was reported to be 150 milligrams daily, in divi
1986).
2) A reduction in clearance and an increase in the half-life of trazodone w
following single intravenous and oral doses (25 and 50 milligrams, respec
The clearance of the drug in elderly females was not significantly affected
patients. Based upon these data, it is suggested that dose reductions of t

chronic therapy in elderly males.

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset
- **1)** Initial Response
  - **a)** 1 week (Prod Info Desyrel(R), 1998b).
    - **1)** Symptomatic relief may be seen during the first week, with optima evident within 2 weeks. Twenty-five percent of those who respond to weeks (up to 4 weeks) of drug administration (Prod Info Desyrel(R), 1

2.2 Drug Concentration Levels

A) Time to Peak Concentration
- **1)** 0.5 to 2 hours (Rawls, 1982a; Georgotas et al, 1982a).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption

A) Bioavailability
- **1)** 65% (Nilsen & Dale, 1992a).

B) Effects of Food
- **1)** increased absorption (Prod Info Desyrel(R), 1998b).
  - **a)** Total drug absorption may be up to 20% higher when the drug is t empty stomach; hence, trazodone should be given shortly after a me side effects may increase under fasting conditions (Prod Info Desyrel

2.3.2 Distribution

A) Distribution Sites
- **1)** Protein Binding
  - **a)** 89% to 95% (Rawls, 1982a; Georgotas et al, 1982a).
- **2)** OTHER DISTRIBUTION SITES
  - **a)** PLASMA
    - **1)** Trazodone does not appear to selectively localize in any one in the plasma (Prod Info Desyrel(R), 1998b).

B) Distribution Kinetics
- **1)** Volume of Distribution
  - **a)** 0.47 to 0.84 L/kg (Nilsen et al, 1993; Nilsen & Dale, 1992a).
    - **1)** The volume of distribution following a single 100-mg oral traz following multiple oral trazodone doses, the Vd ranges from 0.47 (Nilsen et al, 1993; Nilsen & Dale, 1992a).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics
- **1)** Liver, extensive (Rawls, 1982a; Georgotas et al, 1982a).

a) Trazodone is extensively metabolized in the liver by oxidation and
Georgotas et al, 1982a). Cytochrome P450 3A4 metabolizes trazodo
chlorophenylpiperazine (Prod Info Desyrel(R), 2003b). It appears tha
involved in its metabolism (Otani et al, 1998). Only 0.13% of a dose i
unchanged trazodone (Brogden et al, 1981).

B) Metabolites
1) meta-Chlorophenylpiperazine, active (Otani et al, 1998).
2) Conjugated compounds, inactive (Baiocchi et al, 1974).
3) Diol derivative, inactive (Baiocchi et al, 1974).
4) Hydroxy derivative, inactive (Baiocchi et al, 1974).
5) N-oxide, inactive (Baiocchi et al, 1974).

2.3.4 Excretion
A) Kidney
1) Renal Clearance (rate)
a) 3 to 5.3 L/hr (Nilsen & Dale, 1992a; Nilsen et al, 1993).
2) Renal Excretion (%)
a) 70% to 75% (Al-Yassiri et al, 1981; Brogden et al, 1981).
B) Other
1) OTHER EXCRETION
a) FECES
1) 21% (Jauch et al, 1976).

2.3.5 Elimination Half-life
A) Parent Compound
1) ELIMINATION HALF-LIFE
a) 7.1 hours (Nilsen & Dale, 1992a; Nilsen et al, 1993).
1) The manufacturer reports a biphasic elimination pattern with
followed by a slower phase half-life of 5 to 9 hours (Prod Info De

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING
1) Trazodone Hydrochloride
a) Oral (Tablet)
1) Antidepressants increased the risk of suicidal thinking and behavior (s
children and adolescents with Major Depressive Disorder (MDD) and othe
considering the use of trazodone hydrochloride or any other antidepressa
balance this risk with the clinical need. Patients who are started on therap
clinical worsening, suicidality, or unusual changes in behavior. Families a
of the need for close observation and communication with the prescriber.
approved for use in pediatric patients.
2) Pooled analyses of short-term (4 weeks to 16 weeks) placebo-controll
(SSRIs and others) in children and adolescents with major depressive dis
compulsive disorder (OCD), or other psychiatric disorders (a total of 24 tri
have revealed a greater risk of adverse events representing suicidal think
the first few months of treatment in those receiving antidepressants. The
patients receiving antidepressants was 4%, twice the placebo risk of 2%.
trials (Prod Info trazodone hydrochloride oral tablet, 2005).

3.1 Contraindications
A) Trazodone Hydrochloride
1) Hypersensitivity to trazodone

3.2 Precautions

A) Trazodone Hydrochloride
1) Suicidal ideation and behavior or worsening depression; increased risk, pa
adolescents, during the first few months of therapy (Anon, 2004)
2) Bipolar disorder; the possibility that a major depressive episode may be the
disorder should be ruled out prior to initiating antidepressant therapy (Anon, 2
3) Cardiac disease; trazodone is potentially arrhythmogenic
4) Concomitant administration of antihypertensive drugs may require decreas
antihypertensive drug
5) Concomitant treatment with electroconvulsive therapy
6) Discontinue use of trazodone for as long as clinically feasible prior to electi
7) During the acute recovery period after myocardial infarction
8) In suicidal or seriously depressed patients, prescribe in limited quantities u
9) May increase or decrease prothrombin time (PT) in patients taking warfari
10) Pregnancy or lactation
11) Priapism may occur, possibly requiring surgical intervention

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Musculoskeletal Effects

Neurologic Effects

Ophthalmic Effects

Psychiatric Effects

Renal Effects

Reproductive Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

3.3.1.A Trazodone Hydrochloride

Bradyarrhythmia

Cardiac dysrhythmia

Cardiovascular finding

Edema

Heart block

Hypotension

Prolonged QT interval

Tachyarrhythmia

3.3.1.A.1 Bradyarrhythmia

a) Summary

1) Occasional sinus BRADYCARDIA has occurred in long-term
1998a).

3.3.1.A.2 Cardiac dysrhythmia

a) Summary

1) Recent clinical studies in patients with pre-existing cardiac dis
may be arrhythmogenic in some patients in that population. Arrh
premature ventricular contractions, ventricular couplets, and in tv
beats) of ventricular tachycardia. There have also been several p
arrhythmias in trazodone- treated patients who had pre-existing c
of prospective studies are available, patients with pre- existing ca
monitored, particularly for cardiac arrhythmias (Prod Info Desyre
Janowsky et al, 1983a; Aronson & Hafez, 1986; Pellettier & Bart
1983).

b) Incidence: rare

c) LITERATURE REPORTS

1) Trazodone administration has been associated with aggravat
patients with pre-existing cardiac disease (Janowsky et al, 1983;
patient had a mitral valve prolapse and the other had hypertensio
atherosclerosis. Administration of trazodone 50 to 300 milligrams
the frequency of ventricular arrhythmias within 1 to 2 weeks. The
with cardiac arrhythmias and/or mitral valve prolapse should be c
trazodone administration. Although trazodone presumably lacks
manufacturer warns that close monitoring is recommended for pa
(Prod Info Desyrel(R), 1998a).

2) Trazodone was associated with the occurrence of premature
angina in a 45-year-old male when the dose of the drug was incr
daily, following an approximate one month course of 50 to 150 m
After withdrawal from trazodone, the chest pain and arrhythmias
previous history of cardiovascular disease.

3) In a hospitalized patient who developed ventricular fibrillation
of trazodone 75 milligrams for three days was associated with si
bradycardia and sinus arrest, hypotension, and premature ventri
Bartolucci, 1984).

4) In three patients, aged 26, 61 and 41 years with preexisting c
trazodone appears to have exacerbated premature ventricular co
ventricular tachycardia in one case (Janowsky et al, 1983; Vlay &

3.3.1.A.3 Cardiovascular finding

a) Summary

1) In clinical trials, cardiovascular effects of trazodone reported i
HYPERTENSION, hypotension, SYNCOPE, tachycardia or PALI
breath (Prod Info Desyrel(R), 1998a). Additional cardiovascular e
voluntarily reported to the manufacturer include CARDIOSPASM
ACCIDENT OR STROKE, CONGESTIVE HEART FAILURE, ede
CONDUCTION BLOCK, ATRIAL FIBRILLATION, MYOCARDIAL
ARREST, arrhythmia, and ventricular ectopic activity, including v
Desyrel(R), 1998a).

b) Arrhythmia, bradycardia, edema, heart block, hypotension, tachyc
have been reported with the administration of trazodone.

3.3.1.A.4 Edema

a) Summary

1) Peripheral edema was described in 10 of 100 patients admini

to 600 milligrams (mg) daily for depression (Barrnett et al, 1985). was 56 years, with 9 being women. The mean dose of the drug t daily and was associated with a weight gain of 4.5 kilogram (kg) authors failed to provide information on the time of onset of eden Withdrawal of the drug or reduction in dose resulted in edema re edema, with an onset within 24 hours of initiation of trazodone th allergic response in one case, but no immunologic evidence was 1987).

3.3.1.A.5 Heart block

a) Summary

1) Trazodone has been reported to produce minimal to no effect not produced the cardiotoxicity observed with tricyclic antidepres 1981). However, other data have described ventricular arrhythmi in heart patients (Janowsky et al, 1983; Rausch et al, 1984), sug pre-existing cardiac disease (Prod Info Desyrel(R), 1998a; Raus

b) LITERATURE REPORTS

1) Complete heart block occurred in 77-year-old alcoholic with d single dose of trazodone (50 milligrams). The patient had a histo cardiovascular disease, hypertension and mitral regurgitation; a attacks was also present (Rausch et al, 1984). These data sugge trazodone may produce cardiac conduction defects in patients at

3.3.1.A.6 Hypotension

a) Summary

1) The most frequent cardiovascular side effect during therapy is may be accompanied by syncope, especially in patients taking c therapy (Rakel, 1984)(Spivak et al, 1987). The mild hypotension trazodone therapy is usually transient and not requiring discontin 1980a; Rawls, 1982b; Georgotas et al, 1982b). However, adjustr medication may be necessary if administered concurrently (Prod

b) Incidence: rare

3.3.1.A.7 Prolonged QT interval

a) Summary

1) Trazodone 150 milligrams, administered in a single dose to e to significantly prolong the QTc interval and decrease T wave he (Burgess et al, 1982).

3.3.1.A.8 Tachyarrhythmia

a) Summary

1) Trazodone may be associated with the exacerbation of ventri 1990; Himmelhoch et al, 1984; Vlay & Friedling, 1983).

b) LITERATURE REPORTS

1) Exercise-induced nonsustained ventricular tachycardia was d with no underlying heart disease receiving trazodone 50 milligrar trazodone was confirmed by treadmill testing initially, following di rechallenge with trazodone (Vitullo et al, 1990).

2) Trazodone does not appear to produce tachycardia, even in p consistently lowers baseline heart rate in therapeutic doses (Him

3) Exacerbation of ventricular tachycardia was associated with a 41-year-old female patient. The patient had a history of complex symptomatic only with palpitations. On one occasion, while not r started on trazodone 50 milligrams daily for depression. Two wee patient experienced dizzy spells and a Holter recording demonst rate of 160 beats per minute. Trazodone was discontinued and v returned to baseline. Due to potential hazards, the patient was n 1983). Administration of trazodone to patients with ventricular ec cardiac monitoring.

3.3.2 Dermatologic Effects

3.3.2.A Trazodone Hydrochloride

Dermatological finding

Diaphoresis

Erythema multiforme

Rash

3.3.2.A.1 Dermatological finding

a) Summary

1) Dermatologic effects of trazodone therapy voluntarily reporte ALOPECIA, LEUKONYCHIA or white patches under the nails, P URTICARIA (Prod Info Desyrel(R), 1998a).

b) Trazodone has been reported to cause alopecia, pruritus, diaphor rash.

3.3.2.A.2 Diaphoresis

a) Summary

1) Allergic and edematous skin reactions and SWEATING or CL of patients or more treated with trazodone in clinical trials (Prod I

3.3.2.A.3 Erythema multiforme

a) Summary

1) Erythema multiforme was described in a 63-year-old woman days of oral trazodone 300 to 400 milligrams. The patient presen papular eruption and erythematous scaly plaques on both the ha carbonate had also been prescribed and both drugs were discon symptomatic treatment with betamethasone ointment. The patie heel and erosions on the tongue and buccal mucosa two days af foot soaks and Chloraseptic(R) mouthwash were begun. The pat sequelae. Lithium has not been associated with erythema multifo patient for two weeks without incident. The first symptoms of a ra trazodone was begun; this led the authors to suggest that trazod (Ford & Jenike, 1985).

3.3.2.A.4 Rash

a) Summary

1) Skin rashes, which respond to drug withdrawal and/or antihis during trazodone therapy (Trapp et al, 1979); (Al- Yassiri & Bridg

3.3.3 Endocrine/Metabolic Effects

3.3.3.A Trazodone Hydrochloride

Body temperature finding

Endocrine finding

Isolated prolactin deficiency

Metabolic finding

Shivering

Weight change finding

3.3.3.A.1 Body temperature finding

a) Trazodone has been reported to cause chills.

3.3.3.A.2 Endocrine finding

a) Summary

1) Endocrine effects of trazodone therapy voluntarily reported to HYPERAMYLASEMIA and syndrome of inappropriate antidiureti

(Prod Info Desyrel(R), 1998a). Additional endocrine effects of tra
reported to the manufacturer include BREAST ENLARGEMENT
HIRSUTISM (Prod Info Desyrel(R), 1998a).

b) Hyperamylasemia, syndrome of inappropriate antidiuretic hormon
prolactin levels have been reported with the administration of trazodo

3.3.3.A.3 Isolated prolactin deficiency

a) Summary

1) Several studies have demonstrated no change (Nair, 1979) o
prolactin levels (Roccatagliata et al, 1979; Rolandi et al, 1981a)
reports of BREAST TENDERNESS were found in the literature (
manufacturer received 8 incident reports, although none had sub
Comm, 1985).

3.3.3.A.4 Metabolic finding

a) Trazodone has been reported to cause both weight gain and weig

3.3.3.A.5 Shivering

a) Summary

1) Chills has been reported voluntarily to the manufacturer as ar
therapy (Prod Info Desyrel(R), 1998a).

3.3.3.A.6 Weight change finding

a) Summary

1) WEIGHT GAIN and WEIGHT LOSS were both reported in ov
(Prod Info Desyrel(R), 1998a).

3.3.4 Gastrointestinal Effects

3.3.4.A Trazodone Hydrochloride

Constipation

Gastrointestinal tract finding

Loss of appetite

Nausea and vomiting

Xerostomia

3.3.4.A.1 Constipation

a) Summary

1) Constipation has been reported as an adverse effect of trazo
study with imipramine, the incidence of constipation was less in t
imipramine treated patients (20%) (Gershon & Newton, 1980a).

3.3.4.A.2 Gastrointestinal tract finding

a) Summary

1) Other gastrointestinal effects reported in 1% of patients or mo
abdominal or GASTRIC DISORDERS, TASTE DISORDERS, DI
reduced appetite. Increased SALIVATION has also been reporte
Desyrel(R), 1998a).

b) Anorexia, constipation, dry mouth, nausea, vomiting, and diarrhea
administration of trazodone.

3.3.4.A.3 Loss of appetite

a) Summary

1) CASE REPORT - Anorexia and hypomania were reported in
(mg) trazodone and 500 mg of tryptophan three times a week. A
was discontinued (Patterson & Srisopark, 1989).

3.3.4.A.4 Nausea and vomiting

a) Summary

1) Nausea and vomiting are the most frequently reported advers
1998a).

3.3.4.A.5 Xerostomia

a) Summary

1) XEROSTOMIA has been reported with trazodone therapy, bu
than in imipramine-treated patients (45%) (Gershon & Newton, 1

3.3.5 Hematologic Effects

3.3.5.A Trazodone Hydrochloride

Agranulocytosis

Hematology finding

3.3.5.A.1 Agranulocytosis

a) Summary

1) CASE REPORT - A 40-year-old male had been using trazodo
admission, with no history of any other concurrent drug or chemi
perianal furuncles. Hematology laboratory values were normal w
erythrocyte sedimentation rate (ESR) and decreased leukocyte c
of 4.0 - 10.0 x 10(9)). Differential cell count was reported to be 7
and 1% eosinophils (absolute neutrophil count 0). Pus from his f
aureus. Treatment was begun with flucloxacillin. Trazodone thera
later, his leukocyte count had increased and ESR had decreased
laboratory values had returned to normal (Van der Klauw et al, 1

3.3.5.A.2 Hematology finding

a) Summary

1) Hematologic effects of trazodone therapy voluntarily reported
HEMOLYTIC ANEMIA, LEUKOCYTOSIS, and METHEMOGLOE
1998a).

b) Agranulocytosis, hemolytic anemia, leukocytosis, and methemogl
trazodone therapy.

3.3.6 Hepatic Effects

3.3.6.A Trazodone Hydrochloride

Cholestasis

Hepatitis

Increased liver enzymes

Liver finding

3.3.6.A.1 Cholestasis

a) Summary

1) Cholestasis has resulted from the use of trazodone (Rettman
Nies, 1983).

b) LITERATURE REPORTS

1) A 46-year-old Hispanic man developed acute hepatitis and ch
trazodone as part of standard protocol for cocaine withdrawal. Th
Ab positive, and hepatitis C virus positive. The detoxification trea
milligrams (mg) per day, clonidine 0.1 mg twice daily, and trazod
symptoms of depression, listlessness, fatigue, and poor sleep ov
to cocaine withdrawal. However, laboratory tests on day 5 showe
(alanine amino transferase) and a 50-fold increase in AST (aspa
Clonidine and trazodone were discontinued. Ten days later, hepa
Six months later, laboratory results were completely normal and

Since trazodone has been previously associated with hepatotoxi
since the timing and extent of response were not characteristic o
was presumed that trazodone was responsible for the hepatotox
2001).

2) Intrahepatic cholestasis was reported in a 71-year-old womar
milligrams daily for two weeks. The patient presented with increa
transaminase (AST), and alkaline phosphatase levels (ALP). Tes
negative. Upon discontinuation of trazodone, bilirubin levels cont
and ALP levels both decreased. Eight weeks after trazodone wa
bilirubin returned to normal (Sheikh & Nies, 1983). It is suggeste
enzymes and bilirubin be undertaken during the first four weeks
patients.

3.3.6.A.2 Hepatitis

a) Summary

1) Hepatitis has resulted from use of trazodone (Rettman & McC

b) LITERATURE REPORTS

1) A 46-year-old Hispanic man developed acute hepatitis and ch
trazodone as part of standard protocol for cocaine withdrawal. Th
Ab positive, and hepatitis C virus positive. The detoxification trea
milligrams (mg) per day, clonidine 0.1 mg twice daily, and trazod
symptoms of depression, listlessness, fatigue, and poor sleep ov
to cocaine withdrawal. However, laboratory tests on day 5 showe
(alanine amino transferase) and a 50-fold increase in AST (aspa
Clonidine and trazodone were discontinued. Ten days later, hepa
Six months later, laboratory results were completely normal and
Since trazodone has been previously associated with hepatotoxi
since the timing and extent of response were not characteristic o
was presumed that trazodone was responsible for the hepatotox
2001).

2) A 75-year-old Asian woman, who had experienced chronic na
trazodone, presented with dark urine, pale stools, and jaundice f
months of trazodone treatment, 150 milligrams/day, for depressi
elevated prothrombin time (PT), partial thromboplastin time (PTT
Negative immunostains on liver biopsy and serologic tests for he
remote past exposure to hepatitis B but not of ongoing viral infec
discontinuing trazodone, the nausea and anorexia resolved. Ami
and PPT normalized within 2 weeks, while bilirubin and gamma g
gradually returned to normal in 6 months (Beck et al, 1993).

3.3.6.A.3 Increased liver enzymes

a) Summary

1) Trazodone has been reported to cause elevated liver enzyme
normalize after discontinuing the drug (Fernandes et al, 2000; Cl

b) LITERATURE REPORTS

1) Jaundice and elevated liver function tests occurred in a 38-ye
taking trazodone for 18 months and while she was also using lov
arthritis. She presented with itching, nausea, and an episode of v
withdrawn, and her liver tests started to improve. Approximately
own took trazodone for two days. Her bilirubin, aspartate aminotr
transaminase levels promptly rose. Normalization occurred with
(Fernandes et al, 2000).

2) Hepatotoxicity was reported in a 63-year-old male treated for
disorder with trazodone, following three weeks of therapy (doses
that time, liver function tests were mildly elevated. Eight days lat
elevated and biopsy revealed mild portal expansion with modera
several mononuclear and polymorphonuclear leukocytes, scatter
acidophil bodies. Hepatic enzymes returned to normal four week
(Chu et al, 1983). A cause and effect relationship is difficult to es
enzymes did not peak until eight days after discontinuing the dru

3.3.6.A.4 Liver finding

a) Summary

1) Hepatic effects of trazodone therapy voluntarily reported to th
cholestasis, HYPERBILIRUBINEMIA, JAUNDICE, and LIVER EN
Info Desyrel(R), 1998a).

b) Cholestasis, elevated liver enzymes, and hepatitis have been rep

trazodone.

3.3.8 Musculoskeletal Effects

3.3.8.A Trazodone Hydrochloride

Musculoskeletal finding

Myalgia

3.3.8.A.1 Musculoskeletal finding

a) Muscle aches and pains have been reported in some patients with

3.3.8.A.2 Myalgia

a) Summary

1) Musculoskeletal aches and pains were reported in approxima trazodone in clinical trials (Prod Info Desyrel(R), 1998a).

3.3.9 Neurologic Effects

Trazodone

Trazodone Hydrochloride

3.3.9.A Trazodone

3.3.9.A.1 Seizure

See Drug Consult reference: COMPARATIVE INCIDENCE OF SEIZU ANTIDEPRESSANTS

3.3.9.B Trazodone Hydrochloride

Dystonia

Myoclonus

Neurological finding

Parkinsonism

Seizure

Somnolence

3.3.9.B.1 Dystonia

a) Summary

1) Dystonic reactions have been reported only in case reports. A effect is impairment of nigrostriatal dopamine activity by serotoni 1997).

b) LITERATURE REPORTS

1) In one case report, a 14-year-old boy was initially treated with (mg)/day (given in the morning) with gradual increases to 150 mg mg/day (given at night) was added to the regimen on day seven. treatment), the boy developed acute DYSTONIA, manifested as which was controlled with three intramuscular doses of 2 mg ber Trazodone was discontinued and the symptoms did not recur (Te

2) In a case report, dystonia was reported in a 24-year-old man disorder. The patient started on trazodone 25 milligrams (mg) at this dose was increased to 50 mg. Three days after starting the h

the emergency department with his mouth immobile in an open p stiffness and feeling as if his face was "frozen." The symptoms w a single 50 mg dose of intravenous diphenhydramine. Because t noted over a year later in the patient's treatment after he began t authors hypothesized that the mechanism causing the dystonia v possibly associated with enhancement of serotonergic neurotran dopamine activity (Lewis et al, 1997).

3.3.9.B.2 Myoclonus

a) Summary

1) Myoclonus has been reported in patients receiving trazodone upon withdrawal of trazodone (Patel et al, 1988; Garvey & Tollef

b) LITERATURE REPORTS

1) Myoclonus was reported in a 38-year-old woman receiving 3(1988). This may be related to serotonergic activity.

2) A high incidence of myoclonus was reported with cyclic antide imipramine, desipramine, amitriptyline, doxepin, trazodone, nortr Tollefson, 1987). Ninety-eight patients (93%) with major depress with these agents in initial doses of 50 milligrams (mg) daily of im increasing to a maximum of 300 mg daily after several weeks. O developed myoclonus after initiation of therapy, with the myoclor nine (9%) and resulting in withdrawal of the antidepressant or a r occurred within one month of therapy in 81% of the 39 patients, v myoclonus within two weeks; the mean dose of antidepressant b myoclonus was 169 mg daily in imipramine equivalents, which w utilized by the patients not developing myoclonus (164 mg daily) withdrawal of the antidepressant but persisted if medication char spontaneous remission of myoclonus was observed in nine patie development of myoclonus were observed.

3.3.9.B.3 Neurological finding

a) Summary

1) Central nervous system effects reported in over 1% of patient DISORIENTATION, HEADACHE, INSOMNIA, MEMORY IMPAI COORDINATION, PARESTHESIA, and TREMORS (Prod Info D effects of trazodone therapy voluntarily reported to the manufact EXTRAPYRAMIDAL SYMPTOMS, GRAND MAL SEIZURES, IN DYSKINESIA, VERTIGO, and WEAKNESS (Prod Info Desyrel(F FATIGUE have also been reported in relatively high incidence.

b) Delirium, drowsiness, dystonia, myoclonus, headache, ataxia, sei dizziness, and fatigue have been reported with administration of trazo

3.3.9.B.4 Parkinsonism

a) Summary

1) CASE REPORT: A 57-year-old man who had undergone hem stage renal disease was given oral trazodone 100 milligrams/day depressive symptoms disappeared, but over 18 months he gradu symptoms, including cogwheel rigidity, akinesia, and gait disturb within 1 week of discontinuing trazodone. No serum concentratio were obtained, but the clinical course strongly suggested that the induced by trazodone (Fukunishi et al, 2002).

3.3.9.B.5 Seizure

a) Summary

1) Based on reports to the manufacturer, over 30 cases of seizu administration. Sixteen reported cases had previous documente al, 1985; Pers Comm, 1983; Tasini, 1986).

b) Incidence: rare

c) LITERATURE REPORTS

1) Another report described a 47-year-old man who developed c treatment with trazodone 150 mg/day for three weeks. Electroen abnormal after discontinuation of trazodone and it was speculate underlying seizure disorder (Tasini, 1986).

2) Multiple tonic-clonic seizures occurred in a 50-year-old woma following 18 days of trazodone therapy (50 milligrams daily) (Lefl also had fever on admission; it was unclear if this contributed to

3.3.9.B.6 Somnolence

a) Summary

1) The most commonly reported adverse effects of trazodone th LETHARGY. In a study of nine patients who received trazodone days, three were lethargic and two were drowsy (Kellams et al, 1 1982b).

b) LITERATURE REPORTS

1) Twelve of 50 patients who were receiving 200 to 600 milligrar dizzy during a four week treatment period (Feighner, 1980a). Dr patients in another report (Rawls, 1982b).

3.3.10 Ophthalmic Effects

3.3.10.A Trazodone Hydrochloride

Blurred vision

Eye / vision finding

Intraocular pressure finding

3.3.10.A.1 Blurred vision

a) Summary

1) Blurred vision has been reported as an adverse effect of traz patients in clinical trials (Prod Info Desyrel(R), 1998a). However, imipramine, the incidence of blurred vision was less in trazodone patients (20%) (Gershon & Newton, 1980a).

3.3.10.A.2 Eye / vision finding

a) Summary

1) Tired, red, or ITCHING EYES were reported in approximately trazodone in clinical trials. DIPLOPIA, in association with trazodc reported to the manufacturer (Prod Info Desyrel(R), 1998a).

2) The reappearance or persistence of an image has been asso patients receiving trazodone therapeutically (Hughes & Lessell,

b) Trazodone has been reported to cause blurred vision, intraocular and itchy eyes, and vision changes.

3.3.10.A.3 Intraocular pressure finding

a) Summary

1) Trazodone produces a slight decrease in intraocular pressure glaucoma by increasing outflow and decreasing production of aq reduction occurs in 180 minutes. However, after three hours intra level slightly below pretreatment values (Daniel & Fiore, 1972). T beneficial in patients with open-angle glaucoma and concomitan associated trazodone use with increased IOP (Pae et al, 2003).

b) LITERATURE REPORTS

1) A 61-year-old woman, with a 6-year history of angle-closure g increase in intraocular pressure (IOP) following the administratio maintained an IOP of 13 to 19 millimeters of mercury (mmHg) in regimen of daily drops of timolol 0.5% and pilocarpine 5%. Three milligrams (mg) per day for depressive symptoms, she develope eye pain and intermittent headache. Her IOP, 6 days after startin left eye and 40 mmHg in the right eye. Trazodone was discontinu acetazolamide 500 mg/day. Two days later her IOP returned to b

3.3.12 Psychiatric Effects

3.3.12.A Trazodone Hydrochloride

Delirium

Mania

Panic attack

Psychiatric sign or symptom

Suicidal thoughts

3.3.12.A.1 Delirium

a) Summary

1) Trazodone has been reported to cause delirium in patients. T
usually hallucinations, psychomotor agitation, and cognitive char
Damlouji & Ferguson, 1984).

b) LITERATURE REPORTS

1) Trazodone-induced delirium was reported in three patients, tv
organic cerebral lesions and one of whom had thyroid dysfunctio
hallucinations, psychomotor agitation, and cognitive changes, wa
shortly after initiation of trazodone therapy (with aggravation of th
dosage in one patient). Shortly after discontinuation of the trazoc
and, in one patient, symptoms recurred after reinstitution of trazo
that the delirium might be caused by a heightened sensitivity to t
meta- chlorphenylpiperazine, which has specific 5-HT agonist pr
2) Three cases of delirium occurred in patients with bulimia and
following short-term trazodone administration (Damlouji & Fergus
developed within two to three hours of the first dose. In the third
dosing adjustment from 150 to 200 milligrams daily. The authors
be more susceptible to delirium secondary to trazodone, possibly
neuroregulatory system.

3.3.12.A.2 Mania

a) Summary

1) Nine cases of mania following initiation of trazodone therapy
Bick, 1984; Arana & Kaplan, 1985; Lennhoff, 1987; Knobler et al

3.3.12.A.3 Panic attack

a) Summary

1) Panic attacks were reported at doses of 0.26 to 0.5 milligrams
chlorophenylpiperazine (MCPP), a trazodone metabolite and dire
al, 1990).

3.3.12.A.4 Psychiatric sign or symptom

a) Summary

1) Central nervous system effects reported in over 1% of patient
or HOSTILITY, CONFUSION, DREAM DISTURBANCES, EXCIT
general feeling of MALAISE or of a "heavy" or "full" head (Prod In
effects of trazodone therapy voluntarily reported to the manufact
ANXIETY, HALLUCINATIONS, INSOMNIA, PARANOID REACT
and VERTIGO (Prod Info Desyrel(R), 1998a).

b) Mania, panic attacks, hallucinations, agitation, hostility, and psych
result of trazodone use.

3.3.12.A.5 Suicidal thoughts

a) Incidence: rare

b) Adult and pediatric patients being treated with antidepressants for
experience symptoms of anxiety, agitation, panic attacks, insomnia, i
(aggressiveness), impulsivity, akathisia (psychomotor restlessness),
risk of suicidal ideation and behavior (SUICIDALITY). This same con
with other psychiatric and nonpsychiatric disorders. If these symptom
be re-evaluated and it may be necessary to discontinue medications
sudden in onset, or were not part of the patient's initial symptoms. Pa
be provided with the Medication Guide that is available for this drug (

c) A causal role for antidepressants in inducing suicidality has been
Anyone considering the use of antidepressants in a child or adolesce
clinical need. In pooled analyses of 24 short-term, placebo-controlled
(citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, bupropion
venlafaxine extended-release) including over 4400 pediatric patients
obsessive compulsive disorder, or other psychiatric disorders, a grea

ideation during the first few months of therapy was demonstrated in p
as compared with placebo (4% vs 2%, respectively). The risk of suici
observed in the trials that included patients with major depressive dis
emerging from trials in other psychiatric indications, such as obsessiv
anxiety disorder. No suicides occurred in these trials. The risk of suic
beyond several months) in pediatric patients is not known. It is also u
to adult patients (Anon, 2004).

3.3.13 Renal Effects

3.3.13.A Trazodone Hydrochloride

Urinary retention

Urogenital finding

3.3.13.A.1 Urinary retention

a) Summary

1) URINARY HESITANCY has been reported as an adverse eff
comparative study with imipramine, the incidence of urinary hesi
patients (1%) than imipramine patients (4%) (Gershon & Newton

3.3.13.A.2 Urogenital finding

a) Trazodone has been reported to cause both an increase and decr
ejaculatory dysfunction, and urinary retention.

3.3.14 Reproductive Effects

Trazodone

Trazodone Hydrochloride

3.3.14.A Trazodone

3.3.14.A.1 Sexual dysfunction

See Drug Consult reference: DRUG-INDUCED SEXUAL DYSFUNCT

3.3.14.B Trazodone Hydrochloride

Abnormal ejaculation

Increased libido

Priapism

Reduced libido

3.3.14.B.1 Abnormal ejaculation

a) Summary

1) INHIBITION OF EJACULATION was reported in a 51-year-ol
50 milligrams (mg) at bedtime for 3 days, then 100 mg at bedtim
trazodone and substitution with doxepin 50 mg at bedtime result
EJACULATORY INHIBITION (Jones, 1984).

3.3.14.B.2 Increased libido

a) Summary

1) Trazodone administration produced an increase in libido in th
cases, trazodone was given in gradually increasing doses up to
sexual drive were observed when this dose was achieved. Two p

drug due to this effect (Gartrell, 1986).

3.3.14.B.3 Priapism

a) Summary

1) Trazodone therapy has been associated with the occurrence surgical intervention (Prod Info Desyrel(R), 1998a; Pecknold & L Pescatori et al, 1993); (Scher et al, 1983)(Hanno et al, 1988); (C

b) Incidence: rare

c) LITERATURE REPORTS

1) In a case report, a patient treated first with nefazodone and th priapism after beginning trazodone therapy. A 51- year-old man, depressive disorder, participated in a trial of nefazodone at a dos day for a period of 6 weeks. After completion of the experimental therapy with trazodone 300 mg/day. After 17 days of therapy witl allopurinol for gout contracted during this period) the patient repo was discontinued. The patient subsequently was treated with net of priapism were reported (Pecknold & Langer, 1996).

2) A 34-year-old woman who had received fluoxetine 40 milligra treatment of depression was started on trazodone to combat fluo fluoxetine was decreased to 20 mg per day and trazodone 25 mg 50 mg at bedtime was added. Five days after starting trazodone onset irritation in the clitoral region that four days later developed PRIAPISM. Both drugs were discontinued and she received oral hydrochloride/guaifenesin twice daily for 2 days. The clitoral disc within 24 hours and there was no further clitoral dysfunction repo

3) Priapism has been seen as an adverse effect from therapeuti (Hanno et al, 1988); (Carson & Mino, 1988). Surgery was require the manufacturer and permanent impotence has been a sequela

4) In 57 cases reported to the United States Food and Drug Adr be mostly likely to occur during the first 28 days of therapy, with (mg) daily (median, 150 mg daily) (Warner et al, 1987). The med developed priapism was 40 years; however, all age groups appe adverse effect. It is suggested that patients be well informed of th given trazodone and to discontinue the drug if any unusual erect

3.3.14.B.4 Reduced libido

a) Summary

1) Decreased libido was reported in 1% of patients in clinical tria trazodone therapy voluntarily reported to the manufacturer includ incontinence and urinary retention (Prod Info Desyrel(R), 1998a)

3.3.15 Respiratory Effects

3.3.15.A Trazodone Hydrochloride

3.3.15.A.1 Respiratory finding

a) Summary

1) Sinus or NASAL CONGESTION was reported in approximate trials. APNEA, in association with trazodone therapy, was volunt (Prod Info Desyrel(R), 1998a).

b) Nasal congestion and apnea have been reported with the adminis

3.3.16 Other

3.3.16.A Trazodone Hydrochloride

Summary

Anticholinergic adverse reaction

Died without sign of disease

Drug withdrawal

3.3.16.A.1 Summary

a) OTHER EFFECTS

1) Although trazodone produces fewer anticholinergic effects tha these effects have been reported with trazodone use. Unexplain with the administration of trazodone.

3.3.16.A.2 Anticholinergic adverse reaction

a) Summary

1) Trazodone produces significantly fewer anticholinergic effects (Taylor et al, 1980; Georgotas et al, 1982b; Gershon & Newton, one study, the incidence of anticholinergic effects with trazodone similar to placebo, but imipramine, in comparison, produced sign (Gershon & Newton, 1980a). Trazodone's lower degree of antich drug useful in glaucoma patients with depression (Rawls, 1982b) of increased intraocular pressure associated with trazodone use

3.3.16.A.3 Died without sign of disease

a) Summary

1) Unexplained death has been reported voluntarily to the manu trazodone therapy (Prod Info Desyrel(R), 1998a).

3.3.16.A.4 Drug withdrawal

a) Summary

1) Although uncommon, a withdrawal syndrome has been repor discontinuation of trazodone.

b) LITERATURE REPORTS

1) A trazodone withdrawal syndrome has been reported followin therapeutic doses of traxodone. It has been suggested that deve due to serotonergic effects and short half-lives of trazodone and chlorophenylpiperazine, which may result in noradrenergic rebou Withdrawal signs/symptoms have consisted of insomnia, vivid dr abdominal pain. anxiety, palpitations, hypomania, headache. my formication (Otani et al, 1994; Peabody, 1987; Menza, 1986); (TI Rapid withdrawal has been reported to result in predominantly ga respond to administration of atropine. It has been suggested that following rapid withdrawal (Montalbetti & Zis, 1988).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Pro Trimesters)

a) Either studies in animals have revealed adverse effects on the fetus (te other) and there are no controlled studies in women or studies in women a Drugs should be given only if the potential benefit justifies the potential ris

See Drug Consult reference: PREGNANCY RISK CATEGORIES

2) Crosses Placenta: Unknown

3) Clinical Management

a) There is insufficient clinical experience with trazodone to confirm its sa data are available, caution should be exercised with the use of trazodone

4) Literature Reports

a) One report describes the outcomes of 12 pregnancies exposed to traz electively terminated, and the remaining ten resulted in children without m 1996). One hundred newborns (out of 229,101 births in a surveillance stu recipients) had been exposed to trazodone during the first trimester of pre exposures, one major birth defect was observed; no details are available (Rosa & Baum, 1995).

b) Animal studies indicate that high doses in rats and rabbits (15 to 50 tin contributed to increased fetal resorption and congenital anomalies. Early a lower birth weights for offspring in animals receiving high doses (Rivett & These studies were designed with trazodone dosing of 10 to 300 mg/kg d to and during mating, throughout pregnancy and lactation, and in a separa days of pregnancy and throughout lactation. Additionally, rats and rabbits during the middle portion of pregnancy developed no anomalies in offsprin Suzuki, 1973).

B) Breastfeeding

1) American Academy of Pediatrics Rating: Drugs for which the effect on nurs be of concern. (Anon, 2001)

2) Thomson Lactation Rating: Infant risk cannot be ruled out.
a) Available evidence and/or expert consensus is inconclusive or is inade when used during breastfeeding. Weigh the potential benefits of drug trea before prescribing this drug during breastfeeding.
3) Clinical Management
a) Trazodone is excreted into human milk in small amounts. Despite the effects in breast-fed infants, the American Academy of Pediatrics classifie effect on nursing infants is unknown, but may be of concern (Anon, 2001)
4) Literature Reports
a) Trazodone is excreted in low concentrations in breast milk following si were administered single oral doses of 50 mg, with a resultant milk-plasm that newborn infants would ingest less than 0.005 mg/kg of trazodone foll mother and subsequent breast feeding for a 12-hour period (Verbeeck et
5) Drug Levels in Breastmilk
a) Parent Drug
1) Milk to Maternal Plasma Ratio
a) 0.142 (Bennett, 1996)
b) Active Metabolites
1) meta-Chlorophenylpiperazine (Otani et al, 1998a)

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Food Combinations

3.5.1 Drug-Drug Combinations

Acetophenazine

Amiodarone

Amprenavir

Atazanavir

Carbamazepine

Chlorpromazine

Clarithromycin

Darunavir

Delavirdine

Digoxin

Droperidol

Ethopropazine

Fluoxetine

Fluphenazine

Fosamprenavir

Foxglove

Ginkgo

Indinavir

Itraconazole

Ketoconazole

Linezolid

Mesoridazine

Methotrimeprazine

Nefazodone

Nelfinavir

Paroxetine

Perphenazine

Phenytoin

Pipotiazine

Prochlorperazine

Promazine

Promethazine

Propiomazine

Ritonavir

St John's Wort

Thiethylperazine

Thioridazine

Tipranavir

Trifluoperazine

Triflupromazine

Venlafaxine

3.5.1.A Acetophenazine

1) Interaction Effect: hypotension

2) Summary: Concomitant administration of trazodone with chlorpromazi

additive hypotensive effects in two case reports. Withdrawal of trazodone hypotension (Asayesh, 1986f).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor blood pressure, particularly in patients v effect. Advise patient to rise slowly from laying or sitting position.
7) Probable Mechanism: additive hypotensive effects

3.5.1.B Amiodarone
1) Interaction Effect: increased risk of QT interval prolongation and torsac
2) Summary: Both amiodarone and trazodone are metabolized by CYP3A amiodarone is also a CYP3A4 inhibitor (Prod Info CORDARONE(R) oral t prolongation and torsades de pointes has been reported with the coadmir trazodone in 2 cases (Antonelli et al, 2005; Mazur et al, 1995). Caution is coadministered. Cardiac function may need to be closely monitored.
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: QT interval prolongation and torsades de pointe amiodarone and trazodone has been reported (Prod Info CORDARONE(R al, 2005; Mazur et al, 1995). Use caution if these agents are coadminister be monitored.
7) Probable Mechanism: unknown
8) Literature Reports
a) A case report described QT interval prolongation and polymorpho (torsades de pointes) in a 74-year-old woman receiving amiodarone a woman, who had a history of hypertension, stable angina, diastolic he pacemaker for sick sinus syndrome, and depression, presented with medications included nifedipine, furosemide, and aspirin. Amiodarone mg/day, and was later reduced to 100 mg/day 6 months prior to curre been initiated 2 months prior to current presentation at an initial dose increased over 2 weeks to 150 mg/day. While neurological exam and normal, cardiac examination revealed a II/VI systolic ejection murmur prolonged QT, QTc, and JTc intervals (0.72, 0.777, and 0.561 second to an ECG obtained prior to initiation of trazodone (baseline). Subsec trazodone were discontinued. However, recurrent episodes of polymo developed. Although treatment with intravenous lidocaine and magne episodes were managed by increasing the ventricular pacing rate to 9 episodes did not recur following gradual reduction of the ventricular p minutes over 48 hours, and the ECG pattern was similar to baseline, shortening to 0.52, 0.561, and 0.324 seconds, respectively (Mazur et
b) A chart review of 6 patients revealed a case of syncope and TdP i addition of amiodarone (50 mg/day) for paroxysmal atrial fibrillation to mg/day). The patient, who had a history of coronary artery disease, d hyperlipidemia, presented with syncope 2 months following the initiat proposed that in addition to the amiodarone-trazodone combination, p have contributed to the occurrence of torsades in this patient (Antone

3.5.1.C Amprenavir
1) Interaction Effect: an increase in trazodone plasma levels and may inc
2) Summary: Concomitant use of amprenavir and trazodone may result in concentrations due to amprenavir inhibition of CYP3A4-mediated trazodo when using these medications together and consider a reduction of trazoc trazodone side effects such as nausea, dizziness, hypotension, and synco Capsules, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Consider a lower dose of trazodone if it is used amprenavir. Monitor patients receiving trazodone and amprenavir for adve nausea, dizziness, hypotension, and syncope.
7) Probable Mechanism: inhibition of CYP3A4-mediated trazodone metab
8) Literature Reports
a) Coadministration of trazodone with ritonavir, a potent CYP3A4 inh amprenavir, resulted in significant trazodone pharmacokinetic change concurrent administration of a total of 4 doses ritonavir 200 mg twice

trazodone increased the peak plasma trazodone concentration (Cma
the concentration-time curve (AUC) 2.4-fold, increased the half-life 2.
clearance 52%. During concomitant use of trazodone and ritonavir, a
nausea, hypotension, and syncope (Prod Info Desyrel(R) Oral Tablet

3.5.1.D Atazanavir

1) Interaction Effect: an increase in trazodone plasma levels and increase (nausea, dizziness, hypotension)

2) Summary: Atazanavir may inhibit the CYPA-mediated metabolism of tr atazanavir (with or without ritonavir) and trazodone may elevate plasma le should be monitored for increased trazodone side effects including nause hypotension. A reduction in trazodone dosing may be warranted (Prod Inf 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Caution is advised for the concomitant use of at and trazodone. Patients receiving atazanavir and trazodone should be mo effects and hypotension. Consider a reduction in trazodone dosing (Prod 2005).

7) Probable Mechanism: inhibition of CYP3A4-mediated trazodone metab

3.5.1.E Carbamazepine

1) Interaction Effect: decreased trazodone plasma concentrations

2) Summary: An increase in carbamazepine concentration/dose ratio was added to therapy, although the patient did not exhibit any signs of carbam 1999a). Trazodone serum concentrations have been decreased during co carbamazepine. Patients should be closely monitored to see if there is a r trazodone when taking both drugs (Prod Info Desyrel(R), 2003a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When given concurrently with carbamazepine, t should be closely monitored and trazodone dose adjustments made as ne

7) Probable Mechanism: induction of trazodone CYP3A4-mediated metal

8) Literature Reports

a) A 53-year-old male diagnosed with generalized partial epilepsy wa mg daily with a corresponding serum concentration of 7.9 mg/L. The calculated by dividing the serum concentration (mg/L) by the dose (m therapy was initiated for depression, and two months later the carban had increased to 10.0 mg/L with a corresponding concentration/dose concentration of the main pharmacologically active metabolite of carb 10,11-epoxide, was not measured. Although this patient did not show carbamazepine toxicity, this drug interaction may be clinically signific higher carbamazepine steady-state concentration (Romero et al, 199

3.5.1.F Chlorpromazine

1) Interaction Effect: hypotension

2) Summary: Concomitant administration of trazodone with chlorpromazi additive hypotensive effects in two case reports. Withdrawal of trazodone hypotension (Asayesh, 1986o).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor blood pressure, particularly in patients v effect. Advise patient to rise slowly from laying or sitting position.

7) Probable Mechanism: additive hypotensive effects

3.5.1.G Clarithromycin

1) Interaction Effect: an increase in trazodone plasma levels

2) Summary: Patients receiving trazodone therapy concurrently with clari exposure to trazodone due to clarithromycin-mediated inhibition of CYP3A 2009).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Consider a lower dose of trazodone if it is used

clarithromycin. Monitor patients receiving trazodone and clarithromycin fo
sedation, memory impairment, or impaired psychomotor performance.
7) Probable Mechanism: inhibition of CYP3A-mediated trazodone metabo
8) Literature Reports
a) Increased plasma concentrations and pharmacodynamic effects c
with clarithromycin was demonstrated in a randomized, double-blind,
healthy volunteers. The study involved five treatment protocols: (a) pl
(5 mg) plus placebo, (c) zolpidem (5 mg) plus clarithromycin (500 mg
placebo, and (e) trazodone (50 mg) plus clarithromycin (500 mg). Blo
intermittently throughout the study to determine plasma concentratior
clarithromycin. Coadministration of trazodone with clarithromycin con
increase in trazodone Cmax (922 +/- 161 nanogram/mL versus 681 +
trazodone AUC (9,275 +/- 3,216 nanogram/mL per hour versus 4,668
Trazodone elimination half-life increased with coadministration of clar
(13.9 +/- 8.1 hr versus 7.1 +/- 1.6 hr), and oral clearance was reduce
+/- 27 mL/min). The sedative effects of trazodone were also enhance
no significant changes in pharmacokinetics or pharmacodynamics of
clarithromycin treatment groups (Farkas et al, 2009).

3.5.1.H Darunavir
1) Interaction Effect: increased trazodone plasma concentrations
2) Summary: Coadministration of ritonavir-boosted darunavir and trazodo
plasma concentrations of trazodone, possibly due to inhibition of CYP3A-
by darunavir/ritonavir. As this may result in trazodone adverse effects (na
syncope), caution is advised when darunavir/ritonavir and trazodone are a
lower dose of trazodone should be considered (Prod Info PREZISTA(R) fi
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of ritonavir-boosted d
increase trazodone plasma concentrations. Use caution when these agen
patients for signs of increased trazodone adverse effects (nausea, dizzine
consider using a lower trazodone dose (Prod Info PREZISTA(R) film coat
7) Probable Mechanism: inhibition of CYP3A-mediated trazodone metabo

3.5.1.I Delavirdine
1) Interaction Effect: increased plasma concentrations of trazodone and i
adverse effects (nausea, dizziness, hypotension, syncope)
2) Summary: Trazodone is metabolized in the liver by CYP3A4 enzymes.
inhibitors, such as delavirdine, may decrease the metabolism of trazodon
plasma concentrations. Although, the drug interaction between delavirdine
studied, adverse effects such as nausea, dizziness, hypotension and sync
coadministration of trazodone and ritonavir. Therefore, caution is advised
are administered concomitantly and a reduction in trazodone dosage shou
RESCRIPTOR(R) oral tablets, 2006).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Use caution with the coadministration of delavirc
patients for signs of increased trazodone adverse effects (nausea, dizzine
Consider reducing trazodone dosage when administering concomitantly w
7) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated tra

3.5.1.J Digoxin
1) Interaction Effect: increased digoxin serum concentrations and an incr
(nausea, vomiting, arrhythmias)
2) Summary: Digoxin maximum serum concentrations were increased ne
after nefazodone (an antidepressant structurally related to trazodone) wa
randomized, crossover interaction study (Dockens et al, 1996a). Digoxin t
woman after trazodone was added to a stable treatment regimen that incl
had remained within a stable therapeutic range for many months prior to t
(Rauch & Jenike, 1984c). Increased serum digoxin serum concentrations
patients treated concurrently with trazodone and digoxin (Prod Info Desyr
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor digoxin concentrations when trazodone

discontinued from concomitant treatment with digoxin. Also, monitor patie
digoxin toxicity. Adjust digoxin dose accordingly.
7) Probable Mechanism: unknown
8) Literature Reports
a) Digoxin serum concentrations were increased nearly 30% compar
(a phenylpiperazine antidepressant structurally related to trazodone)
digoxin. In an open, randomized, triple-crossover interaction study, h
an 8-day oral regimen of digoxin 0.2 milligrams (mg) daily, nefazodor
drugs administered concomitantly during each 8-day trial period; all s
alternate study regimen after a 10-day wash-out period. Steady-state
time curve (AUC) and peak (Cmax) and trough (Cmin) serum concen
by 15%, 29% and 27%, respectively (p less than 0.05, each paramet
observed in vital signs, heart rate, or PR, QRS, and QT intervals. The
adverse events did not differ between treatment groups (Dockens et
b) Digoxin toxicity occurred in a 68-year-old woman after trazodone
regimen that included digoxin. Prior to beginning trazodone therapy,
remained within therapeutic range for many months (at a dose of digo
and on admission was 0.8 nanograms/milliliter (ng/mL). She was hos
trazodone was initiated at a dose of 50 milligrams (mg) on day 1, and
by day 11. On treatment day 14, the patient complained of nausea ar
measured at 2.8 ng/mL. Trazodone 300 mg daily was continued and
therapeutic digoxin serum levels were restored. The patient's digoxin
therapeutic range after conversion to an every-other-day regimen of
continued to receive trazodone 300 mg daily (Rauch & Jenike, 1984b
c) Increased serum concentrations of digoxin have been observed ir
treatment with trazodone (Prod Info Desyrel(R), 2003b).

3.5.1.K Droperidol
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation,
arrest)
2) Summary: Any drug known to have the potential to prolong the QT inte
with droperidol. Possible pharmacodynamic interactions can occur betwee
arrhythmogenic agents such as antidepressants that prolong the QT inter
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Droperidol should be administered with extreme
factors for development of prolonged QT syndrome, such as treatment wi
7) Probable Mechanism: additive cardiac effects

3.5.1.L Ethopropazine
1) Interaction Effect: hypotension
2) Summary: Concomitant administration of trazodone with chlorpromazi
additive hypotensive effects in two case reports. Withdrawal of trazodone
hypotension (Asayesh, 1986a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor blood pressure, particularly in patients v
effect. Advise patient to rise slowly from laying or sitting position.
7) Probable Mechanism: additive hypotensive effects

3.5.1.M Fluoxetine
1) Interaction Effect: trazodone toxicity (sedation, dry mouth, urinary rete
(hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: When given concurrently, trazodone and fluoxetine have be
effective with and without side effects (Metz & Shader, 1990; Swerdlow &
1992; Maes et al, 1997a). Coadministration of trazodone and fluoxetine ha
speech dysfunction in a 43-year old man following traumatic brain injury (
have also been several reports of serotonin syndrome due to interactions
reuptake inhibitors and antidepressants (George & Godleski, 1996a; Reev
Lee, 1996). Serotonin syndrome is a rare but potentially fatal condition of
characterized by hypertension, hyperthermia, myoclonus and changes in
Further clinical studies are necessary to determine the incidence and impl
associated with this drug combination.
3) Severity: major
4) Onset: delayed

5) Substantiation: probable
6) Clinical Management: Due to the potential for impairment in trazodone monitored for any signs of trazodone toxicity. Occasional dosage reductio Serotonin syndrome, characterized by hypertension, hyperthermia, myocl may also occur during concomitant therapy.
7) Probable Mechanism: decreased trazodone clearance
8) Literature Reports
a) Five cases of elevated antidepressant levels, four involving tricycli imipramine, desipramine) and one involving trazodone, have been re fluoxetine, the ratio of antidepressant level to dose increased by 109 tricyclics and by 31% in the patient on trazodone. The trazodone-trea and unstable gait (Aranow et al, 1989).
b) A 44-year-old man developed symptoms characteristic of serotoni interaction between fluoxetine and trazodone. The patient had been t trazodone 100 mg daily for approximately two months before sympto experienced disorientation, tremor, diaphoresis, and anxiety, followec loss of consciousness. After the patient was treated with cyproheptac resolved over the next 30 minutes. Trazodone was discontinued and fluoxetine 40 mg daily without further complications (George & Godle
c) Serotonin syndrome was also reported in a 29-year-old woman ta The patient was treated with trazodone 200 mg daily at bedtime for a depression and insomnia. The patient's depressive symptoms were u trazodone was subsequently decreased to 50 mg daily at bedtime for mg every morning was added. Within 24 hours after the first dose of agitated, confused, shaky, and diaphoretic. Upon examination, the pa intermittent myoclonus in all extremities, hyperreflexia, tremor, and di antidepressant medications, the patient's symptoms resolved (Reeve
d) A 43-year-old male with traumatic brain injury developed speech fluoxetine and trazodone. The patient was being treated with trazodo pain as a result of a fall. After undergoing a comprehensive psychiatr rehabilitation, fluoxetine 20 mg every morning was added to the patie symptoms of depression. Within one week of starting therapy with flu his speech and later exhibited a slow rate of speech, increased paus phonemes, and word-finding difficulties. After discontinuation of fluox therapy, the patient had marked improvement in speech difficulty and week (Patterson et al, 1997).
e) The pharmacokinetic effect of trazodone and fluoxetine cotherapy a major depressive episode. All were treated with trazodone 100 mg the addition of fluoxetine 20 mg daily, pindolol 7.5 mg daily, or placeb placebo had no significant effect on the plasma concentrations of traz meta-chlorophenylpiperazine (mCPP). However, when fluoxetine was of mCPP increased from a mean baseline value of 11.3 ng/mL to 38. increase was also associated with an improvement in the clinical resp (Maes et al, 1997).

3.5.1.N Fluphenazine

1) Interaction Effect: hypotension
2) Summary: Concomitant administration of trazodone with chlorpromazi additive hypotensive effects in two case reports. Withdrawal of trazodone hypotension (Asayesh, 1986n).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor blood pressure, particularly in patients v effect. Advise patient to rise slowly from laying or sitting position.
7) Probable Mechanism: additive hypotensive effects

3.5.1.O Fosamprenavir

1) Interaction Effect: an increase in trazodone plasma levels
2) Summary: Concomitant use of amprenavir, the active metabolite of fos result in increased trazodone plasma concentrations due to amprenavir in trazodone metabolism. Exercise caution when using these medications to of trazodone dosing. Monitor for trazodone side effects such as nausea, d syncope (Prod Info LEXIVA(R) oral solution, oral tablets, 2009; Prod Info 2005).
3) Severity: moderate
4) Onset: unspecified

5) Substantiation: theoretical
6) Clinical Management: Concomitant use of fosamprenavir (with or witho
cause increased trazodone plasma concentrations, and should be used w
dose of trazodone if it is used with a CYP3A4 inhibitor such as fosampren
fosamprenavir and trazodone for adverse effects, including sedation, naus
syncope (Prod Info LEXIVA(R) oral solution, oral tablets, 2009).
7) Probable Mechanism: inhibition of CYP3A4-mediated trazodone metal
metabolite of fosamprenavir
8) Literature Reports
a) Coadministration of trazodone with ritonavir, a potent CYP3A4 inh
fosamprenavir, resulted in significant trazodone pharmacokinetic cha
concurrent administration of a total of 4 doses ritonavir 200 mg twice
trazodone increased the peak plasma trazodone concentration (Cma
fold, increased the half-life 2.2-fold, and decreased trazodone clearar
of trazodone and ritonavir, adverse effects reported included nausea,
Info Desyrel(R) Oral Tablet, 2005).

3.5.1.P Foxglove

1) Interaction Effect: increased risk of digitalis toxicity
2) Summary: A single case report documents digoxin toxicity resulting fro
(Rauch & Jenike, 1984a). Theoretically, foxglove may be similarly affected
to digoxin.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Avoid concomitant use of foxglove and trazodor
intermittent trazodone doses will affect foxglove clearance (i.e., delayed e
to digitalis toxicity). Patients who choose to combine foxglove with trazodo
closely for signs and symptoms of toxicity (e.g., nausea, vomiting, drowsir
muscle weakness, hallucinations).
7) Probable Mechanism: not specified
8) Literature Reports
a) Trazodone added to a previously stable dose of digoxin resulted i
days. A 68-year-old woman with a 30-year history of unipolar affectiv
inpatient psychiatric service. Medical history was significant for conge
atrial tachyarrhythmias, and impaired renal function presumed secon
She was stabilized on digoxin (125 mcg/day) and quinidine with achie
levels for each drug. Digoxin level on admission was 0.8 ng/mL (thera
and quinidine level was 4.0 mcg/mL (therapeutic range 1.5 to 5.0 mcg
bedtime was begun and increased in 50 mg increments every other d
on Day 11. On Day 14 she complained of nausea and vomiting. A dig
The quinidine level remained within therapeutic limits at 1.6 mcg/mL.
nausea and vomiting resolved within 3 days. She continued trazodon
resumed at 125 mcg every other day resulting in therapeutic levels (F

3.5.1.Q Ginkgo

1) Interaction Effect: excessive sedation and potential coma
2) Summary: A single case report has described a semicomatose state fo
trazodone. Since no rechallenge of either agent alone or together was per
reaction was due to the combination or an unusual reaction to either agen
agonist activity at GABA receptors (Sasaki et al, 1999; Cott, 1995), as we
cytochrome P450 3A4 (CYP3A4) activity, producing more of the active me
which further enhances the release of GABA (Galluzzi et al, 2000a). In co
in vitro (Budzinski et al, 2000a). However, in vitro findings may not transla
therefore the clinical significance of this in vitro finding is unknown.
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: A single case report has described a semicomat
with trazodone. Since no rechallenge of either agent alone or together wa
the reaction was due to the combination or an unusual adverse reaction to
known about this potential interaction, avoid concomitant use of ginkgo ar
cannot be avoided, use a low dose of trazodone and monitor the patient c
sedation.
7) Probable Mechanism: induction of cytochrome P450 3A4 by ginkgo to
metabolite mCPP of trazodone
8) Literature Reports

a) An 80-year-old female diagnosed with probable Alzheimer's disea
80 mg twice daily and trazodone 20 mg twice daily following treatmer
bromazepam 3.5 mg daily, donepizil 5 mg at bedtime, and vitamin E
donepezil, and vitamin E were discontinued. On the third day of treat
the patient developed gait instability and drowsiness, fell asleep one
awakened. Blood pressure was 120/55, Glasgow coma scale was 6/
and the patient woke immediately. Trazodone and ginkgo were disco
bromazepam. At evaluation 2 months later, cognitive function and be
mechanism of the interaction between gingko and trazodone was hyp
combination of weak GABA agonist activity of ginkgo, and induction
increased production of the active metabolite of trazodone, mCPP wh
release (Galluzzi et al, 2000).
b) Ginkgo biloba inhibited CYP3A4 in vitro with an IC50 of 4.75 mmo
CYP3A4 inhibitor, was compared with ginkgo and other phytochemic
mmol, making it 23.3 times more inhibitory than the most inhibitory pl
with an IC50 of 0.03 mmol. Ginkgo was a much weaker inhibitor of C
significant drug interactions may occur with the inhibitory phytochemi
metabolized by CYP3A4 (Budzinski et al, 2000).

3.5.1.R Indinavir

1) Interaction Effect: an increase in trazodone plasma levels
2) Summary: Coadministration of trazodone with ritonavir (an indinavir-re
potent CYP3A4 inhibition) produced increases in peak plasma trazodone
elimination half-life, increased area under the concentration-time curve, a
clearance. During concomitant use of trazodone and ritonavir, adverse eff
hypotension, and syncope. Other signs and symptoms associated with ex
included priapism, respiratory arrest, seizures, and EKG changes (Prod Ir
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Consider a lower dose of trazodone if it is used
indinavir. Monitor patients receiving trazodone and indinavir for adverse e
hypotension, syncope, and/or priapism.
7) Probable Mechanism: inhibition of CYP3A-mediated trazodone metab

3.5.1.S Itraconazole

1) Interaction Effect: increased trazodone serum concentrations
2) Summary: Substantial elevations are expected in trazodone serum co
concomitantly with itraconazole, a potent CYP3A4 inhibitor (Prod Info Des
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Consider a lower dose of trazodone if it is used
CYP3A4 inhibitor such as itraconazole. Monitor patients receiving trazodo
effects, including sedation, nausea, hypotension, syncope, and/or priapis
7) Probable Mechanism: inhibition of CYP3A4-mediated trazodone meta

3.5.1.T Ketoconazole

1) Interaction Effect: an increase in trazodone plasma levels
2) Summary: Patients receiving trazodone therapy concurrently with keto
exposure to trazodone due to ketoconazole-mediated inhibition of CYP3A
of trazodone with ritonavir (another potent CYP3A4 inhibitor) produced in
concentration, prolongation of elimination half-life, increases in area unde
and decreased trazodone clearance. During concomitant use of trazodon
reported included nausea, hypotension, and syncope. Other signs and sy
trazodone exposure have included priapism, respiratory arrest, seizures,
Desyrel(R), 2003).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Consider a lower dose of trazodone if it is used
ketoconazole. Monitor patients receiving trazodone and ketoconazole for
sedation, nausea, hypotension, syncope, and/or priapism.
7) Probable Mechanism: inhibition of CYP3A-mediated trazodone metab

3.5.1.U Linezolid

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, h

status changes)
2) Summary: Linezolid is a reversible, nonselective inhibitor of monoamir interactions reported with the concomitant administration of selective sero and monoamine oxidase inhibitors (MAOIs), concurrent administration or trazodone and linezolid may result in CNS toxicity or serotonin syndrome HCl, 1993). Serotonin syndrome is a hyperserotonergic state characterize restlessness, myoclonus, changes in mental status, hyperreflexia, diapho There have been spontaneous reports of serotonin syndrome associated and serotonergic agents (Prod Info ZYVOX(R) IV injection, oral tablets, or and trazodone are used concomitantly, monitor closely for symptoms of s syndrome can be life-threatening. If serotonin syndrome develops, discon provide supportive care and other therapy as necessary (Boyer & Shanno
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: If linezolid and trazodone are used concomitantl of serotonin syndrome such as neuromuscular abnormalities (including hy rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hypera mydriasis, diaphoresis, and diarrhea), and mental status changes (includi Serotonin syndrome can be life-threatening. If serotonin syndrome develo agents and provide supportive care and other therapy as necessary (Boye
7) Probable Mechanism: inhibition of serotonin metabolism by monoamin
8) Literature Reports
a) In one case report, a 37-year-old male experienced symptoms of concomitant treatment with citalopram and linezolid. He was admitted right leg. His medical history consisted of hypertension, multiple myel passive-aggressive behavior, and adaptation trouble. The patient was resistant staphylococcus aureus (MRSA) with intravenous vancomyci was receiving oral citalopram 40 mg daily, olanzapine 2.5 mg daily, tr clonazepam 2 mg three times daily, hydromorphone 125 mg subcuta medications. On day five, the patient's infection improved and vancor discharged two days later on a regimen of oral linezolid 600 mg twice days of linezolid therapy, the patient reported having panic attacks ar linezolid, he was readmitted to the hospital for these symptoms, when tremors, excessive sweating, palpitations, and peribuccal numbness. mmHg) and heart rate (112 bpm) were elevated. On day two, his bloc he was still anxious and experiencing multiple panic attacks. Methotri bisoprolol 5 mg daily, and ondansetron 8 mg as needed were introdu increased to 12.5 mg/day. One day four, linezolid was suspected as a syndrome and was discontinued. Only one dose of linezolid remained five, the patient's level of anxiety decreased and blood pressure varie his symptoms subsided and blood pressure (140/80 mmHg) and hea normal (Bergeron et al, 2005).

3.5.1.V Mesoridazine
1) Interaction Effect: hypotension
2) Summary: Concomitant administration of trazodone with chlorpromazi additive hypotensive effects in two case reports. Withdrawal of trazodone hypotension (Asayesh, 1986h).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor blood pressure, particularly in patients v effect. Advise patient to rise slowly from laying or sitting position.
7) Probable Mechanism: additive hypotensive effects

3.5.1.W Methotrimeprazine
1) Interaction Effect: hypotension
2) Summary: Concomitant administration of trazodone with chlorpromazi additive hypotensive effects in two case reports. Withdrawal of trazodone hypotension (Asayesh, 1986d).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor blood pressure, particularly in patients v effect. Advise patient to rise slowly from laying or sitting position.
7) Probable Mechanism: additive hypotensive effects

3.5.1.X Nefazodone

1) Interaction Effect: increased trazodone serum concentrations
2) Summary: Substantial elevations are expected in trazodone serum co concomitantly with nefazodone, a CYP3A4 inhibitor (Prod Info Desyrel(R)
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Consider a lower dose of trazodone if it is used inhibitor such as nefazodone. Monitor patients receiving trazodone and ne including sedation, nausea, hypotension, syncope, and/or priapism.
7) Probable Mechanism: inhibition of CYP3A4-mediated trazodone metal

3.5.1.Y Nelfinavir

1) Interaction Effect: increased plasma concentrations of trazodone and i adverse effects (nausea, dizziness, hypotension, syncope)
2) Summary: Trazodone is metabolized by cytochrome P450 3A4 (CYP3 nelfinavir, which are cytochrome P450 3A substrates and inhibitors, may trazodone, causing increased trazodone plasma concentrations. Althoug nelfinavir and trazodone has not been studied, adverse effects such as na syncope have occurred following coadministration of trazodone and ritona when nelfinavir and trazodone are administered concomitantly. Reduction considered (Prod Info VIRACEPT(R) oral tablets, oral powder, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the coadministration of nelfina patients for signs of increased trazodone adverse effects (nausea, dizzine Consider reducing trazodone dosage when administering concomitantly w VIRACEPT(R) oral tablets, oral powder, 2005).
7) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated tra

3.5.1.Z Paroxetine

1) Interaction Effect: serotonin syndrome (hypertension, hyperthermia, m
2) Summary: There have been several reports of serotonin syndrome du selective serotonin reuptake inhibitors and antidepressants, including one and trazodone coadministration (George & Godleski, 1996c; Reeves & Bu 1996a). Serotonin syndrome is a rare but potentially fatal condition of ser characterized by hypertension, hyperthermia, myoclonus and changes in Further clinical studies or case reports are necessary to determine the inc serotonin syndrome associated with this drug combination.
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of paroxetine and trazodone sh Monitor patients for signs and symptoms of serotonin syndrome (hyperter mental status changes).
7) Probable Mechanism: additive serotonergic effects
8) Literature Reports
a) Serotonin syndrome was reported in a 29-year old woman taking patient was treated with trazodone 200 mg daily at bedtime for appro depression and insomnia. The patient's depressive symptoms were u trazodone was subsequently decreased to 50 mg daily at bedtime for mg every morning was added. Within 24 hours after the first dose of agitated, confused, shaky, and diaphoretic. Upon examination, the pa intermittent myoclonus in all extremities, hyperreflexia, tremor, and di antidepressant medications, the patient's symptoms resolved (Reeve
b) A 44-year old man developed symptoms characteristic of serotoni interaction between fluoxetine and trazodone. The patient had been t trazodone 100 mg daily for approximately two months before sympto experienced disorientation, tremor, diaphoresis, and anxiety, followed loss of consciousness. After the patient was treated with cyproheptac resolved over the next 30 minutes. Trazodone was discontinued and fluoxetine 40 mg daily without further complications (George & Godle

3.5.1.AA Perphenazine

1) Interaction Effect: hypotension

2) Summary: Concomitant administration of trazodone with chlorpromazi additive hypotensive effects in two case reports. Withdrawal of trazodone hypotension (Asayesh, 1986l).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor blood pressure, particularly in patients v effect. Advise patient to rise slowly from laying or sitting position.
7) Probable Mechanism: additive hypotensive effects

3.5.1.AB Phenytoin
1) Interaction Effect: increased phenytoin serum concentrations and an ir (ataxia, hyperreflexia, nystagmus, tremor)
2) Summary: Increased phenytoin serum concentrations have occurred i treatment with trazodone and phenytoin (Prod Info Desyrel(R), 2003d). Ph patient receiving concurrent treatment with the 2 drugs (Dorn, 1986).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Measure serum levels of phenytoin after initiatio discontinuation of trazodone; adjust dosage accordingly.
7) Probable Mechanism: unknown
8) Literature Reports
a) In 1 case concomitant administration of phenytoin and trazodone increases in phenytoin serum concentrations and phenytoin toxicity. may competitively inhibit the metabolism of phenytoin, binding of phe phenytoin excretion. It may be prudent to monitor phenytoin serum co the combination until further data is available (Dorn, 1986).

3.5.1.AC Pipotiazine
1) Interaction Effect: hypotension
2) Summary: Concomitant administration of trazodone with chlorpromazi additive hypotensive effects in two case reports. Withdrawal of trazodone hypotension (Asayesh, 1986).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor blood pressure, particularly in patients v effect. Advise patient to rise slowly from laying or sitting position.
7) Probable Mechanism: additive hypotensive effects

3.5.1.AD Prochlorperazine
1) Interaction Effect: hypotension
2) Summary: Concomitant administration of trazodone with chlorpromazi additive hypotensive effects in two case reports. Withdrawal of trazodone hypotension (Asayesh, 1986e).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor blood pressure, particularly in patients v effect. Advise patient to rise slowly from laying or sitting position.
7) Probable Mechanism: additive hypotensive effects

3.5.1.AE Promazine
1) Interaction Effect: hypotension
2) Summary: Concomitant administration of trazodone with chlorpromazi additive hypotensive effects in two case reports. Withdrawal of trazodone hypotension (Asayesh, 1986b).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor blood pressure, particularly in patients v effect. Advise patient to rise slowly from laying or sitting position.
7) Probable Mechanism: additive hypotensive effects

3.5.1.AF Promethazine
1) Interaction Effect: hypotension

2) Summary: Concomitant administration of trazodone with chlorpromazi additive hypotensive effects in two case reports. Withdrawal of trazodone hypotension (Asayesh, 1986j).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor blood pressure, particularly in patients v effect. Advise patient to rise slowly from laying or sitting position.
7) Probable Mechanism: additive hypotensive effects

3.5.1.AG Propiomazine
1) Interaction Effect: hypotension
2) Summary: Concomitant administration of trazodone with chlorpromazi additive hypotensive effects in two case reports. Withdrawal of trazodone hypotension (Asayesh, 1986i).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor blood pressure, particularly in patients v effect. Advise patient to rise slowly from laying or sitting position.
7) Probable Mechanism: additive hypotensive effects

3.5.1.AH Ritonavir
1) Interaction Effect: an increase in trazodone plasma levels and increase
2) Summary: Ritonavir inhibits the CYPA-mediated metabolism of trazod with trazodone produced a 34% (95% CI) increase in peak plasma trazod (95%CI) increase in total area under the concentration-time curve, and a life. Patients should be monitored for increased trazodone side effects inc syncope and hypotension. A reduction in trazodone dosing may be warra liquid-filled capsule, oral solution, 2005; Greenblatt et al, 2003a).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Patients receiving trazodone and ritonavir shoul sedative effects and hypotension. Consider a reduction in trazodone dosi
7) Probable Mechanism: inhibition of CYP3A-mediated trazodone metab
8) Literature Reports
a) Coadministration of ritonavir and trazodone produces a significant trazodone concentration (Cmax), prolongation of elimination half-life, reduction in oral clearance. Ten subjects participated in a randomize study with 7 days elapsing between treatments. The four treatment c placebo to match trazodone, plus placebo to match ritonavir; Treatme ritonavir placebo; Treatment C: placebo to match trazodone plus ritor Treatment D: trazodone 50 mg plus ritonavir 200 mg X 4 doses. Rito coadministration produced a significant increase in trazodone Cmax 842 +/- 64 ng/mL (treatment B) and 1125 +/- 111 ng/mL (treatment D SE elimination half-life in treatment B was 6.7 +/- 0.7 h and in treatme 0.05). The mean +/- SE total AUC for treatment B was 5.86 +/- 0.83 r was 13.88 +/- 2.89 (p less than 0.01). The mean +/- SE apparent ora B was 155 +/- 23 and for treatment D was 75 +/- 12 (p less than 0.00 psychomotor performance (the DSST), and a quantitatively small incr EEG caused by trazodone were all enhanced by coadministration of

3.5.1.AI St John's Wort
1) Interaction Effect: an increased risk of serotonin syndrome (hypertensi mental status changes)
2) Summary: One pooly defined case of a patient developing serotonin s therapy with St. John's Wort has been reported (DeMott, 1998a). Four ca serotonin syndrome-like symptoms following the addition of St. John's Wo case with nefazodone therapy (Lantz et al, 1999). A patient exhibited a s sedative/hypnotic intoxication after adding St. John's Wort to paroxetine t Wort is thought to inhibit serotonin reuptake and may have mild monoami (Singer et al, 1999; Thiede & Walper, 1994), which when added to selecti may result in serotonin syndrome. This interaction may be extended to tra SSRI, inhibits serotonin uptake. Serotonin syndrome is a condition of ser manifests as restlessness, myoclonus, changes in mental status, hyperre tremor. If the syndrome is not recognized and correctly treated, death can

3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Avoid concomitant use of St. John's Wort and tr
trazodone of up to 15 hours, St. John's Wort should be avoided for at leas
trazodone discontinuation.
7) Probable Mechanism: additive pharmacologic effects resulting in exce
8) Literature Reports
a) A patient discontinued trazodone treatment, replacing it with St. Jo
patient then experienced mental confusion, muscle twitching, sweatir
authors characterized as serotonin syndrome. Dosage for neither of t
the exact time frame of the reaction (DeMott, 1998).

3.5.1.AJ Thiethylperazine
1) Interaction Effect: hypotension
2) Summary: Concomitant administration of trazodone with chlorpromazi
additive hypotensive effects in two case reports. Withdrawal of trazodone
hypotension (Asayesh, 1986g).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor blood pressure, particularly in patients v
effect. Advise patient to rise slowly from laying or sitting position.
7) Probable Mechanism: additive hypotensive effects

3.5.1.AK Thioridazine
1) Interaction Effect: hypotension
2) Summary: Concomitant administration of trazodone with chlorpromazi
additive hypotensive effects in two case reports. Withdrawal of trazodone
hypotension (Asayesh, 1986m).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor blood pressure, particularly in patients v
effect. Advise patient to rise slowly from laying or sitting position.
7) Probable Mechanism: additive hypotensive effects
8) Literature Reports
a) In one study, 11 depressed patients received trazodone 150 mg o
weeks. In addition, thioridazine 40 mg daily was given for one week,
obtained prior to and after the coadministration. Thioridazine significa
concentrations of both trazodone and m-chlorophenylpiperazine, the
These results suggest the involvement of cytochrome P4502D6 (CYP
trazodone, since thioridazine is a known inhibitor of this isozyme (Yas

3.5.1.AL Tipranavir
1) Interaction Effect: increased plasma concentrations of trazodone and i
adverse effects (nausea, dizziness, hypotension, syncope)
2) Summary: Coadministration of tipranavir/ritonavir with trazodone may i
trazodone metabolism, causing increased trazodone plasma concentratio
between tipranavir and trazodone has not been studied, adverse effects s
hypotension and syncope have occurred following coadministration of traz
caution is advised when tipranavir/ritonavir and trazodone are administere
a lower dose of trazodone (Prod Info APTIVUS(R) oral capsules, 2006).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concurrent administration of tipranavir/ritonavir
trazodone plasma concentrations. Use caution when these agents are co
a lower trazodone dose (Prod Info APTIVUS(R) oral capsules, 2006). Mor
increased trazodone adverse effects (nausea, dizziness, hypotension, syr
7) Probable Mechanism: inhibition of CYP3A4-mediated trazodone metab
8) Literature Reports
a) Coadministration of ritonavir and trazodone produces a significant
trazodone concentration (Cmax), prolongation of elimination half-life,
reduction in oral clearance. Ten subjects participated in a randomized
study with 7 days elapsing between treatments. The four treatment co
placebo to match trazodone, plus placebo to match ritonavir; Treatme

ritonavir placebo; Treatment C: placebo to match trazodone plus ritor
Treatment D: trazodone 50 mg plus ritonavir 200 mg X 4 doses. Ritor
coadministration produced a significant increase in trazodone Cmax
842 +/- 64 ng/mL (treatment B) and 1125 +/- 111 ng/mL (treatment D
SE elimination half-life in treatment B was 6.7 +/- 0.7 h and in treatme
0.05). The mean +/- SE total AUC for treatment B was 5.86 +/- 0.83 r
was 13.88 +/- 2.89 (p less than 0.01). The mean +/- SE apparent oral
B was 155 +/- 23 and for treatment D was 75 +/- 12 (p less than 0.00
psychomotor performance (the DSST), and a quantitatively small incr
EEG caused by trazodone were all enhanced by coadministration of

3.5.1.AM Trifluoperazine

1) Interaction Effect: hypotension
2) Summary: Concomitant administration of trazodone with chlorpromazi
additive hypotensive effects in two case reports. Withdrawal of trazodone
hypotension (Asayesh, 1986c).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor blood pressure, particularly in patients v
effect. Advise patient to rise slowly from laying or sitting position.
7) Probable Mechanism: additive hypotensive effects

3.5.1.AN Triflupromazine

1) Interaction Effect: hypotension
2) Summary: Concomitant administration of trazodone with chlorpromazi
additive hypotensive effects in two case reports. Withdrawal of trazodone
hypotension (Asayesh, 1986k).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor blood pressure, particularly in patients v
effect. Advise patient to rise slowly from laying or sitting position.
7) Probable Mechanism: additive hypotensive effects

3.5.1.AO Venlafaxine

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Concurrent use of trazodone and venlafaxine resulted in sy
a 50-year-old male who was also taking methadone (McCue & Joseph, 2(
are used concomitantly, monitor closely for symptoms of serotonin syndrc
life-threatening. If serotonin syndrome develops, discontinue the offendinç
care and other therapy as necessary (Boyer & Shannon, 2005).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: A case of serotonin syndrome was reported with
and venlafaxine (McCue & Joseph, 2001). If trazodone and venlafaxine a
closely for symptoms of serotonin syndrome such as neuromuscular abnc
tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), au
tachycardia, mydriasis, diaphoresis, the presence of bowel sounds, and d
changes (including agitation and delirium). Serotonin syndrome can be life
syndrome develops, discontinue the offending agents and provide suppor
necessary (Boyer & Shannon, 2005).
7) Probable Mechanism: additive pharmacologic effects
8) Literature Reports

a) A 50-year-old male experienced serotonin syndrome 18 days afte
trazodone. Venlafaxine extended release for depression, trazodone f
dependence, and docusate were started after he was admitted to the
anhedonia, hopelessness, insomnia, and suicidal ideation. The dose
over 7 days to 225 mg/day. Eighteen days after hospitalization, he be
experienced myoclonic jerking, gross tremulousness, and diaphoresis
signs were unremarkable. All his drugs were discontinued because h
worsened. Intravenous hydration was initiated. He significantly impro
and docusate were restarted and mirtazapine was started. He experi
Significant past medical history includes selective serotonin reuptake
methadone, without any similar symptoms (McCue & Joseph, 2001).

3.5.2 Drug-Food Combinations

3.5.2.A Food

1) Interaction Effect: increased time to peak levels
2) Summary: Although the rate of absorption of trazodone is reduced whe
may be a slight increase in the total amount of drug absorbed. The maxim
up to 30%, and the time to reach peak levels is prolonged (Nilsen & Dale,
Rawls, 1982). Trazodone should be taken shortly after a meal or light sna
3) Severity: minor
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Trazodone should be taken shortly after a meal
7) Probable Mechanism: delayed absorption

4.0 Clinical Applications

4.1 Monitoring Parameters

A) Trazodone Hydrochloride
1) Toxic
a) Laboratory Parameters
1) blood pressure (Prod Info Desyrel(R) Oral Tablet, 2005)
2) ECG in patients with cardiac disease (Prod Info Desyrel(R) Oral T
3) white blood cell and differential count; in patients with signs of infe
Tablet, 2005)
b) Physical Findings
1) Monitor patients receiving antidepressants for worsening of depre
changes in behavior, especially at the initiation of therapy or when th
Such monitoring should include at least weekly face-to-face contact v
members or caregivers during the initial 4 weeks of treatment, then vi
4 weeks, then at 12 weeks, and then as clinically indicated beyond 1
should be advised of the need for close observation (i.e., daily obser
communication with the prescriber (Anon, 2004).
2) Patients who experience symptoms of anxiety, agitation, panic att
hostility, impulsivity, akathisia, hypomania, or mania may be at an inc
depression or suicidality. If these symptoms are observed, therapy sh
be necessary to discontinue medications when symptoms are severe
part of the patient's initial symptoms (Anon, 2004).

4.2 Patient Instructions

A) Trazodone (By mouth)
Trazodone

Treats depression, and depression with anxiety.

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

How to Use This Medicine:
Tablet
Your doctor will tell you how much of this medicine to use and how often.
changed several times in order to find out what works best for you. Do no

more often than your doctor tells you to.
It is best to take this medicine with food or milk.
This medicine should come with a Medication Guide. Read and follow the
doctor or pharmacist if you have any questions. Ask your pharmacist for t
have one. Your doctor might ask you to sign some forms to show that you

If a Dose is Missed:
If you miss a dose or forget to use your medicine, use it as soon as you c
dose, wait until then to use the medicine and skip the missed dose. Do nc
for a missed dose.

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

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over
and herbal products.
Make sure your doctor knows if you are taking digoxin, phenytoin (Dilantir
you drowsy such as sleeping pills, tranquilizers, other medicine for depres
narcotic pain killers.
Tell your doctor if you are using carbamazepine (Tegretol®), an antiviral c
Crixivan®, Norvir®), or a medicine to treat fungal infections (such as fluco
ketoconazole, Diflucan®, Nizoral®, Sporanox®).
Make sure your doctor knows if you are also using medicine to decrease y
pressure medicines are atenolol, hydrochlorothiazide (HCTZ), lisinopril, m
Diovan®, Lotrel®, Norvasc®, Prinivil®, Toprol®, and Zestril®.

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant or breast feeding, or if y
For some children and teenagers, this medicine can increase thoughts of
leaflet are true for a child or teenager who is using this medicine.Tell your
feel more depressed. Also tell your doctor right away if you have thoughts
any unusual thoughts or behaviors that trouble you, especially if they are
sure your caregiver knows if you have trouble sleeping, get upset easily, h
start to act reckless. Also tell your doctor if you have sudden or strong fee
angry, restless, violent, or scared.Let your doctor know if you or anyone ir
(manic-depressive) or has tried to commit suicide.
Do not stop using this medicine suddenly without asking your doctor. You
your dose before stopping it completely.
You may need to take trazodone for 2 to 4 weeks before you start to feel l
Get up slowly from a lying or sitting position to decrease dizziness caused
This medicine may make you dizzy or drowsy. Avoid driving, using machi
could be dangerous if you are not alert.
Make sure any doctor or dentist who treats you knows that you are using
stop using this medicine several days before having surgery or medical te
Your doctor will need to check your progress at regular visits while you ar
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
chest tightness, trouble breathing.
Painful, prolonged erection of your penis.
Skin rash.
Unexplained fever or sore throat.

If you notice these less serious side effects, talk with your doctor:
Changes in vision, such as trouble focusing.
Constipation or diarrhea.
Drowsiness or dizziness.
Dry mouth.
Headache.
Nausea, vomiting, upset stomach.

Nervousness, trouble sleeping.

If you notice other side effects that you think are caused by this medicine, tell y

4.3 Place In Therapy

A) Depression is a complicated disorder and consequently this disease's treatmer most prevalent diagnostic syndromes among affective disorders are major depress tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), ar inhibitors (MAOIs) are considered the most effective agents for treating major depr disorders, lithium is the preferred therapy; carbamazepine and valproic acid are co

B) Trazodone is equally effective for treating mild typical or endogenous depressic questions remain as to the effectiveness of trazodone for treating moderate-to-sev patients seem to have difficulty tolerating adequate doses. Trazodone possesses t without anticholinergic effects. Other advantageous characteristics of this agent inc anxiety disorders, agitation, obsessive compulsive behavior, and a comparatively s following overdoses. Trazodone may also be safely combined with MAOIs for refra of trazodone include a high incidence of priapism, orthostatic hypotension, and indi and ventricular arrhythmias. However, compared with the TCAs, trazodone is still c

C) Trazodone does have a place in therapy for treating endogenous or typical dep secondary to the TCAs, the SSRIs, and the MAOIs in most circumstances. Trazod without anticholinergic effects may be useful in elderly patients refractory to standa patients with an unusually high potential for suicide, trazodone may be considered that commonly treat elderly depressed patients, refractory depressed patients, or o threatening suicide should consider trazodone for formulary inclusion.

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) Trazodone, which was first synthesized in 1966, represents a different clas triazolopyridines. Structurally, it does not bear any similarity to tricyclic antidep antidepressants, or MAO inhibitors. The antidepressant activity of trazodone a selectively inhibit serotonin reuptake. At low doses, trazodone appears to act a higher doses as an agonist (Maj et al, 1979; Stefanini et al, 1976).

2) Unlike other antidepressants, trazodone does not potentiate catecholamine It does appear to have a sedative effect and slight muscle relaxant properties, (Silvestrini et al, 1968). Trazodone does not have any significant effect on prol 1979)(Rolandi et al, 1981).

3) Trazodone appears to be equally effective in bipolar and unipolar depressic antidepressant therapy is its short onset of action and low incidence of anticho effects. However, some studies have indicated the onset of action of trazodon (Rawls, 1982a; Brogden et al, 1981; Rickels, 1981). Some data has suggested which may be less than or equal to other benzodiazepines; however, sufficient determine that these effects are related directly to properties of the drug or sec existing depression.

B) REVIEW ARTICLES

1) A comprehensive review of the second-generation antidepressant agents (trazodone, nomifensine) has been presented (Caccaro & Siever, 1985).

2) Other uses of antidepressant agents, including enuresis, bulimia, anorexia pain, migraine headache, and peptic ulcer disease have been reviewed (Orsul

3) A review of clinical guidelines for utilizing antidepressants in the treatment is available (Salzman, 1985).

4) Drug-interactions of antidepressants are reviewed in German language (Za

4.5 Therapeutic Uses

Trazodone

Trazodone Hydrochloride

4.5.A Trazodone

Dementia

Electroconvulsive therapy

4.5.A.1 Dementia
See Drug Consult reference: BEHAVIORAL AND PSYCHOLOGICAL SY

4.5.A.2 Electroconvulsive therapy
See Drug Consult reference: DRUGS FOR SEIZURE PROLONGATION I

4.5.B Trazodone Hydrochloride

Adverse reaction to drug - Insomnia

Agoraphobia

Alcohol withdrawal syndrome

Benzodiazepine withdrawal

Chronic pain

Dementia

Depression

Diabetic neuropathy

Erectile dysfunction; Diagnosis

Essential tremor

Insomnia

Migraine, Pediatric; Prophylaxis

Neuroleptic-induced acute akathisia

Schizophrenia

4.5.B.1 Adverse reaction to drug - Insomnia

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE

b) Summary:

Effective for treatment of INSOMNIA induced by monoamine oxidase

c) Adult:

1) In a small double-blind, placebo-controlled, crossover trial (n=7), a TRAZODONE 50 milligrams each evening improved sleep disturbanc who had responded to brofaromine, but who had experienced insomr oxidase inhibitor (MAO-I). Mean number of nightly awakenings and n lower after trazodone therapy compared with baseline (p=0.019 and Subjectively, some patients felt they had better and deeper sleep with mild. Larger controlled trials are needed (Haffmans & Vos, 1999).

2) The benefits of trazodone in the treatment of insomnia secondary (MAOI) therapy were demonstrated in a small, open study (Nierenbe patients with depression were treated with either tranylcypromine, ph developed insomnia after receiving MAOI therapy for 5 to 60 days. Tr 200 milligrams daily (mean, 85 milligrams daily) was reported to prod 12 patients (92%) within 1 week of treatment; 9 of the 13 patients we

inhibitors with trazodone without the occurrence of intolerable advers
are required to further evaluate the efficacy of trazodone in this clinic

4.5.B.2 Agoraphobia

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE

b) Summary:

Effective for symptomatic improvement

c) Adult:

1) Trazodone 300 milligrams daily was effective in reducing anxiety,
symptoms in outpatients with PANIC DISORDER or agoraphobia wit
study involving 11 patients (Mavissakalian et al, 1987).

4.5.B.3 Alcohol withdrawal 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

b) Summary:

Appears to be beneficial in the treatment of acute alcohol withdrawal

c) Adult:

1) Total abstinence was reported after 90 days of trazodone treatme
patient open study. After completing acute detoxification (mean perio
(50 to 100 milligrams (mg) per day) and tiapride (300 to 600 mg/day),
detoxification program and began trazodone therapy with daily doses
(mean 135 mg). Baseline and 90-day Discan scale scores for anxiety
exhibited a significant reduction in mean score at the end of the trial (
abstinence combined with the rate of controlled drinking patterns was
drugs used in this indication, as was the recidivism rate (Janiri et al, 1
2) Seventeen chronic alcoholics abruptly stopped drinking ethanol a
trazodone 100 milligrams/day. Based on the Hamilton anxiety rating s
significant global improvements and regression of pre-treatment clinic
depression, fear, and insomnia. After 3 to 5 days of trazodone therap
completely. It is thought that trazodone is beneficial due to the dopam
activity (Roccatogliata et al, 1980).

4.5.B.4 Benzodiazepine withdrawal

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

b) Summary:

Effective as an aid to discontinuing benzodiazepine in a small study

c) Adult:

1) Ten patients experienced generally mild and transitory benzodiaz
receiving trazodone (100 mg three times a day) during a 2- to 4-week
benzodiazepine dependence. After their benzodiazepines were progr
discontinued, the patients were discharged on trazodone 300 milligra
benzodiazepine-free during a 1-year follow-up and showed significan
(300 to 185 milligrams/day) and in Hamilton Rating Scales scores for
screens were not performed; benzodiazepine abstinence was determ
general practitioner assessments (Ansseau & De Roeck, 1993).

4.5.B.5 Chronic pain

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

b) Summary:
NOT effective for relief of BURNING MOUTH SYNDROME in a small

c) Adult:
1) An 8-week course of oral TRAZODONE 200 milligrams every eve analgesic efficacy for CHRONIC MOUTH PAIN than did placebo in a weeks, patient-rated visual analog pain scores dropped by 13.9 and trazodone and control groups (NS). Overall, 8 of 11 (73%) trazodone (76%) placebo-treated patients rated themselves as 'improved' (NS). more dizziness (p less than 0.001) and drowsiness (p less than 0.05) 1999).

4.5.B.6 Dementia

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

b) Summary:
May offer some benefit to patients with aggressive behavior or repetit dementia

c) Adult:
1) A pilot open-label study found that oral TRAZODONE produced s behavior of 14 consecutive patients (mean age 70.5 years) with FRO diagnosed according to criteria of the Lund and Manchester Groups (received trazodone 50 milligrams (mg) 3 times a day, followed by a 2 day. Ratings on the Neuropsychiatric Inventory (NPI) showed signific aggression, anxiety, and irritability, comparing scores after 4 weeks c than 0.05). After completion of the 300-mg dosing period, significant disinhibition, and aberrant motor behavior were also noted (p less tha 1999).
2) Trazodone was effective in the treatment of PALILALIA, a conditic involuntary repetition (two or more times) of a phrase or word, in an 8 dementia. Within three weeks of treatment, an oral dose level of 300 and the palilalia was no longer evident. The patient had also exhibite and aggressiveness. These conditions disappeared as well and the p sedation. The patient died 9 months later but had no further episodes that time (Serra-Mestres et al, 1996).
3) Trazodone, gradually increased to 300 milligrams/day, effectively SCREAMING (10 to 12 hours per day) of a 84-year-old psychiatric pa episodes stopped 2 weeks after receiving trazodone, and no serious Her repetitive screaming was previously unaltered by trials of either h hydroxyzine (Pasion & Kirby, 1993).
4) Combined therapy with trazodone and tryptophan was effective in dementia (Wilcock et al, 1987). Trazodone 50 milligrams two times a milligrams two times a day, with dosing adjustments to achieve thera effects, was reported effective in improving aggressiveness in 4 of 6 dementia.
5) One case report described benefits of a combination of trazodone L-tryptophan (up to 2.5 grams daily) in the treatment of disordered be in an 82-year-old woman with moderately advanced dementia (Greer

4.5.B.7 Depression

FDA Labeled Indication

a) Overview
FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE

b) Summary:
Effective for depression with or without prominent anxiety (Prod Info I

c) Adult:
1) In a randomized trial of 379 patients from 16 centers, patients rec milligrams/day, imipramine 100 to 300 milligrams/day, or placebo for Hamilton scores were reduced by 25% in the placebo-treated patient

imipramine-treated patients. Anticholinergic effects were much more imipramine than in patients treated with trazodone or placebo. Fifteer 44% of the imipramine patients had dry mouth. Blurred vision occurre imipramine-treated patients. Bowel disturbances occurred in 8% and urine flow in 1% and 4%, respectively (Gershon & Newton, 1980b).
2) A year-long study was conducted in 79 subjects to evaluate the lo trazodone compared to imipramine in the treatment of primary depres (36%) and 7 (24%) patients remained on either trazodone or imipram found to be more effective in HAM-D illness rating and clinical global statistical significance not presented). Anticholinergic side effects wer imipramine group but drowsiness was more frequent in the trazodone
3) In a double-blind study of 60 geriatric patients receiving trazodone milligrams/day) or imipramine (average dose 145 milligrams/day) for treatment of unipolar depression, both trazodone and imipramine sho significant improvement in the Hamilton depression scale for both dru difference in the Beck depression scale between trazodone and imipr efffects seen with the trazodone-treated patients (Gerner et al, 1980b
4) Several reports have suggested efficacy of trazodone in the treatr suggesting the drug has anxiolytic effects separate from its antidepre One study has reported that trazodone 75 mg daily and diazepam 15 effective than placebo in the treatment of anxiety. In the treatment of was reported superior to diazepam. Another report indicated that traz daily had definite anxiolytic properties, but it was not superior to chlor (Rawls, 1982c).
5) Many clinical trials have compared the effectiveness of trazodone studies found trazodone to be as effective as imipramine in treating d than placebo, with trazodone causing more sedation but fewer antich (Davis & Vogel, 1981; Mann et al, 1980; Gershon et al, 1981; Kellam Feighner, 1980b; Escobar et al, 1980a).

4.5.B.8 Diabetic neuropathy

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

b) Summary:

61.3% rate of symptomatic improvement; 22.6% complete relief
Controlled studies needed
Trazodone has been used to treat painful diabetic neuropathy (P of chronic pain (Manufacturer comment., 5/88.; Panel comment.,

c) Adult:

1) In a prospective, open-label study, 19 of 31 adult patients (61.3%) diabetic neuropathy with use of oral TRAZODONE 50 or 100 milligra patients (22.6%) obtained complete relief. Therapeutic failures includ no relief (100-mg doses) and 8 patients (25.8%) who discontinued th doses), which included dizziness (5), headache (2), and insomnia (1) 50 mg/day at bedtime; after 2 weeks, doses were raised to 100 mg/d and had not experienced complete relief (Wilson, 1999).

4.5.B.9 Erectile dysfunction; Diagnosis

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

b) Summary:

No efficacy shown in the treatment of ERECTILE DYSFUNCTION

c) Adult:

1) Oral trazodone in a total daily dose of 150 milligrams (mg) was no the treatment of erectile dysfunction in a double-blind, placebo-contro run-in period, patients randomized to the trazodone treatment group t morning and two 50-mg capsules in the evening for 4 weeks; patients identical capsules on the same schedule. To avoid selection bias, the impotence was not identified until after completion of the treatment re

results demonstrated no significant difference (p=0.98) between the t
group treated with placebo. Patients with psychogenic impotence res
other patients, 23% versus 15%, respectively, but the difference was
(p=0.45) (Meinhardt et al, 1997a).
2) A 3-month course of TRAZODONE 50 milligrams orally at bedtime
placebo for treatment of erectile dysfunction, according to a randomiz
the group receiving trazodone, 19% reported improved erections com
placebo (p less than 0.5) (Costabile & Spevak, 1999).

4.5.B.10 Essential tremor

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

b) Summary:

Efficacy suggested in early case report, but not supported in subsequ

c) Adult:

1) Trazodone 150 milligrams orally per day was ineffective in the trea
in a small, controlled study (Koller, 1989). This study suggests that al
neurotransmission are most likely not involved in the pathophysiology
2) Trazodone 100 to 150 milligrams daily, in divided doses, appeared
of essential tremor in 2 patients (McLeod & White, 1986). Improveme
after 3 weeks of treatment; both patients had not responded to propra
milligrams daily).

4.5.B.11 Insomnia

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

b) Summary:

Improved sleep latency and duration in primary insomnia, although d
placebo diminished over time

c) Adult:

1) Single-dose TRAZODONE orally at bedtime improved insomnia ir
accompanied by a depressive state (concomitant hypnotics were pro
study). Patients received bedtime trazodone 50 milligrams (mg)/day f
of either 50-mg (n=16), 75-mg (n=6), or 100-mg doses (n=11). Score
(HAS) (related to sleep disorders) and the Hamilton Rating Scale for
morning awakening, lack of sound sleep, difficulty in initiating sleep) v
weeks of trazodone therapy (p values not reported) and showed furth
(p=0.01, HAS scores for 50- and 100-mg groups). After 6 weeks, tota
prolonged for patients receiving 50-mg (p less than 0.05) or 100-mg c
Depressive state symptoms also improved. No one dropped out due
considered the 100-mg nightly dose to be the most effective (Mashiko
2) Trazodone 50 milligrams (mg) before bedtime was somewhat effe
insomnia in a parallel-group, double-blind, 2-week randomized study
zolpidem 10 mg and placebo (n=278). At the end of the first week, th
lower in trazodone-treated patients (p=0.01), relative to placebo. How
week, sleep latency in trazodone-treated patients (54.5 minutes) did
patients treated with placebo (64.7 minutes). Sleep duration was sign
with trazodone therapy (366.4 minutes) than with placebo (344.6 min
difference in these 2 treatment groups was no longer significant at th
clinical significance in both parameters was primarily due to improver
over time while the level of improvement with both drugs was essenti
week of treatment. Zolpidem was slightly superior to both trazodone a
(Walsh et al, 1998a).

4.5.B.12 Migraine, Pediatric; Prophylaxis

a) Overview

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

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

b) Summary:
May be effective in decreasing frequency and duration of headaches
See Drug Consult reference: MIGRAINE - RECOMMENDATIONS FO AND ADOLESCENTS

c) Pediatric:
1) The effectiveness of trazodone in the prophylaxis of PEDIATRIC M measured in a double-blind, placebo-controlled study. Thirty-five pedi subjects received either trazodone (1 milligram/kilogram/day) or place week washout period, the groups were switched to the opposite treat There was no difference in frequency or duration of migraine attacks either the first 12 weeks or during the 4-week washout period. During the trazodone group was significantly improved in relation to both freq compared to the placebo group. The strong placebo effect demonstra not unusual in migraine studies, and the authors concluded that trazo antidepressants in the prophylaxis of pediatric migraine headaches (E

4.5.B.13 Neuroleptic-induced acute akathisia

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

b) Summary:
Improved symptoms of neuroleptic-induced akathisia in pilot study

c) Adult:
1) Symptoms of neuroleptic-induced akathisia improved following tra schizophrenia. In an open-label, pilot study, schizophrenic patients (n received trazodone (50 milligrams (mg)/day for 1 day, then increased addition to their current, stable, neuroleptic medication for 5 days. Me scores improved significantly from baseline to endpoint (p less than 0 anxiety, and psychosis were also improved from baseline to endpoint of insomnia during treatment. All patients withdrawn from treatment a reemergence of neuroleptic-induced akathisia within 1 day after the n when therapy was re- initiated in one patient, relief was reported with (Stryjer et al, 2003).

4.5.B.14 Schizophrenia

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

b) Summary:
Appears to have no effect on psychotic episodes, but may improve so depression

c) Adult:
1) Trazodone has been evaluated in the treatment of schizophrenia, drug has any effect on psychotic episodes (Deutsch et al, 1977; Sing reports trazodone did appear to improve depression associated with s prove useful in these types of patients. Trazodone apparently does n as opposed to other tricyclic antidepressants (Rawls, 1982c).

4.6 Comparative Efficacy / Evaluation With Other Therapies

Amitriptyline

Chlordiazepoxide

Clorazepate

Desipramine

Dothiepin

Doxepin

Fluoxetine

Imipramine

Mianserin

Triazolam

Venlafaxine

Zolpidem

4.6.A Amitriptyline

Depression

Impaired cognition

Rheumatoid arthritis

4.6.A.1 Depression

a) SUMMARY: Many comparative studies have reported that trazodone i
the treatment of endogenous depression (Rickels & Case, 1982; Goldberg
Finnerty, 1980; Goldberg et al, 1981).

b) In a study of 40 depressed patients (20 agitated, 20 retarded), patients
milligrams (mg) three times a day or trazodone 50 mg three times a day a
washout period (LaPierre et al, 1980). The agitated, depressed patients w
and the retarded, depressed patients who were treated with trazodone we
than the agitated, depressed patients on trazodone and the retarded, dep
Based on multivarient analysis of the clinical global impression, amitriptyli
agitated depressed patients and trazodone was more effective in retarded

c) The efficacy of trazodone was compared with amitriptyline and placebo
depression in 202 outpatients (Rickels & Case, 1982). Patients were rand
milligrams (mg), amitriptyline 25 mg, or lactose placebo. Initial dose of all
for 7 days followed by adjustment to the maximum of eight capsules daily
effective than placebo with clinical efficacy of each agent being similar. Th
toxicity was lower in trazodone-treated patients. This study suggests that
as effective as amitriptyline 75 to 200 mg in treating depression in outpati
less anticholinergic toxicity.

d) No significant difference between trazodone 150 to 300 milligrams (mg
150 mg/day in antidepressant effect or onset was seen in a study of 50 pa
depression (Carney et al, 1984). Trazodone demonstrated an early superi
caused dry mouth more commonly; other side effects were comparable.

4.6.A.2 Impaired cognition

a) The effects of trazodone 100 milligrams (mg), amitriptyline 50 mg, and
healthy, geriatric patients in a double-blind, cross-over study (Burns et al,
tracking multiple stimuli to perform simultaneous tasks (DA), rapidly coord
output (CTT), processing information gathered in short-term memory (VBI
task (vigilance). Amitriptyline impaired DA, CTT, and vigilance, while trazo
authors concluded that trazodone caused less impairment of the central n
amitriptyline.

4.6.A.3 Rheumatoid arthritis

a) Amitriptyline 1 milligram/kilogram (mg/kg) per day for 3 days, followed
reported superior to both desipramine 1 mg/kg/day for 3 days, followed by

trazodone 1.5 mg/kg/day for 3 days, followed by 3 mg/kg/day thereafter, i
depressed and nondepressed patients with rheumatoid arthritis (Frank et
regimens produced significant decreases in pain relative to baseline, only
better than placebo; amitriptyline was associated with a significant reducti
tender joints.

4.6.B Chlordiazepoxide

4.6.B.1 Anxiety

a) No significant difference in improvement of anxiety in patients treated
chlordiazepoxide has been reported (Wheatley, 1976). A double-blind stu
mg/day and chlordiazepoxide for a 4-week period using the Hamilton Anx
from each treatment group were very much improved. Ten trazodone and
were much improved and 10 trazodone and 11 chlordiazepoxide patients
worse. Three patients were not evaluable. For both treatment groups drov
adverse effect with 22 patients experiencing the effect.

4.6.C Clorazepate

Adjustment disorder - Cancer

Adjustment disorder - HIV infection

4.6.C.1 Adjustment disorder - Cancer

a) SUMMARY: TRAZODONE may have equal or greater efficacy compa
treatment of adjustment disorders in breast-cancer patients; trazodone an
and tolerability.

b) A small, double-blind pilot study (n=23; efficacy analysis=18) found tha
TRAZODONE had equal or greater benefit compared with CLORAZEPAT
adjustment disorders (DSM-III-R) accompanied by anxiety or depressed r
emotion and conduct (Razavi et al, 1999). Included were women with a 1
Hospital Anxiety and Depression Scale (HADS). Enrollees were randomiz
milligrams (mg)/day (n=13) or oral clorazepate 10 mg/day (n=10), with up
days. Trazodone mean daily dose was 111.5 mg, and clorazepate, mean
investigator ratings on the Clinical Global Impression (CGI) scale showed
group (10 of 11) and 57.1% of the clorazepate group (4 of 7) were 'very m
'minimally improved' (p=0.14). Improvement on the Global Severity Index
trazodone-treated patients (-0.68) compared with clorazepate-treated pati
adverse events rated as severe occurred in the trazodone and 5 severe a
clorazepate group. One patient receiving trazodone withdrew due to adve

4.6.C.2 Adjustment disorder - HIV infection

a) SUMMARY: TRAZODONE may be more efficacious than CLORAZEP
adjustment disorders in patients with HIV; trazodone appeared to have gr

b) A small, double-blind trial (n=21) found a 28-day course of TRAZODO
treatment than CLORAZEPATE for HIV-positive patients with adjustment
accompanied by anxiety or depressed mood and/or mixed disturbance of
were patients with a 14 or greater score on the French Hospital Anxiety a
Enrollees were randomized to oral trazodone 50 milligrams/day (mg/day)
mg/day (n=11), with upward titration of both drugs over 5 days. After 28 d
Clinical Global Impression (CGI) scale showed that 80% of the trazodone
clorazepate group were 'very much improved', 'improved', or 'minimally im
appeared to be more marked in the trazodone group for depressive symp
slightly more pronounced in the clorazepate group for anxiety symptoms (
adverse event occurred in 8 clorazepate-treated patients and 6 trazodone
treatment, doses were reduced in 1 patient treated with trazodone and 2 t
adverse effects. More adverse events and a higher number of severe adv
clorazepate treatment. One patient in each group withdrew due to adverse
to lack of efficacy (De Wit et al, 1999).

4.6.D Desipramine

4.6.D.1 Depression

a) A double-blind study of 30 patients with endogenous, endoreactive, re
compared the effects of trazodone 200 to 400 mg/day to desipramine. Aft

similar results for both drugs for the parameters of depression, suicide, ins agitation as measured by the Hamilton Rating scale. Trazodone-treated p anxiety than did desipramine treated patients (Piccione et al, 1975).

4.6.E Dothiepin

4.6.E.1 Depression

a) No significant differences in efficacy or type of adverse effects were se with trazodone in 196 patients with mixed anxiety/depression (Moon et al, preferable to dothiepin because of lesser severity of side effects. In a 6-w study, either trazodone 150 mg (n=97) or dothiepin 75 mg (n=99) were ac included the 17- item and 21-item Hamilton Depression Rating Scales (HI Scale (HARS), and the investigator's judgement of global severity and imp improvement in depression scores (P=0.0001) and anxiety scores (P=0.0 Global severity significantly improved in both groups; at week 6, improven improved for 54 patients (71%) in the trazodone group and 52 patients (69 Although types of adverse effects were similar for both groups, the trazod proportion of mild symptoms compared with the dothiepin group; at weeks reported a lower percentage of symptoms as severe.

b) Dothiepin (75 to 150 mg/d) and trazodone (150 to 300 mg/d) were equ depression in a single-blind, 24-week study of 35 depressed patients (Pie were not matched for severity of depression which varied greatly among t completed the 6-month trial. Both treatment groups showed significant rec ratings from 4 weeks onward, and there was significant improvement in th first week onward. There were no significant differences between the 2 gr Drowsiness was the most frequent side effect in the trazodone-treated gro were more common in the dothiepin-treated group.

c) In a 6-week, double-blind study, lofepramine and dothiepin had similar depression in elderly patients (range 65 to 88 years); lofepramine had an incidence of dry mouth, blurred vision, and drowsiness (Fairbairn et al, 19 dothiepin-treated group and 6 in the lofepramine-treated group did not co patients in each group. Many of the participants were receiving other med phenothiazines, benzodiazepines, and chlormethiazole, throughout the tri lofepramine 70 mg/d were given for 1 week, then doses were doubled for measured on the Montgomery-Asberg Depression Scale (MADRS) at wee improvement occurred in both treatment groups. There were not significar Compared with dothiepin-treated patients, the lofepramine-treated patient and day-time drowsiness; only 1 patient in each group withdrew from the

4.6.F Doxepin

4.6.F.1 Depression

a) No significant difference in safety or efficacy was seen in a comparison during weeks 1, 3, and 6 was 125 milligrams (mg), 221 mg, and 246 mg) during weeks 1, 3, and 6 was 58 mg, 105 mg, and 127 mg) in 30 outpatie in a 6-week, double-blind, parallel study (Himmelhoch, 1986).

b) No significant difference was reported in a double-blind study of 101 p trazodone and doxepin in the treatment of depression (Murphy & Ankier,

4.6.G Fluoxetine

Depression

Mania

4.6.G.1 Depression

a) Fluoxetine was as effective as trazodone in the treatment of major dep outpatient study involving 43 patients (Debus et al, 1988). The mean final fluoxetine in the responding patients were 284 and 29 mg daily, respectiv corresponding doses were 327 and 33 mg, respectively. HAM-D scores w fluoxetine when compared to trazodone and sleep was improved to a grea Adverse effects occurred to a similar degree with each agent with the exc frequent with fluoxetine) and dizziness (more frequent with trazodone).

b) A six-week, double-blind trial compared fluoxetine (21 patients) with tra treatment of major depression (Perry et al, 1989). Although trazodone app

greater improvement in HAM-D and Clinical Global Impressions scores at
not statistically significant at 4, 5, and 6 weeks. The authors surmise that
been due to: an insufficient fluoxetine dose early in the trial (mean daily d
during week 3 were 21 mg and 241 mg, respectively), which was mitigate
in fluoxetine doses compared to trazodone doses; a slower onset of antid
compared to trazodone; or a higher incidence of depressive illness lasting
fluoxetine group (67%) than in the trazodone group (37%, reported incorre
authors cite the statistically significant fluoxetine-associated weight loss s
lb/patient) as a clinically significant advantage for this agent, trazodone wa
loss in this study (mean 0.13 lb/patient), and the weight losses exhibited b
significantly different.

4.6.G.2 Mania

a) In literature reports of drug-induced mania caused by fluoxetine or traz
manifested symptoms of mania more slowly than trazodone-treated patien
onset of mania in fluoxetine-treated patients was significantly longer than
days (range = 10 to 154 days) versus 16 days (range =4 to 70 days) resp

4.6.H Imipramine

4.6.H.1 Depression

a) Trazodone is not therapeutically superior to imipramine, but its side eff
et al, 1979; Feighner, 1980; Gerner et al, 1980; Escobar et al, 1980; Work
1984). Anticholinergic side effects occurred more frequently in patients tre
treated with trazodone in a multi-centre trial (Gershon & Newton, 1980).

b) A multicenter trial involving 379 patients treated with trazodone 200 to
imipramine 100 to 300 mg/day or placebo for 21 to 24 days demonstrated
of equal efficacy (Gershon & Newton, 1980). Another study involving 28 p
depression receiving an average trazodone dose of 287 mg/day or an ave
mg/day for 28 days also demonstrated equal effectiveness between the 2
results of a double-blind study involving 45 patients suggested that trazod
a more rapid and prolonged improvement than did imipramine 100 to 300
double-blind controlled study of 40 patients with endogenous depression,
300 mg) produced more improvement of Hamilton depression scale score
trazodone (maximum daily dose 600 mg) (Escobar et al, 1980).

c) Seventy-four patients were enrolled in a nonrandomized study with pla
evaluate the efficacy of imipramine, alprazolam, and trazodone in the trea
al, 1986). Twenty-nine patients were assigned to imipramine, 28 to trazod
treatment. All patients were treated with placebo for 3 weeks and then blir
for clinical response and side effects. Both imipramine and alprazolam we
agoraphobia, however, alprazolam had a faster onset of action. Clinical re
one week with alprazolam therapy and were generally not observed in imi
third or fourth week of therapy. Trazodone therapy was considered not eff
agoraphobia.

d) In a double-blind controlled study, imipramine and placebo were comp
treatment of 45 hostile patients with primary depression. The mean doses
6.26 capsules/day of 50 milligrams (mg) trazodone, 6.37 capsules/day of
capsules/day of placebo. Three of 17 patients in the trazodone groups ex
Hamilton total score on or before day 7 of therapy. On day 14, 8 patients
achieved this level of improvement. Of the imipramine- treated patients, n
improvement at day 7. However, by day 14, eight patients in the group ha
reduction in total Hamilton differences in the subjects tested through the s
Clinical global impressions showed a highly significant difference betweer
proportion of improved patients at the end of 28 days of treatment. Global
trazodone was significantly (p less than 0.01) better than placebo for tens
behavior and difficulty in sleeping. It was significantly (p less than 0.05) be
lacking energy behavior and anxious, worried, afraid behavior and concer
was slightly better (p less than 0.10) for irritable, annoyed, impatient or an
most frequent side effect experienced by trazodone treated patients. Antic
common effects in the imipramine group (Feighner, 1980).

e) Ten institutions participated in a multi-center, double-blind, placebo-co
trazodone or imipramine in 263 in-patients. Inclusion criteria included prim
endogenous type, minimum score of 18 on the Hamilton Rating Scale for
7 of 21 symptoms in 3 of 5 categories of the symptom profile for depressic
100 mg daily for trazodone or imipramine. At the end of 28 days, 113 patic
efficacy or side effects. Drop out rates were 37% each for imipramine and
Both drugs were statistically superior to placebo in improvement of HAM-

There was no significant difference between trazodone and imipramine. B
caused statistically significantly fewer anticholinergic side effects, 19% an
imipramine 52% (Gershon, 1981).

4.6.I Mianserin

Depression

Erectile dysfunction

4.6.I.1 Depression

a) SUMMARY: Several clinical trials have shown mianserin to be equally
treatment of depression (Altamura et al, 1989; Bucknall et al, 1988; Beaur
double-blind trial, 100 to 200 milligrams (mg) trazodone was compared wi
(Beaumont et al, 1984) . Although there were significant dropouts in the m
equally effective. Due to side-effects associated with mianserin, trazodone
(30 to 80 mg) was compared with trazodone (150 to 400 mg) and placebo
study involving 16 cardiac patients (Bucknall et al, 1988) . Both drugs wer
significant cardiovascular effects detected. A trend toward hypotension wa
b) Oral mianserin 30 to 120 milligrams (mg) daily was reported as effectiv
mg daily in the treatment of mild-to-moderate depression (endogenous or
(Bennie et al, 1984).
c) Trazodone in doses of 100 to 200 milligrams (mg) daily was reported s
(60 to 120 mg daily) and diazepam (15 to 30 mg daily) in reducing sympto
study over 3 to 6 weeks compared the antidepressant and anxiolytic effec
diazepam in patients with mild to moderate depression (with or without an
superior to diazepam in improving the patients ability to concentrate and r
Significantly more patients developed side effects with mianserin than eith
(Richards et al, 1982).
d) Clinical outcomes were equal in all 3 groups of patients in a double-bli
trazodone, mianserin, and amitriptyline in the treatment of 106 elderly dep
associated with fewer overall side effects (Altamura et al, 1989).

4.6.I.2 Erectile dysfunction

a) Trazodone was more effective than mianserin, ketanserin, or placebo i
double-blind, randomized, placebo-controlled trial. One hundred patients v
trazodone 50 milligrams (mg) three times a day, ketanserin 20 mg twice a
times a day, or placebo. Patients were evaluated after 30 days. Positive r
of trazodone-treated patients, 19.1% of ketanserin-treated patients, 31.6%
and 13.6% with placebo. Response to trazodone was significantly greater

4.6.J Triazolam

1) Adverse Effects
a) In a comparison of adverse effects of triazolam in doses of 0.125, 0.25
trazodone in doses of 50, 100, and 200 mg and placebo, trazodone did no
of study tasks. Triazolam, in the highest dose, significantly impaired learni
Subjective ratings of drug effect and sedation demonstrated comparable d
drugs, indicating some equivalence on a behavioral basis. Test subjects v
0.5, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours after drug administration. Testing o
rated by subjects and/or observers, including: Profile of Mood States (POI
Inventory (ARCI); drug effect questionnaire; end-of-day questionnaire; obs
learning, recall, and performance measures; repeated acquisition procedu
Symbol-Substitution Test (DSST); circular lights test; balance task; and pi
did not investigate the relative abuse potential of the drugs, but the author
in this area would be useful because of the high incidence of anxiety and
histories of drug abuse (Rush et al, 1997).

4.6.K Venlafaxine

4.6.K.1 Depression

a) Venlafaxine produced antidepressant efficacy comparable to trazodon
controlled trial. In this outpatient study, 225 patients were randomized to v
(mg) per day, trazodone (mean = 300 mg/day) or placebo. Response rate
respectively. Venlafaxine appeared to be more effective than trazodone ir
disturbance and retardation factor as evidenced on the Hamilton Rating S

was noted that this effect may have been due to the sedating nature of tra common in the venlafaxine group compared to dizziness and somnolence (Cunningham et al, 1994).

4.6.L Zolpidem

4.6.L.1 Insomnia

a) Zolpidem 10 milligrams (mg) was slightly superior to trazodone 50 mg increasing sleep duration in a 2-week, randomized, parallel-group, double The periods of sleep latency at the end of week 1 were 48.2 minutes and treated with zolpidem or trazodone, respectively (p less than 0.037), but d end of week 2 (64.7 minutes versus 54.5 minutes, respectively). The slee in both groups compared to the group treated with placebo (p=0.001). Pat reported longer sleep durations at week 1 than those treated with trazodo minutes, respectively) with a trend toward significance (p less than 0.060) between drugs at week 2. The reduction in clinical significance in both pa compared with placebo, was primarily due to improvement in the placebo level of improvement with both drugs was essentially unchanged in the se of the slightly shorter period of sleep latency, zolpidem may have some ac treatment of primary insomnia (Walsh et al, 1998).

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Last Modified: July 02, 2009

DRUGDEX® Evaluations

DEXTROAMPHETAMINE

0.0 Overview

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

2) Dosing Information
- **a)** Dextroamphetamine Sulfate
  - **1)** Adult
    - **a)** Narcolepsy
      - **1)** immediate-release, 5 to 60 mg ORALLY in 2 to 3 divided doses daily (Prod Info dextroamphetamine s
      - **2)** sustained-release, 5 to 60 mg ORALLY as single daily dose (Prod Info DEXEDRINE(R) oral tablets, s
  - **2)** Pediatric
    - **a)** (immediate-release) not FDA approved for children under 3 yr of age with attention deficit hyperactivity dis
    - **b)** (sustained-release) not FDA approved for children under 6 yr of age with attention deficit hyperactivity dis
    sustained-release oral capsules, 2007)
      - **1)** Attention deficit hyperactivity disorder
        - **a)** (immediate-release, age 3 to 5 yr) initial, 2.5 mg ORALLY once daily, increase by 2.5 mg/day at
        mg/day (Prod Info dextroamphetamine sulfate oral tablets, 2007)
        - **b)** (immediate-release, age 6 yr and older) initial, 5 mg ORALLY once or twice daily, increase by 5 r
        40 mg/day (Prod Info dextroamphetamine sulfate oral tablets, 2007)
        - **c)** (sustained-release, age 6 yr and older) initial, 5 mg ORALLY once or twice daily, increase by 5-m
        response; MAX 40 mg/day (Prod Info DEXEDRINE(R) oral tablets, sustained-release oral capsules,
      - **2)** Narcolepsy
        - **a)** (age 6 to 12 yr) 5 mg/day ORALLY, increase by 5 mg/day at 1 wk intervals to optimum response
        should be dosed once daily, immediate-release doses may be given at intervals of 4 to 6 hours (Pro
        2007; Prod Info DEXEDRINE(R) oral tablets, sustained-release oral capsules, 2007)
        - **b)** (age 12 yr and older) 10 mg/day ORALLY, increase by 10 mg/day at 1 wk intervals to optimum re
        tablets should be dosed once daily, immediate-release doses may be given at intervals of 4 to 6 hou
        tablets, 2007; Prod Info DEXEDRINE(R) oral tablets, sustained-release oral capsules, 2007)

3) Contraindications
- **a)** Dextroamphetamine Sulfate
  - **1)** advanced arteriosclerosis (Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006)
  - **2)** agitated states; may aggravate symptoms (Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab
  - **3)** cardiovascular disease, symptomatic (Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets,
  - **4)** concomitant use of monoamine oxidase inhibitors (MAOI), or within 14 days of MAOI use; hypertensive crisis r
  release oral capsules, oral tablets, 2006)
  - **5)** drug dependence, history of; potential for abuse (Prod Info DEXEDRINE(R) sustained-release oral capsules, c
  - **6)** glaucoma (Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006)
  - **7)** hypersensitivity/idiosyncrasy to sympathomimetic amines (Prod Info DEXEDRINE(R) sustained-release oral ca
  - **8)** hypertension, moderate to severe (Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 20
  - **9)** hyperthyroidism (Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006)

4) Serious Adverse Effects
- **a)** Dextroamphetamine Sulfate
  - **1)** Body temperature above normal
  - **2)** Central nervous system stimulation (Severe)
  - **3)** Dead - sudden death
  - **4)** Hypersensitivity disorder
  - **5)** Psychotic disorder
  - **6)** Tachyarrhythmia

5) Clinical Applications
- **a)** Dextroamphetamine Sulfate
  - **1)** FDA Approved Indications
    - **a)** Attention deficit hyperactivity disorder
    - **b)** 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

B) Synonyms

D-Amphetamine
Dexamfetamine
Dexamphetamine
Dextroamphetamine
Dextroamphetamine Sulf
Dextroamphetamine Sulfate

1.2 Storage and Stability

A) Dextroamphetamine Sulfate

1) Preparation

a) Oral route

1) Avoid late evening doses due to resulting insomnia (Prod Info DEXEDRINE(R) oral tablets, sustained Dexedrine(R), 2002)

2) Give first dose of immediate-release tablet on awakening, and additional doses at intervals of 4 to 6 h

B) Oral route

1) Dextroamphetamine tablets should be stored in well-closed containers, and the elixir in tight, light-resistant cor degrees Centigrade, preferably at 15 to 30 degrees Centigrade (59 to 86 degrees F); freezing of the elixir should should be stored at temperature, between 20 and 25 degrees C (68 and 77 degrees F) (Prod Info Dexedrine(R), (R) capsules, 1999; Prod Info Dextrostat(R), 1998).

1.3 Adult Dosage

1.3.1 Normal Dosage

1.3.1.A Cataplexy - Narcolepsy

See Drug Consult reference: NARCOLEPSY AND CATAPLEXY - DRUG THERAPY

1.4 Pediatric Dosage

1.4.1 Normal Dosage

1.4.1.A Dextroamphetamine Sulfate

1.4.1.A.1 Oral route

Attention deficit hyperactivity disorder

Narcolepsy

1.4.1.A.1.a Attention deficit hyperactivity disorder

1) Immediate-Release

a) For children 3 to 5 years of age with attention deficit disorder, the recommended initial oral d milligrams/day. The daily dosage is increased by 2.5 milligrams at weekly intervals until the opti should rarely exceed 40 milligrams. The first dose should be given on awakening if tablets or lic intervals of 4 to 6 hours (Prod Info dextroamphetamine sulfate oral tablets, 2007).

b) For children 6 years of age and older with attention deficit disorder, the recommended initial once or twice daily. The daily dosage is increased by 5 milligrams at weekly intervals until the o total daily dose exceed 40 milligrams . The first dose should be given on awakening, with subse (Prod Info dextroamphetamine sulfate oral tablets, 2007).

2) Extended-Release

a) For children aged 6 years and older with attention deficit disorder, the recommended initial d release is 5 milligrams (mg) once or twice daily, with 5-mg increases at weekly intervals until the daily dose of 40 mg is rarely necessary (Prod Info DEXEDRINE(R) oral tablets, sustained-relea

1.4.1.A.1.b Narcolepsy

1) Immediate-release

a) For children 6 to 12 years of age with narcolepsy, the recommended initial dose of oral dextı milligrams (mg) daily, with 5-mg increases at weekly intervals until the optimum dose is attainec tablets, 2007).
b) For children 12 years of age and older with narcolepsy, the initial dose of oral dextroamphet 10-mg increases at weekly intervals until the optimum dose is attained. The first dose should be or 2) spaced at intervals of 4 to 6 hours. Exceeding a total dose of 40 mg/day is rarely necessai recommended to determine if there is a recurrence of behavioral symptoms sufficient to require dextroamphetamine sulfate oral tablets, 2007).

2) Sustained-release
a) For children 6 to 12 years of age with narcolepsy, the recommended initial dose of oral dextı (mg) once daily, with 5-mg increases at weekly intervals until the optimum dose is attained (Pro release oral capsules, 2007).
b) For children 12 years of age and older with narcolepsy, the recommended initial dose of ora once daily, with 10-mg increases at weekly intervals until the optimum dose is attained (Prod In release oral capsules, 2007).
c) Dosage should be reduced if adverse reactions become intolerable (Prod Info DEXEDRINE(2007).

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset
1) Initial Response
a) 2 to 3 hours (Angrist et al, 1987).
B) Duration
1) Single Dose
a) 4 to 24 hours (Johnson et al, 1971).
1) The duration of the effects may be prolonged by alkalinization or shortened by acidification of the urin
2) Each dextroamphetamine sustained-release capsule is prepared such that an initial dose is promptly released gradually over a prolonged period of time. Dextroamphetamine's therapeutic effects may persis

2.2 Drug Concentration Levels

A) Time to Peak Concentration
1) Oral, tablets: 60 to 180 minutes (Prod Info Dexedrine(R), dextroamphetamine sulfate tablets and Spansule(R) 1998a).
2) Oral, extended-release capsules: approximately 8 hours (Prod Info Dexedrine(R), dextroamphetamine sulfate
3) Oral, extended-release capsules: approximately 7 hours (Prod Info Adderall XR(TM), 2002);(Tulloch et al, 200
B) URINE ASSAY
1) A semiquantitative EMIT(R) homogenous enzyme immunoassay is available for measurement of the commonl limit (sensitivity) is 2 mcg/mL for amphetamine or methamphetamine. The assay also detects phenylethylamines a to eliminate interference from over-the-counter cold medications that contain ephedrine, pseudoephedrine, or phe assay is also available that detects as little as 0.7 mcg/mL of amphetamine; this method correlated well with GLC studies (Prod Info EMIT(R) urine amphetamine assay, 1983).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

Extracorporeal Elimination

2.3.1 Absorption
A) Bioavailability
1) well-absorbed (Becket & Tucker, 1968; Becket et al, 1968).
a) The bioavailability of the extended-release capsule is similar to that of the immediate-release tablet (F sulfate tablets and Spansule(R) capsules, 1999a).
B) Effects of Food
1) none (Angrist et al, 1987).
a) Absorption of the extended-release capsule is similar in either the fed or fasted state (Prod Info Dexe Spansule(R) capsules, 1999a).
b) Food does not affect absorption, but it prolongs time to reach maximal plasma concentration by 2.5 h high-fat meal) (Prod Info Adderall XR(TM), 2002);(Tulloch et al, 2002).

2.3.2 Distribution
A) Distribution Sites
1) Tissues and Fluids
a) CEREBROSPINAL FLUID
1) Cerebrospinal fluid levels of dextroamphetamine are approximately 80% of plasma levels (Angga
B) Distribution Kinetics
1) Volume of Distribution
a) 6.11 L/kg (Anggard, 1970a).

2.3.3 Metabolism
A) Metabolism Sites and Kinetics
1) Liver, extensive
a) Amphetamine is hepatically metabolized to both acidic and basic metabolites primarily by deaminatio et al, 1972; Anggard et al, 1973b; Beckett & Shenoy, 1973). Dextroamphetamine is the dextrorotatory isc behave in a similar fashion.
B) Metabolites
1) Hippuric acid (Davies et al, 1971)(Caldwell et al, 1972; Anggard et al, 1973b; Sever et al, 1973).
2) Benzoic acid (Davies et al, 1971)(Caldwell et al, 1972; Anggard et al, 1973b; Sever et al, 1973).
3) Norephedrine (Davies et al, 1971)(Caldwell et al, 1972; Anggard et al, 1973b; Sever et al, 1973).
4) 4-hydroxynorephedrine (Davies et al, 1971)(Caldwell et al, 1972; Anggard et al, 1973b; Sever et al, 1973)
5) Benzyl methyl ketone (Davies et al, 1971)(Caldwell et al, 1972; Anggard et al, 1973b; Sever et al, 1973).

2.3.4 Excretion
A) Kidney
1) Renal Excretion (%)
a) 17% to 73% (Anggard et al, 1973b).
1) The urinary excretion of dextroamphetamine is dependent on pH; at a pH of less than 6.6, 67% t urine (Olin, 1990; Anggard et al, 1973b; Caldwell et al, 1972; Beckett & Shenoy, 1973). At a urine pH unchanged in the urine (Anggard et al, 1973b).

2.3.5 Elimination Half-life
A) Parent Compound
1) ELIMINATION HALF-LIFE
a) 7 to 34 hours (Prod Info Dextrostat(R), 1998a; Anggard et al, 1973b).
1) The half-life of dextroamphetamine is dependent on urine pH. In patients with a urine pH of less t in patients with a urine pH of greater than 6.7, the half-life ranges from 17 to 34 hours (Anggard et a
2) Average half-life of dextroamphetamine tablets is 10 to 12 hours (Prod Info Dexedrine(R), dextro capsules, 1999a; Prod Info Dextrostat(R), 1998a). Half-life of the extended-release capsules is appr

2.3.6 Extracorporeal Elimination
A) Hemodialysis
1) Dialyzable: Yes (Zalis & Parmley, 1963).
a) Hemodialysis has been demonstrated to enhance the elimination of amphetamine in animals (Zalis & procedure in human overdoses has not been proven. Dextroamphetamine is the dextrorotatory isomer o behave in a similar fashion.
B) Peritoneal
1) Dialyzable: Yes (Zalis & Parmley, 1963).
a) Peritoneal dialysis has been demonstrated to enhance the elimination of amphetamine is animals (Za procedure in human overdoses has not been proven. Dextroamphetamine is the dextrorotatory isomer o behave in a similar fashion.

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING
1) Dextroamphetamine Sulfate
a) Oral (Tablet; Capsule, Extended Release)
1) Amphetamines have a high potential for abuse. Administration of amphetamines for prolonged periods of avoided. Particular attention should be paid to the possibility of subjects obtaining amphetamines for non-the drugs should be prescribed or dispensed sparingly. Misuse of amphetamines may cause sudden death and s DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006).

3.1 Contraindications
A) Dextroamphetamine Sulfate
1) advanced arteriosclerosis (Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006)
2) agitated states; may aggravate symptoms (Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab
3) cardiovascular disease, symptomatic (Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets,
4) concomitant use of monoamine oxidase inhibitors (MAOI), or within 14 days of MAOI use; hypertensive crisis r release oral capsules, oral tablets, 2006)
5) drug dependence, history of; potential for abuse (Prod Info DEXEDRINE(R) sustained-release oral capsules, c
6) glaucoma (Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006)
7) hypersensitivity/idiosyncrasy to sympathomimetic amines (Prod Info DEXEDRINE(R) sustained-release oral ca
8) hypertension, moderate to severe (Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 20
9) hyperthyroidism (Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006)

3.2 Precautions
A) Dextroamphetamine Sulfate
1) amphetamine misuse; may cause sudden death and serious cardiovascular events (Prod Info DEXEDRINE(R) 2006)
2) bipolar disorder, comorbid; may precipitate a mixed/manic episode (Prod Info DEXEDRINE(R) sustained-relea
3) cardiovascular conditions which may be compromised by increases in blood pressure or heart rate (eg, pre-ex myocardial infarction, or ventricular arrhythmia) (Prod Info DEXEDRINE(R) sustained-release oral capsules, oral t
4) EEG abnormalities, especially with history of; may lower convulsive threshold (Prod Info DEXEDRINE(R) susta
5) psychosis, pre-existing; may exacerbate symptoms of behavior disturbance and thought disorder (Prod Info DI oral tablets, 2006)
6) seizures, especially with a history of; may lower convulsive threshold (Prod Info DEXEDRINE(R) sustained-rel
7) structural cardiac abnormalities/conditions, serious, especially in children and adolescents; sudden death has (Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006)
8) tartrazine (FD&C Yellow No. 5) sensitivity, especially with aspirin sensitivity; may cause allergic-type reaction (release oral capsules, oral tablets, 2006)
9) tics, motor and phonic, history of; risk of exacerbation (Prod Info DEXEDRINE(R) sustained-release oral capsu
10) Tourette's syndrome, history of; risk of exacerbation (Prod Info DEXEDRINE(R) sustained-release oral capsu

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Immunologic Effects

Neurologic Effects

Psychiatric Effects

Reproductive Effects

Other

3.3.1 Cardiovascular Effects

3.3.1.A Dextroamphetamine Sulfate

Dead - sudden death

Increased blood pressure

Palpitations

Tachyarrhythmia

3.3.1.A.1 Dead - sudden death

a) Incidence: rare

b) Children and Adolescents - With Preexisting Cardiac Risk

1) Over the 5-year period (1999 to 2003), the US Food and Drug Administration (FDA) received 12 among pediatric patients using Adderall(R) for ADHD. Five of the 12 cases were found to have card (1), idiopathic hypertrophic subaortic stenosis (1), bicuspid aortic valve (1), and cardiac hypertrophy increase or toxic amphetamine level (2), family history of ventricular arrhythmia (1), extreme exercis who were all male, ranged from 7 to 16 years (mean 12 years); duration of therapy ranged from 1 da (1), 20 mg (5), 30 mg (1), 40 mg (1), and 50 mg (1), with dose not reported in 3 cases. With respect mentioned in 9 cases and 1 other medication noted in 3 cases. Eleven of the 12 were autopsied. Th Canada (the Canadian agency which regulates drugs) to suspend marketing of Adderall XR(R) in th professionals that Adderall(R) products should not be used in adults or children with structural cardia

2) In children with structural cardiac abnormalities, sudden death has been reported in association v (Prod Info Adderall XR(R), 2004).

c) Children and Adolescents - Healthy

1) A retrospective, case-controlled study examines the association between stimulant medication, i unexplained sudden death in healthy children and adolescents. In a collection of data from state vita States, 564 cases of sudden death in children and adolescents between the ages of 7 to 19 years w who died as passengers in motor vehicle accidents. The study determined that 1.8% (n=10) of youth were taking stimulant medication compared with only 0.4% (n=2) of youths in the motor vehicle acci 74.9; p=0.02). Limitations to this study included the time lag between the youths stimulant medicatio recall of information regarding clinical diagnoses, inconsistent postmortem inquiry, and the exclusion authors stated that this finding should be considered when evaluating the overall risk and benefit of adolescents (Gould et al, 2009). Given the limitations of this study, the U.S. Food and Drug Adminis and benefits associated with stimulant medications (US Food and Drug Administration, 2009).

3.3.1.A.2 Increased blood pressure

a) Cardiovascular toxicities, including elevations of blood pressure, have been reported during dextroam 1988). One clinician reports a case of acute myocardial infarction that was complicated by chronic amph

3.3.1.A.3 Palpitations

a) Cardiovascular toxicities, including palpitations, have been reported during dextroamphetamine thera reports a case of acute myocardial infarction that was complicated by chronic amphetamine abuse (Orze

3.3.1.A.4 Tachyarrhythmia

a) Cardiovascular toxicities, including tachycardia, have been reported during dextroamphetamine thera reports a case of acute myocardial infarction that was complicated by chronic amphetamine abuse (Orze

b) In children with structural cardiac abnormalities, sudden death has been reported in association with Info Adderall XR(R), 2004).

c) Increases in heart rate and blood pressure were reported with use of dextroamphetamine. In a placeb effects, dextroamphetamine 30 mg in 3 divided doses (midnight, 0400 hours, and 0800 hours) was admi pilots during sleep-deprivation periods (Caldwell, 1996). Heart rates were elevated from 2 hours after the

third dose. In females, average heart rates associated with dextroamphetamine and placebo were 84 an
males, these rates were 70 and 63 bpm, respectively. Systolic blood pressure (SBP) in males was eleva
hours after the third dose; SBP in females was increased 1 hour after the third 10-mg dose and remaine
pressure (DBP) was elevated from 2 hours after the second dose and continued for 6 hours after the las
dextroamphetamine and placebo was 128 and 120 mmHg, respectively, and DBP was 72 and 69 mmHg
respectively.

3.3.2 Dermatologic Effects

3.3.2.A Dextroamphetamine Sulfate

Rash

Urticaria

3.3.2.A.1 Rash

a) Rash has been associated with amphetamine use (Prod Info ADDERALL XR(R) extended-release or

3.3.2.A.2 Urticaria

a) Urticaria has been associated with amphetamine use (Prod Info ADDERALL XR(R) extended-release

3.3.3 Endocrine/Metabolic Effects

3.3.3.A Dextroamphetamine Sulfate

3.3.3.A.1 Hyperthyroidism

a) One group of clinicians reports 4 cases of amphetamine abuse that resulted in an elevated free thyro
and symptoms of hyperthyroidism (Morely et al, 1980). The levels of T4 appeared to be inappropriately e
HYPERTHYROXINEMIA appeared to be secondary to an increase in circulating TSH. All levels returned
amphetamine in 2 of the 4 cases; the remaining 2 patients refused further follow-up after the initial levels
dextrorotatory isomer of amphetamine and would be expected to behave in a similar fashion.
b) The signs and symptoms of amphetamine abuse are similar to those of THYROTOXICOSIS; it is unc
secondary to hyperthyroxinemia (Morely et al, 1980).

3.3.4 Gastrointestinal Effects

3.3.4.A Dextroamphetamine Sulfate

3.3.4.A.1 Gastrointestinal tract finding

a) A variety of gastrointestinal effects including DRY MOUTH, UNPLEASANT TASTE, DIARRHEA, CON
have been reported during dextroamphetamine therapy (Prod Info Dexedrine(R), dextroamphetamine su
Prod Info Dextrostat(R), 1998).

3.3.5 Hematologic Effects

3.3.5.A Dextroamphetamine Sulfate

3.3.5.A.1 Leukemia

a) One report describes a case of a 24-year-old white male who ingested 8 to 16 tablets/day of amphet
myeloblastic leukemia that was heralded by weakness, sweating, calf pain, and fever (Berry, 1966). Des
rapidly deteriorated into coma, apnea, and death. A possible cause and effect relationship with chronic a
drug possesses a benzene ring that has been known to cause hematologic effects. Dextroamphetamine
and would be expected to behave in a similar fashion.

3.3.7 Immunologic Effects

3.3.7.A Dextroamphetamine Sulfate

3.3.7.A.1 Hypersensitivity disorder

a) Hypersensitivity reactions, including angioedema and anaphylaxis, have been associated with amphe
extended-release oral capsules, 2006).

3.3.9 Neurologic Effects

3.3.9.A Dextroamphetamine Sulfate

Central nervous system finding

Cerebrovascular disease

Disturbance in speech

Extrapyramidal sign

Gilles de la Tourette's syndrome

3.3.9.A.1 Central nervous system finding

a) Children with attention deficit hyperactive disorder (ADHD) who have normal electroencephalograms they receive stimulant therapy for ADHD (METHYLPHENIDATE, DEXTROAMPHETAMINE, or combinat DEXTROAMPHETAMINE (Adderall(R)). However, children with epileptiform EEGs may have considerab occurrence of seizure may or may not be attributable to use of the stimulant. These conclusions were ba epilepsy who were diagnosed with ADHD. All had EEGs prior to parental choosing of stimulant treatmen children's ADHD. Overall, 36 children (15.4%) demonstrated epileptiform abnormalities compared with 1 abnormalities, 30 received stimulant treatment for ADHD. Three of the 30 who received stimulant therap including a 9-year-old female, a 7-year-old male, and a 6-year- old male. The girl was treated uneventful months after withdrawal of methylphenidate experienced a 4-minute generalized tonic-clonic seizure. He abnormality. Of the 2 boys, the first experienced a 2-minute generalized tonic clonic seizure with focal or second boy had an episode at 10 months after initiation of methylphenidate; he was heard to fall and wa minutes. EEGs of both boys had shown rolandic spikes, a focal epileptiform abnormality. One child who beginning methylphenidate (Hemmer et al, 2001).

b) Dextroamphetamine 0.15 mg/kg intravenously induced a dysphoric reaction, with DROWSINESS, an postmenopausal women (Halbreich et al, 1981). Young healthy men, who received the same dose, expe patients were screened to rule out physical and mental disorders.

c) One author reports 3 cases of OBSESSIVE-COMPULSIVE BEHAVIOR as a result of dextroampheta diagnosed as suffering from attention deficit disorder. The duration of stimulant therapy before the devel and 7 years, and the duration of symptoms was 4 to 7 months. A case of amphetamine-induced COMPU responsive to pyridoxine (B6) therapy (Frye & Arnold, 1981).

d) Due to its mechanism of action, dextroamphetamine may cause central nervous system (CNS) stimu DIZZINESS, INSOMNIA, EUPHORIA, dysphoria, TREMOR, and HEADACHE (Prod Info Dexedrine(R),

3.3.9.A.2 Cerebrovascular disease

a) Investigators reported 4 cases of INTRACRANIAL HEMORRHAGE following oral or nasal use of amp al, 1983). Two of these patients had abnormal appearing cerebral blood vessels on angiography. Availab hemorrhage may also occur in patients who use these drugs for the first time and nonrecreationally.

b) One article reports a case of intracranial hemorrhage that occurred 3 hours after the ingestion of amp (D'Souza & Shraberg, 1981). The admitting blood pressure was 210/120 (systolic/diastolic). No evidence was found on CT Scan. Others report INTRACRANIAL HYPERTENSION in a chronic amphetamine abu prednisone without a residual neurologic deficit. Dextroamphetamine is the dextrorotatory isomer of amp similar fashion (Delaney & Estes, 1981).

c) Four cases of STROKE were reported in patients (29 to 45 years of age) thought to have abused me hemorrhaging and 2 had cerebral ischemic infarctions (Perez et al, 1999).

3.3.9.A.3 Disturbance in speech

a) Central nervous system (CNS) stimulants can increase the rate of speech and reduce the fine coordi DYSPHONIA and VOICE TREMORS (Damste, 1978).

3.3.9.A.4 Extrapyramidal sign

a) Chronic amphetamine abuse may induce extrapyramidal effects such as choreiform or ATHETOID M that resemble the gait seen in Huntington's chorea. The syndrome generally develops during amphetami abstinence; however, the symptoms may persist for long periods of time. Dopamine receptor-blocking ag (Lundh & Lunving, 1981)(Rundell et al, 1988). Dextroamphetamine is the dextrorotatory isomer of amphe similar fashion.

3.3.9.A.5 Gilles de la Tourette's syndrome

a) The incidence of TICS emergence was 7.8% in children treated with stimulant medication (METHYLF PEMOLINE) for attention deficit hyperactivity disorder, based on a retrospective chart review (n=555). Th children if they were free of tics and without a history of tics according to the practice of the settings in wh 8.3% of subjects treated with methylphenidate, 6.3% treated with dextroamphetamine, and 7.7% treated dose or duration of stimulant therapy. Mean age of subjects was 11 years. A significant correlation occur tics. As the authors noted, these children may have developed tics, regardless of treatment with the med

b) Tourette's syndrome may be precipitated with the use of stimulant medications in the treatment of att
TOURETTE'S syndrome are difficult to distinguish from the attention deficit disorder symptoms. Children
additional stimulant medications. Stimulants may exacerbate severe motor and PHONIC TICS; discontin
initiation of haloperidol therapy is often required. In patients diagnosed as having an attention deficit disc
Tourette's syndrome in children and their families should precede the use of stimulant medication. The u
children with Tourette's syndrome or tics. In children with no symptoms of Tourette's syndrome or tics bu
very cautiously. If tics emerge during dextroamphetamine therapy, the drug should be discontinued (Low
c) These authors present several cases of children with attention deficit disorders who experienced hyp
cases, MOTOR TIC symptoms (Lowe et al, 1982a). The patients were placed on stimulant therapy and e
or Tourette's syndrome. Stimulant withdrawal and haloperidol therapy controlled the motor and phonic sy
d) Researchers reviewed the medication histories of 200 children with Tourette's syndrome (Erenberg e
stimulant drugs: 42 methylphenidate, 5 dextroamphetamine, 13 pemoline. Thirty-nine of the 48 (81%) pa
of the tics. Of these, the stimulant drugs increased tics in 8 patients, caused no change in 22, and decrea
therapy resulted in no difference in the incidence or frequency of tics in 8 patients. The patients who dev
decrease in the incidence and frequency after discontinuation of the stimulant.
e) Another report describes 2 cases of hyperactive boys who developed motor and phonic tics during de
Patterson, 1986). The tics disappeared in both cases after the discontinuation of dextroamphetamine an
suggest that neuroleptic-induced tics may be the result of presynaptic dopamine blockade.

3.3.12 Psychiatric Effects

3.3.12.A Dextroamphetamine Sulfate

3.3.12.A.1 Psychotic disorder

a) Incidence: rare
b) Amphetamine psychosis can present with visual, tactile, auditory and/or olfactory HALLUCINATIONS
AGGRESSIVENESS, SUSPICION, PARANOIA, increased motor activity, and CONCENTRATION DIFFI
treatment with benzodiazepines have been useful in resolving the symptoms (Bell, 1965; Ladewig et al,
1970; Hasse et al, 1973; Dow & Silver, 1973). The administration of amphetamines to patients with schiz
PSYCHOTIC BEHAVIOR (West, 1974; Alverno et al, 1975). Healthy persons who ingest dextroampheta
clinically indistinguishable from paranoid SCHIZOPHRENIA (Morley et al, 1980).
c) It was reported that patients whose urine is acidified with ammonium chloride have a shorter duration
days) than patients with amphetamine psychosis who have alkaline urine (approximately 4.5 days) (Angg
behavior was the first symptom to clear; this occurred within 1 day.
d) Others report a case of PARANOID PSYCHOSIS from intoxication with dextroamphetamine; the drug
(DeVeaugh-Geiss & Pandurangi, 1982). Use of amphetamines may exacerbate symptoms of BEHAVIOR
psychotic pediatric patients (Prod Info Dexedrine(R), dextroamphetamine sulfate tablets and Spansule(R
1998).

3.3.14 Reproductive Effects

3.3.14.A Dextroamphetamine Sulfate

3.3.14.A.1 Sexual dysfunction

a) IMPOTENCE and LIBIDO CHANGES have been reported during dextroamphetamine therapy (Prod I
tablets and Spansule(R) capsules, 1999).

3.3.16 Other

3.3.16.A Dextroamphetamine Sulfate

3.3.16.A.1 Drug withdrawal

a) The cessation of, or reduction in, amphetamine use that has been heavy and prolonged can result in
DYSPHORIC MOOD, FATIGUE, VIVID and UNPLEASANT DREAMS, INSOMNIA or HYPERSOMNIA, I
RETARDATION or AGITATION, ANHEDONIA, and DRUG CRAVING. Withdrawal symptoms may devel
cessation of or reduction in amphetamine use (Prod Info Adderall XR(TM), 2002; American Psychiatric A
b) Marked withdrawal symptoms can occur following intense, high dose amphetamine use. Characterist
feelings of LASSITUDE and DEPRESSION, and a marked INCREASE IN APPETITE with rapid WEIGH
days and may be accompanied by SUICIDAL IDEATION (American Psychiatric Association, 1994).

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 Dexedrine(R), 2002) (All Tri
a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other)
studies in women and animals are not available. Drugs should be given only if the potential benefit justifies th
See Drug Consult reference: PREGNANCY RISK CATEGORIES
2) Crosses Placenta: Unknown
3) Clinical Management

a) Amphetamines are not recommended for use during pregnancy except possibly in the case of narcolepsy drug is indicated and according to established regimens, amphetamines are not expected to create a significa abuse of amphetamines does increase the potential risk of maternal, fetal, and neonatal morbidity. Although evidence suggests an increased incidence of cardiac defects and cleft palate in neonates born to mothers tak et al, 1981).

4) Literature Reports

a) Eleven infants were born with biliary atresia to mothers who had taken amphetamines in various doses du development of a biliary tree) (Levin, 1971). In a controlled group of 50 normal infants, it was noted that 3 of 5

b) A large prospective, observational study of pregnancy and child development was undertaken related to a phenmetrazine) prescribed to gravid women during different stages of pregnancy and evaluated for their tera The severe congenital anomaly rate (SCA) per 100 live-born children at age 5 years did not differ from the SC did not use these drugs. There was, however, an excess of oral clefts in the offspring of mothers who had am the last menstrual period. A rough test of efficacy of anorectic drugs was made by comparing mean weight ga prescription; it showed only short-term and limited reduction of weight gain.

c) In a further report, clinicians evaluated the outcome of pregnancy in 52 women who had abused intravenc pregnancy, with results being compared to a control group of 52 nonabusing women (Little et al, 1988). Body was decreased significantly in neonates born to mothers abusing methamphetamine during pregnancy. Howe not increased significantly compared to the control group.

d) A statistically significant correlation between aggressive behavior and amphetamine exposure during fetal 1994).

B) Breastfeeding

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

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

2) Clinical Management

a) Amphetamines are concentrated in human breast milk. Adverse effects reported in exposed infants includ 2001). The manufacturer of Adderal(R) suggests that breastfeeding women taking amphetamines be counse 2003).

3) Literature Reports

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

4) Drug Levels in Breastmilk

a) Parent Drug

1) Milk to Maternal Plasma Ratio

a) One study reported that concentrations of amphetamine were 3 and 7 times higher in breast milk delivery, respectively, following administration of dextroamphetamine 20 mg daily to a nursing moth untoward effects occurred in the infant. Although only a small fraction of the maternal dose is expect the authors 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

Amitriptyline

Amoxapine

Calamus

Citalopram

Clomipramine

Clorgyline

Desipramine

Dothiepin

Doxepin

Furazolidone

Imipramine

Iproniazid

Isocarboxazid

Lofepramine

Moclobemide

Nialamide

Nortriptyline

Opipramol

Pargyline

Phenelzine

Procarbazine

Protriptyline

Selegiline

Sibutramine

Sodium Bicarbonate

Toloxatone

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. Monitc
7) Probable Mechanism: decreased renal clearance

3.5.1.B 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 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.C 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 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.D 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.E 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 anc
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.F 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 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.G 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 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, 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.H 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 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 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.I Dothiepin

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 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.J 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 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.K 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 mo
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 n
7) Probable Mechanism: increased norepinephrine availability

3.5.1.L 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 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.M 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 mo
(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 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, 1991n).

3.5.1.N 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 mo (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.O 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 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.P 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 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, 1991).

3.5.1.Q 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 monc more norepinephrine being made available at nerve receptor sites through inhibition of catecholamine degrac 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 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, 1991p).

3.5.1.R 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 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.S 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 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.T 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 m (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 r
7) Probable Mechanism: increased norepinephrine availability

3.5.1.U Phenelzine

1) Interaction Effect: a hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Amphetamines cause the release of norepinephrine, and the use of monoamine oxidase inhibi 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 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, 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.V 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 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, 1991l).

3.5.1.W 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 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.X 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 m (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.Y 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.Z 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.AA 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 degrac 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 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, 1991f).

3.5.1.AB 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 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, 1964c).
b) 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, 1991j).

3.5.1.AC Trimipramine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with 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.AD 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 s 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 dextroampheta 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 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

3.5.2 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

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters

A) Dextroamphetamine Sulfate

1) Therapeutic

a) Physical Findings

1) Attention Deficit Hyperactivity Disorder (ADHD)

a) Improvement in mental and behavioral symptoms of ADHD, including inappropriate inattention, i performance.

2) Narcolepsy

a) Decreased frequency of narcoleptic attacks.

2) Toxic

a) Physical Findings

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 (AI 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 dextroamphetamine, for ADHD (Perrin et al, 2008; Vetter et al, 2008):

- Conduct a thorough examination prior to initiating dextroamphetamine therapy for a diagnosis symptoms indicative of a cardiac condition, including palpitations, near syncope, or syncope.
- Obtain a complete family and patient history for conditions associated with SCD, and 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 (Perrin et al, 2008).
- 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.

c) It is not conclusive whether chronic use of stimulants in children may be associated with suppres monitored during treatment (Prod Info DEXEDRINE(R) oral tablets, sustained-release oral capsules

4.2 Patient Instructions

A) Dextroamphetamine (By mouth)

Dextroamphetamine

Treats attention deficit hyperactivity disorder (ADHD). Also treats narcolepsy (a sleep problem). This medicine is a

When This Medicine Should Not Be Used:
You should not use this medicine if you or your child have had an allergic reaction to dextroamphetamine. You sh glaucoma, heart disease, blood vessel problems, an overactive thyroid, or high blood pressure. Do not use this m you are very nervous, tense, or agitated most of the time. You should not use this medicine if you have used a dru (MAOI), such as Eldepryl®, Marplan®, Nardil®, or Parnate®, in the past 14 days. Do not give the tablet and oral s the extended-release capsule to a child younger than 6 years old.

How to Use This Medicine:
Tablet, Liquid, Long Acting Capsule

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.
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.
It is best to take the extended-release capsule form in the morning. Taking this medicine in the afternoon or e asleep.
If you use the short-acting tablet form of this medicine, take your last dose for the day about 6 hours before b instructions.
Swallow the extended-release capsule whole. Do not crush, break, or chew it.
This medicine is part of an ADHD treatment program that may also include counseling or special education. C all treatment measures.

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 the missed dose. Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after 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 using ammonium chloride, sodium acid phosphate, acetazolamide (D furazolidone (Furoxone®), glutamic acid, guanethidine (Ismelin®), norepinephrine (Levophed®), reserpine (H blood pressure medicines (such as atenolol, lisinopril, metoprolol, Cozaar®, or Diovan®), or certain pain mec Demerol®, or Darvon®).
Tell your doctor if you are also using cold or allergy medicines, ethosuximide (Zarontin®), haloperidol (Haldol medicines for depression (such as amitriptyline, doxepin, nortriptyline, Pamelor®, or Sinequan®), methenami or phenytoin (Dilantin®).
Do not eat citrus fruits (oranges, lemons, limes, grapefruit) or drink citrus juice when you take this medicine. D medicine.

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant or breastfeeding, or if you or your child have heart problems
Tell your doctor if you or your child have muscle tics or Tourette's syndrome, a condition that causes you to h not able to control.
Your doctor should know if you or your child have epilepsy, or a history of seizures, depression, or mental illn problems. Also tell your doctor if you or anyone in your family has tried to commit suicide.
This medicine may be habit-forming. If you feel that the medicine is not working as well, do not use more thar instructions.
Do not stop using this medicine suddenly without asking your doctor. You may need to slowly decrease your
This medicine may cause blurred vision or make you dizzy or drowsy. If any of these occur, do not drive, use dangerous if you are not alert or not able to see well.
This medicine may cause slow growth. If your child is using this medicine, the doctor will need to keep track c that your child is growing properly.
Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to ke

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
Blurred vision.
Changes in your mood or behavior.
Chest pain, shortness of breath, or fainting.
Fast, pounding, or uneven heartbeat.
Feeling very excited, fearless, restless, or happy.
Seeing, hearing, or feeling things that are not there.
Seizures.
Tremors or shaking.
Uncontrollable muscle movements or twitching.

If you notice these less serious side effects, talk with your doctor:
Constipation, diarrhea, or upset stomach.
Dry mouth or bad taste in your mouth.
Feeling restless or nervous.
Headache or dizziness.
Loss of appetite or weight loss.
Mild skin rash or itching.
Problems having sex.
Trouble sleeping.

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

4.3 Place In Therapy

A) The primary indication for the use of amphetamines is the clinical condition of narcolepsy which relies on the centr stimulant properties of the drugs. In children with hyperkinesia and other abnormal behavioral problems, the amphetar remedial measures to reduce observed motor activity from baseline levels (Green & Warshauer, 1981). This reduced hyperactive children given dextroamphetamine) accompanied by improved behavior and improved attention seems to (classroom situations) but also physically active tasks (structured sports situations).

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) Dextroamphetamine is a non-catechol sympathetic amine with pharmacologic actions that are similar to ephec
Dextroamphetamine produces central nervous system (CNS) and respiratory stimulation, a pressor response, my
urinary sphincter. The drug is felt to have a direct effect on both alpha- and beta-receptor sites in the peripheral sy
nerve terminals. The central nervous system action is thought to occur in the cerebral cortex and reticular activati
dextroamphetamine is probably secondary to the CNS stimulating effect in the hypothalamic feeding center (Weir
2) Dextroamphetamine sulfate is used to treat narcolepsy because of its CNS and respiratory stimulant properties
abnormal behavioral problems, dextroamphetamine appears to be of value in combination with other remedial me
baseline levels (Green & Warshauer, 1981a). This reduced observed motor activity from baseline values (in hyper
accompanied by improved behavior and improved attention seems to occur not only in physically inactive tasks (c
tasks (structured sports situations) (Rapoport et al, 1980).

4.5 Therapeutic Uses

Dextroamphetamine

Dextroamphetamine Sulfate

4.5.A Dextroamphetamine

4.5.A.1 Cataplexy - Narcolepsy

See Drug Consult reference: NARCOLEPSY AND CATAPLEXY - DRUG THERAPY

4.5.B Dextroamphetamine Sulfate

Attention deficit hyperactivity disorder

Cocaine dependence

Depression

Mania

Narcolepsy

Personality disorder

Schizophrenia

Sleep deprivation

4.5.B.1 Attention deficit hyperactivity disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, no; Pediatric, yes (immediate-release, age 3 to 16 years ; sustained-release, a
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 attention deficit disorder with hyperactivity (ADHD) as an integral part
psychological, educational and social measures (Prod Info dextroamphetamine sulfate oral tablets,
sustained-release oral capsules, 2007)
May cause anxiety in susceptible individuals

c) Adult:

1) Some adult patients with a diagnosis of hyperactivity have also responded well to dextroamphetamin
paradoxical response to stimulant medication is exhibited only in prepubertal children (Woods et al, 1986
1980). One report describes a 20-year-old male with hyperkinetic syndrome who responded to dextroam
activity, increased concentration, depression of mood, drowsiness, reduction in aggression, and disappe
Joseph, 1980). The patient also showed typical amphetamine responses of tachycardia, hypertension, a

d) Pediatric:

1) Investigators examined 29 children (ages 6 to 13 years) who were referred for evaluation of hyperacti

dextroamphetamine, levoamphetamine, or placebo in a random, double-blind fashion. Medication was c
week, the procedure was repeated for each drug. While off medication, the hyperactive responders to ar
frequency (EEG) and shorter latencies of selected EP (evoked potential; visual or auditory) waves than c
electrophysiologic parameters may be of practical use in the selection of potential nonresponders. It was
found in the clinical efficacy between d-amphetamine and l-amphetamine as reported by the parents anc
2) One study found that once an effective dose of dextroamphetamine sulfate is determined, tolerance t
collected from neurophysiologic tests were used to assess tolerance to dextroamphetamine in 6 hyperac
The lack of tolerance displayed in this study is encouraging from many points of view, but the small popu
generalizations difficult (Golinko et al, 1981).
3) Others studied the urinary and plasma monoamines and metabolites within the same clinical sample
hyperactivity treated with dextroamphetamine (up to 1.5 milligrams/kg/day), methylphenidate (up to 3 mil
double-blind, crossover trial. Both drugs showed striking clinical efficacy. Dextroamphetamine, but not m
methoxy-4-hydroxyphenyl glycol and whole body norepinephrine turnover. Either drug did not alter the u
acid. Methylphenidate but not dextroamphetamine increased plasma norephinephrine. Urinary epinephri
drugs (Elia et al, 1990).
4) Ten boys diagnosed as having attention deficit disorder with hyperactivity and conduct problems were
crossover trial to determine the aggression lowering effect of dextroamphetamine. Drug dosages ranged
milligram/kilogram) divided over a 2-week period. The authors concluded that dextroamphetamine reduc
playroom observation of overt aggressive behavior (Amery et al, 1984).
5) Dextroamphetamine in doses ranging from 2.5 to 15 milligrams/day has been found to improve symp
MINIMAL BRAIN DYSFUNCTION in certain selected pediatric patients as measured by increase in atter
(Green & Warshauer, 1981b; Gross, 1976; Burks, 1964).

4.5.B.2 Cocaine dependence

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:

Dextroamphetamine may diminish cocaine responsiveness (Grabowski et al, 2001)

c) Adult:

1) DEXTROAMPHETAMINE sustained-release (DEX) appears to warrant further study as agonist treatr
double-blind, placebo-controlled trial (n=128). At entry, subjects were randomized to 1 of 3 regimens: pla
mg, or DEX 30 mg later raised to 60 mg. Study drugs were administered twice daily, within 2 hours of aw
period was 10 days in length, followed by a 4-week study period. Then doses were doubled and the seco
followed by 8-week study period. Participants attended the clinic twice a week for obtaining medication, p
behavioral therapy session. Study completion/retention rates were 22.9%, 40.4%, and 8.7% for the place
group, respectively (p=0.0012 for the rate differences). Amphetamine-positive urine screens indicated th
ranged from 81% to 82%. Urine screens were considered positive for cocaine if benzoylecgonine levels
subjects had no positive urine screens from intake through study completion; these subjects were remov
the study, the proportion of cocaine urine screens that were positive approximated 80% for the placebo g
32% to 33% for the 30/60-mg group. The difference between the placebo and 30/60-mg group almost re
month (p=0.061). Scores on the Beck Depression Inventory declined for the 30/60-mg group, increased
the placebo group. Six subjects dropped out due to side effects of study medication (Grabowski et al, 20

4.5.B.3 Depression

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Dextroamphetamine has been used successfully to treat depression, including AIDS patients with lo
Placebo-controlled studies are lacking

c) Adult:

1) Dextroamphetamine was found to be effective for treatment of post-stroke depression. Researchers r
stroke depression treated with either DEXTROAMPHETAMINE or METHYLPHENIDATE during a 5-year
of patients improved on psychostimulants; 47% of patients demonstrated a marked or moderate improve
difference in efficacy existed between the 2 agents. Patients improved quickly within the first 2 days. Onl
treatment due to side effects.
2) A positive therapeutic response to DEXTROAMPHETAMINE therapy in 3 medically-ill and depressed
1982). The patients were diagnosed as having a secondary depression that met DSM-III criteria for majc
with, a medical illness. In a pilot open-label study, DEXTROAMPHETAMINE was used successfully to in
patients (Wagner et al, 1997).
3) Arousal, mood, and anorexic effects improved in a dose-related manner with DEXTROAMPHETAMIN

evaluated for the effect of DEXTROAMPHETAMINE on visual analogue scale (VAS) ratings of hunger, a
Subjects were given placebo, dextroamphetamine 10 milligrams, and dextroamphetamine 20 milligrams
effect of the 2 dextroamphetamine doses were statistically significant. Subjective ratings of arousal and r
compared to placebo.
4) One study examined the effect of intravenous DEXTROAMPHETAMINE in 21 depressed patients (Pc
as having unipolar disease and 10 as having bipolar disease. All patients received piribedil (a direct-actir
(100 to 240 milligrams/dose) and dextroamphetamine 20 milligrams. Results showed consistent psychor
following dextroamphetamine administration, although a range of effects on mood (from euphoria to dysp

a) Combination Therapy

1) The combination of monoamine oxidase (MAO) inhibitors (tranylcypromine, isocarboxazid, p
methylphenidate) has been effective therapy in severe treatment-resistant depression. In additi
stimulants plus tricyclic antidepressants (amitriptyline, protriptyline, amoxapine, nortriptyline) ha
intractable depression (Sovner, 1990)(Feighner et al, 1985). Although no serious side-effects w
an overdose situation could be fatal. With the advent of newer and safer agents such as the ser
MAO Inhibitors, stimulants, and cyclic antidepressants should have a limited role in the treatme

4.5.B.4 Mania

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:

Case reports have suggested that amphetamines may be of benefit in the treatment of acute mania

c) Adult:

1) One group of investigators conducted a study to evaluate the effect of dextroamphetamine on mania
dextroamphetamine 15 milligrams every 6 hours (total daily dose, 60 milligrams) for 72 hours (Garvey et
of the 6 (83%) patients experienced a 50% or greater reduction in their Raskin Severity of Mania scores,
therapy: 2 refused participation, 1 was lethargic and nauseated, 1 complained of "skipped" heart beats, a
severe manic symptoms. No patient demonstrated a worsening of manic or other psychiatric symptoms v

4.5.B.5 Narcolepsy

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (age 6 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:

Dextroamphetamine is indicated for the treatment of narcolepsy, and dosage should be individualize
dextroamphetamine sulfate oral tablets, 2007; Prod Info dextroamphetamine sulfate oral tablets, 200
Dextroamphetamine is effective in reducing the frequency and duration of narcoleptic attacks (Schin

4.5.B.6 Personality disorder

a) Overview

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

b) Summary:

Dextroamphetamine, administered to patients with borderline personality disorder, may lead to symp
al, 1985)

c) Adult:

1) Dextroamphetamine 30 milligrams was administered to 8 BORDERLINE PERSONALITY DISORDEF
study. The results were compared to the responses of healthy patients under identical conditions. All pat
Dextroamphetamine led to symptoms of psychosis in 50% of the borderline patients, while none of the h
procedure. Global feelings of well-being were significantly elevated in the borderline group as compared
reduced response to growth hormone after dextroamphetamine compared to healthy patients, but this w
borderline personality disorder patients respond differently to dextroamphetamine than healthy patients (
2) Researchers studied 16 patients in whom borderline personality disorder was suspected to determine
following ingestion of a dopamine-agonist. In this double-blind study, none of the patients had been rece
Patients were randomly assigned to receive placebo or 30 milligrams dextroamphetamine and then cros
received only dextroamphetamine because they became transiently psychotic during testing and were gi
Psychiatric Rating Scale (BPRS) scores significantly increased from baseline after dextroamphetamine a
disturbance were the symptoms that significantly changed. Those patients with borderline personality dis

more psychotic symptoms after receiving amphetamine than did the patients with borderline personality
p=0.06). The authors conclude that not only do borderline patients change significantly following dextroa
response to dextroamphetamine in borderline patients is not heterogeneous as some patients have a wo
(Schulz et al, 1988).

4.5.B.7 Schizophrenia

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:

Amphetamine improves symptoms in some patients with schizophrenia.
Dopaminergic functions are reduced in the frontal cortex in schizophrenia; the use of a dopamine ag
cortical function in patients with schizophrenia.
However, because amphetamines are not selective, it would also increase dopamine release and bl
systems, possibly exacerbating psychotic symptoms.

c) Adult:

1) One report briefly describes 2 patients diagnosed with schizophrenia and nonresponsive to neurolept
in disease after the initiation of dextroamphetamine 5 to 10 milligrams/day (Desai et al, 1984).

2) One study demonstrated that intravenous dextroamphetamine (20 milligrams) induced an acute chan
Of the 45 drug-free SCHIZOPHRENIC PATIENTS studied, 18 patients worsened, 13 improved, and 14 h
Placebo produced no change in 14 patients. The 18 patients who worsened after dextroamphetamine ha
for the main metabolite of norepinephrine, 3-methoxy-4-hydroxyphenylglycol, as compared to those patie
who worsened were also significantly more psychotic at baseline than those patients who indicated no cl
schizophrenia is state-dependent and not trait-dependent (van Kammen et al, 1982).

3) Investigators administered dextroamphetamine 0.25 milligram/kilogram orally to 21 patients with chro
controlled, crossover study. All patients were receiving haloperidol 0.4 milligram/kilogram day. The result
more active and performed psychomotor tests more quickly while receiving amphetamine. Six patients w
terms of affect, cooperation, and engagement with the environment. However, the authors do not advoca
of schizophrenia (Goldberg et al, 1991).

4.5.B.8 Sleep deprivation

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Dextroamphetamine enhanced aviator performance during periods of forced wakefulness and sleep
placebo (Caldwell et al, 2000)

c) Adult:

1) Oral dextroamphetamine (DXT) maintained helicopter pilots (n=6; 5 men, 1 woman) in simulator flight
cycles, based on a double-blind, placebo-controlled trial. The greatest difference in the effects of DXT ar
periods (from approximately 0300 to 1200) on the second and third days without sleep (sleep deprivatior
Dextroamphetamine 10 milligrams or placebo was given at midnight, 0400, and 0800 on sleep deprivatic
deprivation cycles, with a 2-day interval between cycles. Performance on the flight simulator was worse
and 1300 on the first deprivation day, and on all flight-simulation times during the second deprivation day
monitoring showed higher delta and theta brain activity (normally predominant during sleep) under place
DXT, self-perceptions of vigor were maintained, while perceptions of fatigue and confusion were reduced
placebo than DXT. Recovery sleep was lighter after DXT, with disturbed REM sleep. No clinically signific
(Caldwell et al, 2000).

4.6 Comparative Efficacy / Evaluation With Other Therapies

Diethylpropion

Fenfluramine

Mazindol

Methylphenidate

Modafinil

Pemoline

Phentermine

4.6.A Diethylpropion

4.6.A.1 Obesity

a) The amphetamines (amphetamine sulfate, dextroamphetamine sulfate, methamphetamine HCl) are no lor
their high incidence of cardiovascular side effects and high abuse potential (Douglas & Munro, 1981; AMA De
effective as amphetamines in suppressing appetite (Scoville, 1973) but produces minimal cardiovascular effe

4.6.B Fenfluramine

Attention deficit hyperactivity disorder

Obesity

4.6.B.1 Attention deficit hyperactivity disorder

a) Dextroamphetamine was better than fenfluramine and placebo in reducing motor activity and in improving
diagnoses of attention deficit disorder with hyperactivity during a randomized, double-blind, crossover trial (D
b) Dextroamphetamine sulfate (0.5 milligram/kilogram/day, given in 2 divided doses) was reported effective i
hyperactivity (ADD) in a double-blind comparison with placebo and fenfluramine (Donnelly et al, 1989). Dextr
improvement in disruptive, overactive behavior. However, fenfluramine (in doses of 0.6 milligram/kilogram/da
milligrams/kilogram/day) produced no effect on any behavioral measure. Both drugs reportedly decreased lev
hydroxyphenylglycol (MHPG) and vanillylmandelic acid; however, fenfluramine also produced decreases in p
urinary norepinephrine. Urinary epinephrine levels were increased with dextroamphetamine but decreased si
decreased significantly with both agents. The results of this double-blind, crossover study suggest that fenflu
or other behaviors in children with ADD who are responsive to dextroamphetamine therapy. Differences in ef
similarity of the 2 agents, as well as some common overall effects on catecholamine metabolism and similar

4.6.B.2 Obesity

a) Dextroamphetamine was superior to fenfluramine and placebo in terms of weight loss, behavioral treatme
habit change in 59 overweight female volunteers during a 5-week, randomized, double-blind study (Bigelow e
no significant differences in mean weight between the 3 treatment groups. Also, none of the groups differed s
Patients in the fenfluramine group reported the most gastrointestinal upset, while the dextroamphetamine gro
stimulation.
b) Fenfluramine and dextroamphetamine were comparable in the treatment of obesity. In a study with fenflu
were randomly assigned to 1 of 3 groups: fenfluramine 20 mg, dextroamphetamine 5 mg, or placebo. Patient
three times a day at least one hour before meals. The patients who tolerated the drugs were allowed to increa
and were given advice on eating habits, but no specific diet was prescribed. Fenfluramine was clearly more e
dextroamphetamine in producing weight loss. At 7 weeks, fenfluramine patients lost 6.6 pounds compared to
The frequency of adverse effects with fenfluramine was significantly higher than with dextroamphetamine (St

4.6.C Mazindol

Narcolepsy

Obesity

4.6.C.1 Narcolepsy

a) Mazindol and dextroamphetamine were comparable for narcolepsy therapy. Mazindol was retrospectively
treatment of narcolepsy in 34 patients (Parkes & Schachter, 1979). Thirty-two patients had previously receive
daily (mean dose 47 milligrams). Oral mazindol was given as an initial dose of 2 milligrams twice a day 7 day
The dose of mazindol was adjusted by clinical response. After 1 year of treatment, the daily mazindol doses r
mazindol, 25 patients received clomipramine and 6 received clonazepam for cataplexy. Mazindol produced s
day-sleep attacks by 50%. This response was similar to that seen with dextroamphetamine, and both treatme
some patients responded to one drug and not the other. Mazindol had no effect on cataplexy or sleep paralys
with mazindol compared to dextroamphetamine. Mazindol produced less euphoria, sweating, and palpitations
considered as effective as dextroamphetamine 50 milligrams/day in preventing narcolepsy.

4.6.C.2 Obesity

a) Mazindol is as effective or more effective than dextroamphetamine in the treatment of exogenous obesity 1980a). Comparable doses are mazindol 1 milligram three times a day and dextroamphetamine 5 milligrams 1980a). Mazindol is indicated over dextroamphetamine and all amphetamines for the treatment of obesity. In treatment of obesity due to the high probability for dependence and the lack of significant advantages over ot

b) Mazindol is chemically unrelated to amphetamine derivatives; however, the anorectic effects are mediatec not serotoninergic mechanisms) (Garratini et al, 1974). Mazindol has some advantages over amphetamine d dependence potential (Craddock, 1976). Mazindol does produce stimulation to the central nervous system, b less severe than with amphetamines (Craddock, 1976). In addition, mazindol appears to be relatively safe for diabetes mellitus, mild-to-moderate hypertension, and rheumatoid arthritis are present (Weintraub & Lasagna used in patients with hypertension or diabetes.

4.6.D Methylphenidate

4.6.D.1 Attention deficit hyperactivity disorder

a) SUMMARY: In comparative studies, Adderall(R) (combination AMPHETAMINE/DEXTROAMPHETAMINE efficacy in the treatment of attention deficit hyperactive disorder in children. METHYLPHENIDATE requires tv daily doses.

b) The racemic mixture of L- and D-amphetamine (ADDERALL (R)) was at least as effective as methylpheni deficit hyperactivity disorder (ADHD), and was more effective at 4 to 5 hours post-administration (beyond met this within-subject, double-blind, placebo-controlled, crossover study, 25 children with ADHD (mean age 9.6 y (mg), 17.5 mg, Adderall (R) 7.5 mg, 12.5 mg, and placebo twice a day (at 7:45 a.m. and 12:15 p.m.) in a ranc Teachers and counselors rated their behavior throughout the day and at times beyond methylphenidate's exp Parents rated them at the end of the day and in the evening for possible rebound effects. When compared to significantly improved in-school behaviors (p less than 0.0001 and 0.001, respectively), classroom measures than 0.0001), and after-school behaviors (p less than 0.0001). Drug effects were significantly affected by time resulted in higher effect size (ES) than methylphenidate and higher doses consistently resulted in higher ES t significantly more effective than methylphenidate at midday and end of day (p less than 0.05). The ES of both increased in the afternoon, implicating the possibility of reducing the afternoon dose. Side effects were report preclude the use of both medications. Only 1 patient was eliminated from the study due to exacerbation of his to evaluate the possibility of once daily dosing of Adderall(R), and to compare the efficacy of methylphenidate

c) Once-daily Adderall(R) (combination AMPHETAMINE/DEXTROAMPHETAMINE) appeared to be as effec treatment of attention deficit hyperactive disorder in children aged 6 to 12 years, according to a double-blind, Also, a mid-afternoon dose of either Adderall or methylphenidate (MPH) produced better evening behavior th although either active treatment tended to induce loss of appetite and sleep difficulties. In a randomized mani received each day 1 of 7 treatment protocols: (1)MPH 0.3 milligram/kilogram (mg/kg) at 7:30, 11:30, and 15:3 MPH 0.15 mg/kg at 15:30; (3)MPH 0.3 mg/kg at 7:30; (4)Adderall 0.3 mg/kg at 7:30 and 15:30; (5)Adderall 0. 15:30; (6)Adderall 0.3 mg/kg at 7:30; or (7)placebo. While twice-daily MPH 0.3 mg/kg did not differ significant single morning-dose MPH 0.3 mg/kg produced less significant effects than either once-daily Adderall 0.3 mg/ MPH began to lose its effectiveness approximately 6.5 hours later. Evening behavior was rated better after M no evening differences were seen after mid-afternoon doses of either 0.3 or 0.15 mg/kg. Children showed dif responded more positively to MPH, 37% responded more positively to Adderall, and 38% responded equally responding more positively to MPH, one dose of MPH was sufficient to carry them all day and into the evenin positively to Adderall needed only once-daily dosing of the drug (Pelham et al, 1999a).

d) In a direct, double-blind, cross-over comparison of adverse effect profiles, both DEXTROAMPHETAMINE METHYLPHENIDATE 0.3 mg/kg twice daily were well-tolerated in 125 children with attention deficit disorder reported more frequently during drug therapy than at baseline were appetite suppression (both drugs) and ins severity of adverse effects was significantly higher in the dextroamphetamine group. However, only 1.6% of c because of adverse effects (Efron et al, 1997).

4.6.E Modafinil

Attention deficit hyperactivity disorder, Adult

Sleep disorder

4.6.E.1 Attention deficit hyperactivity disorder, Adult

a) Both modafinil and dextroamphetamine demonstrated efficacy and were well tolerated in the treatment of adults. During a double-blind, three-phase crossover study, 22 adults (mean age 40.8 years) who met DSM-I modafinil, dextroamphetamine, and placebo. The study design included three, 2-week drug treatment phases periods. At the beginning of each drug phase, patients received one capsule twice daily containing 50 milligra lactose. The dose was increased by an additional capsule twice daily every 1 to 2 days as tolerated up to a m dextroamphetamine, or 8 capsules of lactose. The mean optimum doses of modafinil and dextroamphetamin respectively. Rating scales and cognitive testing were completed at baseline and on the last day of each drug

When compared to placebo, modafinil and dextroamphetamine were associated with a significant reduction c (p less than 0.001). Although not statistically significant, less severe ADHD symptoms were associated with r Cognitive performance as measured by the Controlled Oral Word Association Test (COWAT) reached trend l compared to placebo (p less than 0.05). Both modafinil and dextroamphetamine were well-tolerated with insc suppression being the most commonly reported adverse effects (Taylor & Russo, 2000).

4.6.E.2 Sleep disorder

a) In studies involving healthy young and elderly subjects, oral modafinil 100 to 200 milligrams (mg) modafin of normal sleep than with dextroamphetamine 10 to 20 mg. Specifically, dextroamphetamine produced greate architecture, and deterioration of subjective sleep quality. The authors suggest the importance of differentiati from "vigilance-increasing" properties of amphetamines (Saletu et al, 1989a; Saletu et al, 1989). However, di significant in these studies. Total sleep time and sleep efficiency were also reduced significantly by modafinil with dextroamphetamine.

4.6.F Pemoline

4.6.F.1 Attention deficit hyperactivity disorder

a) Dextroamphetamine and pemoline are comparable for the treatment of attention deficit disorder. Magnesi dextroamphetamine in a double-blind, randomized, placebo-controlled study of 81 children with minimal brair received a maximum dose of 125 milligrams magnesium pemoline (mean 82 milligrams) and 40 milligrams of psychological tests were administered at baseline and at 8 weeks. At both 4 and 8 weeks, both drugs were s dextroamphetamine patients, 77% of the pemoline patients, and 30% of the placebo patients were improved. significant (p less than 0.003) changes for defiance, inattentiveness, and hyperactivity factors with both drugs showed a significant effect at 2 weeks (p=0.057) and at 4 weeks (p=0.022) compared to pemoline. Only after from placebo. After 8 weeks, however, the 2 treatments were indistinguishable for these factors. Anxiety and either drug. On the eight-factor parent symptom list, conduct disturbance, impulsivity, immaturity, and antisoc than 0.04). Factors not affected were anxiety, somatic complaints, obsessional traits, and hyperactivity. A res weeks and no difference between the 2 drugs was demonstrated at 8 weeks. The psychological test battery s placebo (p less than 0.004) in spelling, reading, Porteus Mazes, Frostig perceptual quotient, eye-motor coord drug-drug differences were noted. The major side effects with both drugs were insomnia and anorexia; insom therapy. Less than 5% of patients on dextroamphetamine experienced moderate or severe insomnia by the e psychological heterogenicity exists among children with minimal brain dysfunction. A child should receive dru probability that he will respond has been determined.

4.6.G Phentermine

4.6.G.1 Obesity

a) Despite differences in the pharmacologic effects and toxicity of the available anorexiant agents, all of the and no drug has been found superior to dextroamphetamine (AMA Department of Drugs, 1983). In addition, t of Drugs has indicated that amphetamines have no advantages over other anorectic agents that have a lowe Diethylpropion, mazindol, and phentermine are the preferred drugs for the management of obesity, based up central nervous system or cardiovascular toxicity (AMA Department of Drugs, 1983).

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Last Modified: June 18, 2009

DRUGDEX® Evaluations

VENLAFAXINE

0.0 Overview

1) Class
- **a)** This drug is a member of the following class(es):
  - Antidepressant
  - Antidepressant, Bicyclic
  - Phenethylamine (class)
  - Serotonin/Norepinephrine Reuptake Inhibitor

2) Dosing Information
- **a)** Venlafaxine Hydrochloride
  - **1)** Adult
    - **a)** may convert to extended-release capsules or tablets based on nearest equivalent dose (mg/day) of stable
    2008; Prod Info venlafaxine extended release oral tablets, 2008)
    - **b)** taper dose prior to discontinuation to minimize risk of withdrawal symptoms (Prod Info EFFEXOR(R) oral
    venlafaxine extended release oral tablets, 2008)
      - **1)** Generalized anxiety disorder
        - **a)** (extended-release capsule) initial, 37.5 to 75 mg/day ORALLY (single dose); may increase dosag
        extended-release oral capsules, 2008)
      - **2)** Major depressive disorder
        - **a)** (immediate-release tablets) outpatients, 75 mg/day ORALLY (2-3 divided doses); may increase d
        oral tablets, 2008)
        - **b)** (immediate-release tablets) inpatients, 75 mg/day ORALLY (2-3 divided doses); may increase do
        Info EFFEXOR(R) oral tablets, 2008)
        - **c)** (extended-release capsules and tablets) 37.5 to 75 mg/day ORALLY (single dose); may increase
        XR(R) extended-release oral capsules, 2008; Prod Info venlafaxine extended release oral tablets, 2
      - **3)** Panic disorder, With or without agoraphobia
        - **a)** (extended-release capsule) starting dose, 37.5 mg/day ORALLY for 7 days; increase dose after
        intervals to a MAX dose of 225 mg/day (Prod Info EFFEXOR XR(R) extended-release oral capsules
      - **4)** Social phobia
        - **a)** (extended-release capsules and tablets) 75 mg/day ORALLY (single-dose) (Prod Info EFFEXOR
        tablets, 2008)
  - **2)** Pediatric
    - **a)** safety and efficacy not established in children (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFE
    release oral tablets, 2008)

3) Contraindications
- **a)** Venlafaxine Hydrochloride
  - **1)** concomitant use of monoamine oxidase inhibitors (MAOI) (Prod Info Effexor(R) oral tablets, 2009; Prod Info Ef
  release oral tablets, 2009)

4) Serious Adverse Effects
- **a)** Venlafaxine Hydrochloride
  - **1)** Bleeding, Abnormal
  - **2)** Depression, exacerbation
  - **3)** Gastrointestinal hemorrhage
  - **4)** Hepatitis
  - **5)** Hypomania
  - **6)** Hyponatremia
  - **7)** Mania
  - **8)** Neuroleptic malignant syndrome
  - **9)** Seizure
  - **10)** Serotonin syndrome
  - **11)** Suicidal thoughts

5) Clinical Applications
- **a)** Venlafaxine Hydrochloride
  - **1)** FDA Approved Indications
    - **a)** Generalized anxiety disorder
    - **b)** Major depressive disorder
    - **c)** Panic disorder, With or without agoraphobia
    - **d)** Social phobia

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

Venlafaxine
Venlafaxine HCl
Venlafaxine Hydrochloride

C) Physicochemical Properties

1) Venlafaxine Hydrochloride

a) Molecular Weight

1) O-desmethylvenlafaxine (ODV): 263 (Howell et al, 1993); Venlafaxine: 277 (Howell et al, 1993); Venla EFFEXOR XR(R) extended-release oral capsules, 2008; Canada, 1997)

b) Partition Coefficient

1) Octanol/water: 0.43 (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extendec

c) pKa

1) 9.4 (Ellingrod & Perry, 1994)

d) Solubility

1) Venlafaxine hydrochloride has a solubility of 572 milligrams/milliliter in water adjusted to ionic strengtl Info EFFEXOR XR(R) extended-release oral capsules, 2008).

1.2 Storage and Stability

A) Venlafaxine Hydrochloride

1) Preparation

a) Oral route

1) Venlafaxine and venlafaxine extended-release should not be administered concurrently with a monoa and initiation of venlafaxine hydrochloride or at least 7 days between discontinuation of venlafaxine hydr EFFEXOR XR(R) extended-release oral capsules, 2008; Prod Info venlafaxine extended release oral tab

2) Administer venlafaxine and venlafaxine extended-release with food at approximately the same time e release oral capsules, 2008; Prod Info venlafaxine extended release oral tablets, 2008).

3) Swallow venlafaxine extended-release (XR) capsules and tablets whole with fluid. Do not divide, crus XR capsules may be administered by opening the capsule and sprinkling the contents on a spoonful of a (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008; Prod Info venlafaxine extended relea

B) Venlafaxine Hydrochloride

1) Oral route

a) Capsule, Extended Release/Tablet

1) Store at controlled room temperature, 20 to 25 degrees Celsius (68 to 77 degrees Fahrenheit) (Prod capsules, 2008).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Geriatric Patients

Dosage Adjustment During Dialysis

Dosage in Other Disease States

1.3.1 Normal Dosage

1.3.1.A Venlafaxine Hydrochloride

1.3.1.A.1 Oral route

Generalized anxiety disorder

Major depressive disorder

Panic disorder, With or without agoraphobia

Social phobia

1.3.1.A.1.a Generalized anxiety disorder

1) The initial recommended dosage for venlafaxine extended-release (XR) is 75 milligrams (mg)/da should be taken consistently at the same time each day. To allow new patients to adjust to therapy, made at intervals of at least 4 days. The maximum recommended dose is 225 mg/day. Although ver the need for continuing medication in patients with generalized anxiety disorder who improve with ve extended-release oral capsules, 2008).

1.3.1.A.1.b Major depressive disorder

1) The initial recommended dosage of regular-release venlafaxine is 75 milligrams (mg)/day, admin mg/day at intervals of at least 4 days. In the outpatient setting, doses above 225 mg/day demonstra inpatients responded to a mean dose of 350 mg/day. Therefore, the maximum recommended dose generally recommended that acute episodes of major depressive disorder be treated with sustained unknown whether the dose of venlafaxine required for maintenance treatment is the same as the do recommended in order to determine need for maintenance treatment and the appropriate maintenar

2) The initial recommended dosage for venlafaxine extended-release capsules and tablets is 75 mil may be taken in the morning or evening but should be taken consistently at the same time each day for 4 to 7 days. Dosage increases of 75 mg/day should be made at intervals of at least 4 days. The episodes of major depressive disorder be treated with sustained pharmacological therapy for severa required for maintenance treatment is the same as the dose needed to achieve an initial response. maintenance treatment and the appropriate maintenance dose (Prod Info EFFEXOR XR(R) extende

3) Administration of immediate-release venlafaxine once daily versus twice daily produced similar ir produced more rapid improvement (at 2 weeks) than once daily administration, but dose escalation once daily dosing, dose escalation proceeded as follows: (1) week 1 - 37.5 milligrams daily, (2) wee The twice daily regimen was similar except for the initial week where patients received 37.5 mg on c

1.3.1.A.1.c Panic disorder, With or without agoraphobia

1) The recommended starting dose of venlafaxine hydrochloride extended-release (XR) capsules fo day orally for 7 days. The dose may be increased to 75 mg per day after 1 week. For patients not re made at intervals of not less than 7 days. The maximum recommended dose is 225 mg per day (Pro

2) Patients may need to be evaluated periodically to determine the need for continuing medication. treatment with venlafaxine XR, patients who continued on venlafaxine XR experienced a significantl extended-release oral capsules, 2008).

1.3.1.A.1.d Social phobia

1) The initial recommended dosage for venlafaxine extended-release capsules and tablets is 75 mil evening but should be taken consistently at the same time each day. There is no evidence that high and efficacy in clinical trials lasting up to 6 months, the need for continuing medication in patients wi periodically reassessed (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008; Prod Inf

1.3.1.A.1.e Conversion To Venlafaxine XR

1) Depressed patients who are stabilized on immediate-release venlafaxine may be switched to the tablets. Further, individual dosage adjustments may be necessary (Prod Info EFFEXOR XR(R) exte 2008).

1.3.1.A.1.f Withdrawal Schedule

1) To minimize the risk of withdrawal symptoms, a gradual reduction in the dose rather than abrupt recommended. During clinical trials, the dose of venlafaxine XR was reduced by 75 milligrams per d EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008;

1.3.2 Dosage in Renal Failure

A) Venlafaxine Hydrochloride

1) During clinical trials, clearance was decreased while the elimination half-life was increased for venlafaxine filtration rate between 10 and 70 milliliters/minute). Therefore, the total daily dose should be reduced by 25% tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008; Prod Info venlafaxine exten

1.3.3 Dosage in Hepatic Insufficiency

A) Venlafaxine Hydrochloride
1) During clinical trials, clearance of venlafaxine was decreased while the elimination half-life was increased and mild to moderate hepatic impairment. Therefore, the total daily dose should be reduced by 50% in patien dose even more than 50%, and further individualization of dose may be necessary in some patients with cirrh EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008; Prod Info

1.3.4 Dosage in Geriatric Patients
A) Venlafaxine Hydrochloride
1) Clearance of venlafaxine is reduced by approximately 15% in the elderly, presumably because of the sligh adjustment based upon age of the patient is generally unnecessary. However, caution should be taken when EFFEXOR XR(R) extended-release oral capsules, 2008; Prod Info venlafaxine extended release oral tablets,

1.3.5 Dosage Adjustment During Dialysis
A) Venlafaxine Hydrochloride
1) Total daily dose should be reduced by 50% in hemodialysis patients (Prod Info EFFEXOR(R) oral tablets, venlafaxine extended release oral tablets, 2008).

1.3.6 Dosage in Other Disease States
A) Venlafaxine Hydrochloride
1) Pregnancy
a) Neonatal complications requiring prolonged hospitalization, respiratory support, and tube feeding hav reuptake inhibitors, and selective serotonin reuptake inhibitors late in the third trimester. The physician m tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008; Prod Info venlafaxine e

1.4 Pediatric Dosage

1.4.1 Normal Dosage

1.4.1.A Venlafaxine Hydrochloride

1.4.1.A.1 Oral route
a) The safety and efficacy have not been established in children (Prod Info EFFEXOR(R) oral tablets, 2(venlafaxine extended release oral tablets, 2008).

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration
A) Onset
1) Venlafaxine Hydrochloride
a) Initial Response
1) Depression, oral: 2 weeks to several months (Cantu et al, 1994; Montgomery, 1993; Prod Info EFFE) 2008)
a) Although some symptoms of major depression may improve within about 2 weeks (Cantu et al, 1 longer (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-release ora

2.2 Drug Concentration Levels
A) Venlafaxine Hydrochloride
1) Peak Concentration
a) Venlafaxine hydrochloride, oral, regular-release tablets: 53 ng/mL (25-mg dose); 167 to 225 ng/mL (75-mg
1) Mean Cmax for venlafaxine regular-release when 75 milligrams was administered every 12 hours wa 2008)
2) Mean Cmax values following administration of 25, 75, or 150 mg of the regular-release dosage form c 167, and 393 nanograms/mL (0.19, 0.603, and 1.42 micromoles/L), respectively (Klamerus et al, 1992a). venlafaxine per day (Prod Info EFFEXOR(R) oral tablets, 2008; Schweizer et al, 1994).
b) Venlafaxine hydrochloride, oral, extended-release capsules: 150 ng/mL (Prod Info EFFEXOR XR(R) exte
1) The mean Cmax value of venlafaxine following administration of 150 milligrams extended-release cap between the regular- and extended-release formulations when equal daily doses were administered. The capsules. Venlafaxine exhibits linear pharmacokinetics over the dose range of 75 to 450 mg of venlafaxi
2) Time to Peak Concentration

a) Venlafaxine hydrochloride, oral, regular-release tablets: 1 to 2 hours (Prod Info EFFEXOR XR(R) extende
1) Mean Tmax for venlafaxine regular-release when 75 milligrams was administered every 12 hours was maximum concentration was not significantly different when venlafaxine was administered as a tablet or
b) Venlafaxine hydrochloride, oral, extended-release capsules: 5.5 hours (Prod Info EFFEXOR XR(R) exten
1) The mean Tmax value of venlafaxine following administration of 150 milligrams extended-release cap regular- and extended-release formulations when equal daily doses were administered. The fluctuation i Venlafaxine exhibits linear pharmacokinetics over the dose range of 75 to 450 mg of venlafaxine per day

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

Extracorporeal Elimination

2.3.1 Absorption

A) Venlafaxine Hydrochloride
1) Bioavailability
a) Oral, regular-release: 12.6% (Ellingrod & Perry, 1994d).
1) About 92% of an oral dose is absorbed. Due to extensive first pass metabolism, only 12.6% is av Perry, 1994d).
2) The relative bioavailability was 100% in tablet form when compared to an oral solution (Prod Info
3) Compared to healthy subjects, venlafaxine oral bioavailability increased 2- to 3-fold when admini Info EFFEXOR(R) oral tablets, 2008).
b) Oral, extended release: 45% (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008).
1) At least 92% of a single oral dose of venlafaxine is absorbed. The absolute bioavailability of venl capsules, 2008).
2) Compared to healthy subjects, venlafaxine oral bioavailability increased 2- to 3-fold when admini Info EFFEXOR XR(R) extended-release oral capsules, 2008).
2) Effects of Food
a) No effect on systemic bioavailability (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR
1) Food had no effect on the absorption or bioavailability of venlafaxine or its active metabolite, O-d EFFEXOR XR(R) extended-release oral capsules, 2008).

2.3.2 Distribution

A) Distribution Sites
1) Venlafaxine Hydrochloride
a) Protein Binding
1) 27% to 30% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-re
a) Venlafaxine and O-desmethylvenlafaxine, the major active metabolite, are approximately 27 Info EFFEXOR XR(R) extended-release oral capsules, 2008; Klamerus et al, 1992).
B) Distribution Kinetics
1) Venlafaxine Hydrochloride
a) Volume of Distribution
1) 7.5 L/kg (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-releas
a) The steady state volume of distribution is 7.5 and 5.7 L/kg for venlafaxine and O-desmethyl XR(R) extended-release oral capsules, 2008).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics
1) Venlafaxine Hydrochloride
a) Liver, extensive (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-rel
1) Venlafaxine is metabolized via the CYP2D6 isoenzyme (Prod Info EFFEXOR XR(R) extended-re
2) Following absorption, venlafaxine undergoes extensive first-pass metabolism in the liver, primaril desmethylvenlafaxine, N,O-didesmethylvenlafaxine, and other minor metabolites. The formation of release oral capsules, 2008; Troy et al, 1997b; Klamerus et al, 1992).
B) Metabolites

1) Venlafaxine Hydrochloride
a) O-desmethylvenlafaxine, active (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(
1) O-desmethylvenlafaxine is the only major active metabolite of venlafaxine hydrochloride (Prod In capsules, 2008).
b) N-desmethylvenlafaxine, active (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008; K
1) This metabolite is less active than O-desmethylvenlafaxine (Prod Info EFFEXOR XR(R) extende
c) N,O-didesmethylvenlafaxine, active (Prod Info EFFEXOR XR(R) extended-release oral capsules, 200
1) This metabolite is less active than O-desmethylvenlafaxine (Prod Info EFFEXOR XR(R) extende

2.3.4 Excretion

A) Kidney
1) Venlafaxine Hydrochloride
a) Renal Clearance (rate)
1) 0.074 to 0.079 L/hr/kg (Troy et al, 1997b).
b) Renal Excretion (%)
1) 87% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-release o
a) Within 48 hours, approximately 87% of a venlafaxine dose is recovered in the urine as eithe conjugated ODV (26%), or other minor inactive metabolites (27%). Renal elimination of venlafa tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008).
b) After single oral doses of venlafaxine 80 to 100 mg, approximately 1 to 10% is excreted in th desmethylvenlafaxine, the active metabolite. Another 6% to 19% and 1%, respectively, is excre al, 1992).

B) Feces
1) Venlafaxine Hydrochloride
a) 2% (Troy et al, 1994; Howell et al, 1993; Klamerus et al, 1992a)
1) Within 35 days, approximately 2% of a venlafaxine dose is excreted in the feces (Troy et al, 199

C) Total Body Clearance
1) Venlafaxine Hydrochloride
a) 1.3 L/hr/kg (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-release
1) Mean steady-state plasma clearance of venlafaxine and its major metabolite, O-desmethylvenlaf 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008).
2) After oral administration of venlafaxine to renally impaired patients (GFR of 10 to 70 milliliters/mi subjects. Clearance of O-desmethylvenlafaxine remained unchanged in patients with renal impairme EFFEXOR XR(R) extended-release oral capsules, 2008).
3) After oral administration of venlafaxine to patients requiring dialysis, the clearance of venlafaxine compared to normal subjects (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R
4) After oral administration of venlafaxine to 9 patients with hepatic cirrhosis, clearance of venlafaxi respectively. Three patients with more severe cirrhosis had an approximate 90% decrease in venlaf Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008).
5) After oral and intravenous administration of venlafaxine to Child-Pugh A (n=8) and Child-Pugh B more than 50% when compared to normal subjects (n=21). Clearance of O-desmethylvenlafaxine w EFFEXOR XR(R) extended-release oral capsules, 2008).

2.3.5 Elimination Half-life

A) Parent Compound
1) Venlafaxine Hydrochloride
a) ELIMINATION HALF-LIFE
1) 5 hours (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-releas
a) The mean steady state elimination half-life of venlafaxine is 5 hours (Prod Info EFFEXOR(R The elimination half-life is independent of the dose (Klamerus et al, 1992).
b) After oral administration of venlafaxine to 9 patients with hepatic cirrhosis, elimination half-lif tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008).
c) After oral and intravenous administration of venlafaxine to Child-Pugh A (n=8) and Child-Pug approximately twice as long as compared to normal subjects (n=21) (Prod Info EFFEXOR(R) or
d) After oral administration of venlafaxine to renally impaired patients (GFR of 10 to 70 milliliter compared to normal subjects (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR X
e) After oral administration of venlafaxine to patients requiring dialysis, the elimination half-life (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral c

B) Metabolites
1) Venlafaxine Hydrochloride
a) O-desmethylvenlafaxine, 11 hours (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR X
b) After oral administration of venlafaxine to 9 patients with hepatic cirrhosis, elimination half-life of O-de 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008).
c) After oral and intravenous administration of venlafaxine to Child-Pugh A (n=8) and Child-Pugh B (n=1 prolonged by approximately 40% as compared to normal subjects (n=21) (Prod Info EFFEXOR(R) oral ta
d) After oral administration of venlafaxine to renally impaired patients (GFR of 10 to 70 milliliters/minute compared to normal subjects (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) ext
e) After oral administration of venlafaxine to patients requiring dialysis, the elimination half-life of O-desv

(Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules,

2.3.6 Extracorporeal Elimination
A) Hemodialysis
1) Venlafaxine Hydrochloride
a) Dialyzable: No (Troy et al, 1994a).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING
1) Venlafaxine Hydrochloride
a) Oral (Tablet; Capsule, Extended Release; Tablet, Extended Release)
Suicidality and Antidepressant Drugs
Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in child
(MDD) and other psychiatric disorders. Anyone considering the use of venlafaxine hydrochloride or any other
clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants comp
antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric c
ages who are started on antidepressant therapy should be monitored appropriately and observed closely for
should be advised of the need for close observation and communication with the prescriber. Venlafaxine hyd
2009; Prod Info Effexor XR(R) extended-release oral capsules, 2009; Prod Info venlafaxine extended release

3.1 Contraindications
A) Venlafaxine Hydrochloride
1) concomitant use of monoamine oxidase inhibitors (MAOI) (Prod Info Effexor(R) oral tablets, 2009; Prod Info Ef
release oral tablets, 2009)

3.2 Precautions
A) Venlafaxine Hydrochloride
1) suicidal ideation and behavior or worsening depression has been reported, particularly in children, adolescents
monitoring recommended (Prod Info Effexor(R) oral tablets, 2009; Prod Info Effexor XR(R) extended-release oral
2) abnormal bleeding has been reported, including life-threatening hemorrhages (Prod Info Effexor(R) oral tablets
venlafaxine extended release oral tablets, 2009)
3) abrupt withdrawal; serious discontinuation symptoms have been reported; monitoring recommended; reduce d
extended-release oral capsules, 2009; Prod Info venlafaxine extended release oral tablets, 2009)
4) bipolar disorder; increased risk of precipitation of a mixed/manic episode; rule out disorder prior to initiating the
oral capsules, 2009; Prod Info venlafaxine extended release oral tablets, 2009)
5) concomitant use of NSAIDs, aspirin, warfarin, or other drugs that affect coagulation (Prod Info Effexor(R) oral t
venlafaxine extended release oral tablets, 2009)
6) concomitant use of serotonergic drugs (SSRIs, serotonin-norepinephrine reuptake inhibitors, triptans); use is n
extended-release oral capsules, 2009; Prod Info venlafaxine extended release oral tablets, 2009)
7) concomitant use with serotonin precursors, (eg, tryptophan supplements); use is not recommended (Prod Info
2009; Prod Info venlafaxine extended release oral tablets, 2009)
8) concomitant use with weight loss agents (eg, phentermine); use is not recommended (Prod Info Effexor(R) ora
venlafaxine extended release oral tablets, 2009)
9) glaucoma, narrow-angle (angle-closure glaucoma) or raised intraocular pressure, history or at risk for; increase
extended-release oral capsules, 2009; Prod Info venlafaxine extended release oral tablets, 2009)
10) hypertension, uncontrolled; may exacerbate condition (Prod Info Effexor(R) oral tablets, 2009; Prod Info Effe
oral tablets, 2009)
11) hypertension (sustained) has occurred; may require dose reduction or discontinuation (Prod Info Effexor(R) o
venlafaxine extended release oral tablets, 2009)
12) increased heart rate has been reported; underlying medical conditions associated with increased heart rate (e
(Prod Info Effexor(R) oral tablets, 2009; Prod Info Effexor XR(R) extended-release oral capsules, 2009; Prod Info
13) hepatic impairment, including cirrhosis; decreased venlafaxine clearance; lower dose may be required (Prod
2009; Prod Info venlafaxine extended release oral tablets, 2009)
14) interstitial lung disease and eosinophilic pneumonia have been rarely reported (Prod Info Effexor(R) oral tabl

venlafaxine extended release oral tablets, 2009)
15) mania, history; risk of activation of mania/hypomania (Prod Info Effexor(R) oral tablets, 2009; Prod Info Effex oral tablets, 2009)
16) medical diseases or conditions that could affect metabolism or hemodynamic responses (eg, myocardial infa XR(R) extended-release oral capsules, 2009)
17) renal impairment (glomerular filtration rate, 10 to 70 mL/min); decreased venlafaxine clearance; lower dose r release oral capsules, 2009; Prod Info venlafaxine extended release oral tablets, 2008)
18) seizures, history (Prod Info Effexor(R) oral tablets, 2009; Prod Info Effexor XR(R) extended-release oral caps
19) serotonin syndrome has been reported, including cases that are life-threatening or that resemble neuroleptic Prod Info Effexor XR(R) extended-release oral capsules, 2009)
20) use of venlafaxine within 14 days of MAOI discontinuation (Prod Info Effexor(R) oral tablets, 2009; Prod Info release oral tablets, 2009)
21) use of MAOIs within 7 days after venlafaxine discontinuation (Prod Info Effexor(R) oral tablets, 2009; Prod In release oral tablets, 2009)
22) volume-depleted, elderly, or concurrent diuretic therapy; hyponatremia, syndrome of inappropriate antidiureti Effexor(R) oral tablets, 2009; Prod Info Effexor XR(R) extended-release oral capsules, 2009; Prod Info venlafaxin

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Musculoskeletal Effects

Neurologic Effects

Ophthalmic Effects

Psychiatric Effects

Renal Effects

Reproductive Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

3.3.1.A Venlafaxine Hydrochloride

Heart failure

Hypertension

Increased heart rate

Palpitations

Prolonged QT interval

Summary

Vasodilatation

3.3.1.A.1 Heart failure

a) Two cases of interstitial pneumonia with heart failure have been reported following the use of venlafa month) in combination with steroid treatment led to a complete recovery in a 21- year-old woman. Howev multiple-organ failure and died despite attempts at treatment (Drent et al, 2003).

3.3.1.A.2 Hypertension

a) Incidence: 3% to 13%(Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extende

b) Immediate-release

1) In a dose comparison study of venlafaxine, a mean increase in supine diastolic blood pressure (S venlafaxine daily. There were essentially no changes observed in patients receiving 75 and 225 mg (Prod Info EFFEXOR(R) oral tablets, 2008).

2) Sustained increases in blood pressure have been reported in patients receiving therapeutic dose sustained increased supine diastolic blood pressure of 3% for venlafaxine doses less than 100 mg/c mg/day, and 13% for doses greater than 300 mg/day. Most of the blood pressure increases were be consequences. There have also been cases of elevated blood pressure during postmarketing use th controlled before treatment with venlafaxine and that blood pressure is routinely monitored during tr patients who experience a sustained increase in blood pressure while receiving venlafaxine (Prod In capsules, 2008).

3) Meta-analysis of controlled clinical studies revealed a crude incidence of sustained elevation in s imipramine, and 2.1% for placebo; this information was obtained during controlled clinical trials. Duri (p=0.0503) (Thase, 1998).

c) Extended-release

1) In premarketing studies, sustained hypertension occurred with the following frequency in patients capsules, 2008):

Studies #	Dose Range	Percent of patients with sustained HTN
Major depressive disorder	75 to 375 mg/day	3% (19/705)
Generalized anxiety disorder	37.5 to 225 mg/day	0.5% (5/101)
Social anxiety disorder	75 to 225 mg/day	0.6% (5/771)
Panic disorder	75 to 225 mg/day	0.9% (9/973)

Key: # = patients were on extended-release venlafaxine; * sustained hypertension (HTN) = defi mmHg or greater above baseline for 3 consecutive on-therapy visits; mg/day = milligrams/day; respectively; ** = up to 12 weeks and up to 6 months, respectively

Studies #	Discontinuation Rate due to sustained HTN ##	Range of SDBP increase
Major depressive disorder	0.7% (5/705)	12 to 16 mmHg
Generalized anxiety disorder	0.7% (10/1381) *	12 to 25 mmHg *
	1.3% (7/535) **	8 to 28 mmHg **
Social anxiety disorder	0.6% (5/771) ***	1 to 24 mmHg ***
Panic disorder	0.5% (5/1001) ***	7 to 19 mmHg ***

Key: # = patients were on extended-release venlafaxine; ## sustained hypertension (HTN) = defined as treatment-emergent supine diastolic blood pressure 90 mmHg or greater and 10 mmHg or greater above baseline for 3 consecutive on-therapy visits; * = up to 8 weeks; ** = up to 6 months;
*** = up to 12 weeks

Across all clinical trials in major depressive disorder, generalized anxiety disorder, social anxiet experienced an increase in supine diastolic blood pressure of 15 mmHg or more compared to 0 release venlafaxine experienced an increase in supine diastolic blood pressure of 20 mmHg or extended-release oral capsules, 2008).

3.3.1.A.3 Increased heart rate

a) Immediate-release

1) During clinical trials, venlafaxine hydrochloride treatment (averaged over all dose groups) was as no change for placebo. In a study with venlafaxine doses ranging from 200 to 375 milligrams (mg)/d approximately 2 beats per minute compared with a mean decrease of approximately 1 beat per minu

2) When electrocardiograms from 769 patients treated with venlafaxine and 450 patients with place baseline was 4 beats per minute in the venlafaxine group. In a flexible-dose study, the mean heart r

from 200 to 375 mg/day (mean dose greater than 300 mg/day) compared with 1.7 beats per minute heart rate include hyperthyroidism, heart failure, or recent myocardial infarction, particularly with dos

b) Extended-release

1) Treatment with extended-release venlafaxine was associated with a mean increase in pulse rate disorder, and panic disorder clinical trials (Prod Info EFFEXOR XR(R) extended-release oral capsul

Trial	Duration	Mean Change In Pulse Venlafaxine Extended-Release	Mean Char Plac
Major Depressive Disorder	up to 12 weeks	+ 2 beats/minute	+ 1 bea
Generalized Anxiety Disorder	up to 8 weeks	+ 2 beats/minute	+ less than 1
Social Anxiety Disorder	up to 12 weeks	+ 3 beats/minute	+ 1 bea
Panic Disorder	up to 12 weeks	+ 1 beat/minute	decrease of less t

2) When electrocardiograms were analyzed, extended-release venlafaxine was associated with an oral capsules, 2008). Results are summarized below:

Trial	Number of Patients With Analyzed Electrocardiograms (venlafaxine extended-release/placebo)	Mean Change In Hear Venlafaxine Exte
Major Depressive Disorder	495 (275/220)	+ 4 beats
Generalized Anxiety Disorder	908 (610/298)	+ 3 beats
Social Anxiety Disorder	1127 (593/534)	+ 5 beats
Panic Disorder	1056 (661/395)	+ 3 beat

3.3.1.A.4 Palpitations

a) Incidence: 3% (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008)

b) Palpitations have been reported in 3% of venlafaxine extended-release treated patients (n=819) com trials involving patients with social anxiety disorder (Prod Info EFFEXOR XR(R) extended-release oral ca

c) Palpitations were reported in 3 of 66 patients receiving venlafaxine 75 to 375 milligrams/day in one st

3.3.1.A.5 Prolonged QT interval

a) The corrected QT interval increased from baseline for venlafaxine extended-release treated patients recent history of myocardial infarction or unstable heart disease. The duration of the studies range from interval in venlafaxine extended-release relative to placebo treated patients (Prod Info EFFEXOR XR(R)

Studies	Mean change from baseline in QTc interval	
	Venlafaxine ER	Placebo
Major depressive disorder (n=495)	+ 4.7 msec	- 1.9 msec
Generalized anxiety disorder (n=908)	no difference from placebo	---
Social anxiety disorder (n=1127)	+ 3.4 msec	- 1.6 msec
Panic disorder (n=1056)	+ 1.5 msec	- 0.7 msec
Key: ER = extended-release; msec = millisecond		

b) A 60-year-old woman receiving 150 mg of venlafaxine daily for depression developed QT interval pro mmHg in both arms and mild dyspnea. An ECG showed sinus rhythm and a corrected QT (QTc) interval venlafaxine administration was stopped, and she was hospitalized for further evaluation. Her CBC, electr was not on any other medications besides venlafaxine and she denied consumption of grapefruit juice or death. A 24-hour ECG recorded multifocal premature ventricular complexes and couplets and a transtho the next several days, the QTc interval gradually decreased before stabilizing at 430 milliseconds (Letsa

3.3.1.A.6 Summary

a) Hypertension, palpitations, and vasodilation, primarily hot flashes have been experienced in patients EFFEXOR XR(R) extended-release oral capsules, 2008). The corrected QT interval increased from base placebo-treated patients. The mean heart rate increase was 8.5 beats per minute in patients receiving ve compared with 1.7 beats per minute for placebo (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EF prolongation has been reported in a 60-year-old woman receiving venlafaxine for depression (Letsas et a following the use of venlafaxine (Drent et al, 2003).

3.3.1.A.7 Vasodilatation

a) Incidence: 2% to 5.6% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR(R) XR oral ex

b) During a dose comparison trial involving 358 patients, the incidence of vasodilatation was 0% for plac 375 milligrams/day, respectively (Prod Info EFFEXOR(R) oral tablets, 2008).

c) Vasodilation, primarily hot flashes, occurred in 3% to 4% of patients on extended-release venlafaxine extended-release oral capsules, 2008).

3.3.2 Dermatologic Effects

3.3.2.A Venlafaxine Hydrochloride

Acquired keratoderma palmaris et plantaris

Alopecia

Subungual hyperkeratosis

Sweating symptom

3.3.2.A.1 Acquired keratoderma palmaris et plantaris

a) A 57-year-old male smoker acquired palmoplantar keratoderma (psoriasiform) and subungual hyperk soles showed evidence of severe hyperkeratosis with an inflammatory red border. The epidermis had ps infiltrate on histopathological specimens. Massive subungual hyperkeratosis with paronychia was noted was noted after topical treatment with 10% urea, salicylic acid, caryolysin and oral retinoids. Within 4 to 5 improvement of the nails occurred (Dalle et al, 2006).

3.3.2.A.2 Alopecia

a) A 50-year-old woman experienced hair loss while being treated for depression with venlafaxine. The of 75 milligrams (mg) per day was raised to 150 mg/day after two weeks. Two weeks later she began to venlafaxine after three months, and her hair loss stopped completely one month later. In another episode days after achieving the dose of 150 mg/day. She discontinued venlafaxine and attained complete remis

3.3.2.A.3 Subungual hyperkeratosis

a) A 57-year-old male smoker acquired palmoplantar keratoderma (psoriasiform) and subungual hyperk soles showed evidence of severe hyperkeratosis with an inflammatory red border. The epidermis had ps infiltrate on histopathological specimens. Massive subungual hyperkeratosis with paronychia was noted was noted after topical treatment with 10% urea, salicylic acid, caryolysin and oral retinoids. Within 4 to 5 improvement of the nails occurred (Dalle et al, 2006).

3.3.2.A.4 Sweating symptom

a) Incidence: 6.7% to 25% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) exter
b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 37 was 12% compared to 3% in patients receiving placebo (n=609) (Prod Info EFFEXOR(R) oral tablets, 20
c) During a dose comparison trial involving 358 patients, the incidence of sweating was 5.4% for placeb 375 milligrams/day, respectively (Prod Info EFFEXOR(R) oral tablets, 2008).
d) During clinical trials, sweating occurred in 10% to 14% of patients on extended-release venlafaxine c release capsules, 2006).

The table below provides the incidence rates of anorexia during clinical trials of extended-release ve

Studies	Incidence of Sweating	
	Venlafaxine ER	Placebo
Major depressive disorder (n=642)	14%	3%
Generalized anxiety disorder (n=1936)	10%	3%
Social anxiety disorder (n=1514)	13%	4%
Panic disorder (n=1663)	10%	2%
Key: ER = extended-release		

e) At 9 and 14 weeks, diaphoresis and pruritus occurred in 2 elderly women who were receiving venlafa (mg)/day and noted profuse night sweats, increased daytime sweating, and generalized itching without r without addition of allergy medications. The second patient noted profuse, generalized sweating and itch venlafaxine XR was effective in resolving her symptoms. The medication history, physical examination, a symptoms (Schwartz, 1999).
f) Profuse sweating has been reported in two patients following oral venlafaxine therapy for the treatmer (Adesanya & Varma, 1997; Garber & Gregory, 1997). The patient was restarted on venlafaxine therapy, diaphoresis did not recur, and the venlafaxine was increased to 75 mg three times daily with no subsequ
g) A study reported a 25% incidence of increased sweating in patients receiving venlafaxine 75 to 375 n (Schweizer et al, 1991).

3.3.3 Endocrine/Metabolic Effects

3.3.3.A Venlafaxine Hydrochloride

Height / growth finding

Hot sweats

Hyponatremia

Serum cholesterol raised

Serum triglycerides raised

Syndrome of inappropriate antidiuretic hormone secretion

Weight loss

3.3.3.A.1 Height / growth finding

a) Pediatric patients, especially patients younger than 12 years of age, on venlafaxine grew less than pe extended-release (n=122), on average, grew 0.3 centimeters (cm) compared with 1 cm for placebo treat disorder study. Pediatric patients on venlafaxine extended-release (n=146), on average, grew 0.8 centim major depressive disorder study. Height increases were less than expected based on data from age-and extended-release capsules, 2006).

3.3.3.A.2 Hot sweats

a) A 52-year-old menopausal woman experienced hot flashes while being treated for depression with ve total hysterectomy and bilateral salpingo-oophorectomy. Although she experienced hot flashes immediat After two weeks of therapy with extended- release venlafaxine 75 mg per day, the woman reported trans flashes were occurring daily and were rated moderate to severe. After seven weeks, the severity and fre was then increased to 150 mg/day to increase the antidepressant response. The woman had five days o Venlafaxine has been used to treat hot flashes (Grady-Weliky & Hartmann, 2001).

3.3.3.A.3 Hyponatremia

a) Summary

1) Hyponatremia has been reported with the use of selective serotonin reuptake inhibitors (SSRIs) a the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Serum sodium levels lower t hyponatremia with SSRIs and SNRIs include the elderly and patients receiving diuretics or who are memory impairment, confusion, weakness, and unsteadiness which may or may not lead to falls. Sig respiratory arrest, and death. Discontinuation of venlafaxine therapy should be considered and appr (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral capsu

b) LITERATURE REPORTS

1) Hyponatremia was reported in 15 patients following therapeutic use of venlafaxine. The average sodium concentrations ranged from 116 to 130 milliequivalents/liter (mEq/L) (normal 135 to 145 mE

2) A 70-year-old woman developed hyponatremia (125 millimoles per liter (mmol/L)) while taking ve She had previously developed SIADH while taking mirtazapine (Blass & Pearson, 2000).

3) A 76-year-old female developed hyponatremia (serum sodium level of 118 milliequivalents/liter) f and the patient's serum sodium level returned to baseline three days later following fluid restriction,

3.3.3.A.4 Serum cholesterol raised

a) Incidence: 5.3% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-rel

b) Clinically relevant increases in serum cholesterol occur in 5.3% of venlafaxine immediate-release trea Clinically relevant was defined as a final or an average on-therapy increase in serum cholesterol of 50 m greater. Significant increases in mean serum cholesterol have been reported in patients receiving venlaf capsules (1 to 11.4 mg/dL) during multiple clinical trials. Periodic monitoring is recommended during long extended-release oral capsules, 2008; Anon, 1993).

c) Treatment with extended-release venlafaxine was associated with increases in serum cholesterol cor extended-release oral capsules, 2008). Results are summarized below:

Trial	Duration	Mean Change in Serum Cholesterol Venlafaxine Extended-Release	Mean Change
Major Depressive Disorder	up to 12 weeks	+ 1.5 mg/dL	-
Generalized Anxiety Disorder	up to 8 weeks up to 6 months	+1.0 mg/dL + 2.3 mg/dL	- -
Social Anxiety Disorder	up to 12 weeks up to 6 months	+ 7.9 mg/dL + 5.6 mg/dL	- -

Panic Disorder	up to 12 weeks	+ 5.8 mg/dL	- 3
mg/dL = milligrams/deciliter			

3.3.3.A.5 Serum triglycerides raised

a) Treatment with extended-release venlafaxine was associated with increases in fasting serum triglyce
(R) extended-release oral capsules, 2008). Results are summarized below:

Trials	Duration	Mean Change in Serum Triglycerides Venlafaxine Extended-Release	Mean Change in S Place
Social Anxiety Disorder	up to 12 weeks up to 6 months	+ 8.2 mg/dL + 11.8 mg/dL	+ 0.4 n + 1.8 n
Panic Disorder	up to 12 weeks up to 6 months	+ 5.9 mg/dL + 9.3 mg/dL	+ 0.9 n - 0.3 n
mg/dL = milligrams/deciliter			

3.3.3.A.6 Syndrome of inappropriate antidiuretic hormone secretion

a) Summary

1) Syndrome of inappropriate secretion of antidiuretic hormone has occurred in patients on venlafax
Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules, 2

b) LITERATURE REPORTS

1) About 8 months after starting venlafaxine, a 92-year-old woman developed the syndrome of inap
the serum sodium gradually fell from 133 to 124 milliequivalents/liter; the antidiuretic hormone conce
milliosmole/kilogram (mOsm/kg) was high compared to a low serum osmolality of 255 mOsm/kg. Ve
month. Due to the temporal relationship and similar reports to other selective serotonin reuptake inh

2) A 65-year-old man developed the syndrome of inappropriate antidiuretic hormone (SIADH) possi
he complained of dizziness; abnormal laboratory values included a serum sodium of 114 millimole/li
239 millimole/24 hours, and urine osmolality of 640 mOsm/L. Venlafaxine was stopped, and the pati
restriction was stopped, the serum sodium concentration and osmolality remained normal. Medical c
is recommended that patients treated with a selective serotonin reuptake inhibitor who develop sym
have a serum sodium measured (Meynaar et al, 1997).

3.3.3.A.7 Weight loss

a) Incidence: 3% to 47% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extend

b) Adults

1) Treatment with immediate-release venlafaxine for several weeks in adults was associated with a
3% and 1% in patients receiving another antidepressant or placebo, respectively. The weight loss a
Info EFFEXOR(R) oral tablets, 2008).

2) During short-term placebo-controlled major depressive disorder trials, weight loss of 5% or more
release and placebo, respectively, and the discontinuation rate due to weight loss was 0.1%. During
7% or more occurred in 3% of venlafaxine extended-release treated patients compared with 1% in p
duration of up to 8 weeks was 0.3% for patients receiving venlafaxine extended-release. During 6-m
occurred in 4% of venlafaxine extended-release treated patients compared with 1% in placebo patie
placebo, respectively, sustained a loss of 7% or more of body weight during up to 12 weeks of treatr
weight loss in either the social anxiety disorder or panic disorder trials (Prod Info EFFEXOR XR(R) e

c) Pediatrics

1) Results of a pooled analysis of four 8-week, double-blind, placebo-controlled, flexible dose trials
(ages 6 to 17 years) indicate that a weight loss of at least 3.5% occurred in 18% of venlafaxine exte
0.001) . On average, 0.45 kilograms (kg) (n=333) was lost in the venlafaxine extended-release grou
less than 12 years old were at a greater risk than adolescents older than 12 years for weight loss, w
open-label study was evaluated (Prod Info EFFEXOR(R) XR oral extended-release capsules, 2006)

2) Pediatric patients enrolled in a 16-week, double-blind, placebo-controlled trial for social anxiety d
(kg) compared to an average gain of 0.76 kg in patients receiving placebo. A weight loss of at least
release compared with 14% of patients receiving placebo (p less than 0.001) (Prod Info EFFEXOR(

3) Children less than 12 years old were at a greater risk than adolescents older than 12 years for w
gain) from an open-label major depressive disorder study was evaluated (Prod Info EFFEXOR(R) X

3.3.4 Gastrointestinal Effects

3.3.4.A Venlafaxine Hydrochloride

Constipation

Diarrhea

Gastrointestinal hemorrhage

Grinding teeth

Loss of appetite

Nausea

Summary

Vomiting

Xerostomia

3.3.4.A.1 Constipation

a) Incidence: 8% to 15% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extend
b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 37
was 15% compared to 7% in patients receiving placebo (n=609) (Prod Info EFFEXOR(R) oral tablets, 20
c) Constipation occurred in 8% to 10% of patients on extended-release venlafaxine compared with 3% t
extended-release capsules, 2006).

The table below provides the incidence rates of constipation during clinical trials of extended-release

Studies	Percent of patients with constipation	
	Venlafaxine ER	Placebo
Major depressive disorder (n=642)	8%	5%
Generalized anxiety disorder (n=1936)	10%	4%
Social anxiety disorder (n=1514)	9%	3%
Panic disorder (n=1663)	9%	3%
Key: ER = extended-release		

3.3.4.A.2 Diarrhea

a) Incidence: 8% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-relea
b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 37
was 8% compared to 7% in patients receiving placebo (n=609) (Prod Info EFFEXOR(R) oral tablets, 200
c) Diarrhea occurred in 8% of patients on extended-release venlafaxine (n=819) compared with 6% of p
EFFEXOR XR(R) extended-release oral capsules, 2008).

3.3.4.A.3 Gastrointestinal hemorrhage

a) Incidence: rare (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR(R) XR oral extended
b) In case reports and epidemiological studies, drugs which interfere with serotonin reuptake (e.g., selec
(SNRIs)) have been associated with an increased incidence of gastrointestinal hemorrhage. Gastrointest
patients) in the premarketing evaluation of patients receiving venlafaxine hydrochloride (HCl). Additionall
venlafaxine HCl in postmarketing reports, although a causal relationship has not been definitively establi
affect coagulation (e.g., NSAIDs, aspirin, warfarin), use caution when these agents are co-administered
therapy should be monitored when venlafaxine is started or discontinued (Prod Info EFFEXOR(R) oral ta

3.3.4.A.4 Grinding teeth

a) A 50-year-old man was prescribed 37.5 mg of oral venlafaxine (a serotonin and norepinephrine reupt
the patient reported anxiety, tremor, insomnia, and clenching and grinding of teeth day and night . After
five weeks of treatment, the patient reported anxiety, tremor, insomnia, and clenching and grinding of tee
two days after the initiation of oral gabapentin 300 mg at night, bruxism ceased (Brown & Hong, 1999).

3.3.4.A.5 Loss of appetite

a) Incidence: 8% to 22% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extend
b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 37
was 11% compared to 2% in patients receiving placebo (n=609) (Prod Info EFFEXOR(R) oral tablets, 20
c) During a dose comparison trial involving 358 patients, the incidence of anorexia was 2.2% for placebo
375 milligrams/day, respectively (Prod Info EFFEXOR(R) oral tablets, 2008).

The table below provides the incidence rates of anorexia during clinical trials of extended-release ve

Studies	Percent of patients with anorexia	
	Venlafaxine ER	Placebo

Major depressive disorder (n=642)	8%	4%
Generalized anxiety disorder (n=1936)	8%	2%
Social anxiety disorder (n=1514)	17%*	2%
Panic disorder (n=1663)	8%*	3%
Key: ER = extended-release; * mostly described as decreased appetite and loss of appetite		

The discontinuation rate for venlafaxine extended-release due to anorexia was 1% in major depress in social anxiety disorder studies of up to 12 weeks, and 0.4% in panic disorder studies of up 10 12

d) Pediatrics

1) The incidence of anorexia in pediatric patients (aged 6 to 17 years) during clinical trials for gener were treated with venlafaxine extended-release and placebo, respectively. None of the patients in th disorder trials in patients aged 8 to 17 years, the incidence of anorexia was 22% and 3% in patients discontinuation rates of venlafaxine extended-release and placebo due to anorexia were 0.7% and venlafaxine extended-release and placebo (Prod Info EFFEXOR XR(R) extended-release oral capsu

3.3.4.A.6 Nausea

a) Incidence: 21% to 58% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) exten

b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 3 37% compared to 11% in patients receiving placebo (n=609) (Prod Info EFFEXOR(R) oral tablets, 2008)

c) During a dose comparison trial involving 358 patients, the incidence of nausea was 14.1% for placeb 375 milligrams/day, respectively. Over a 6-week period, there was evidence of adaptation to nausea with

The table below provides the incidence rates of nausea during clinical trials of extended-release ver

Studies	Percent of patients with nausea	
	Venlafaxine ER	Placebo
Major depressive disorder (n=642)	31%	12%
Generalized anxiety disorder (n=1936)	35%	12%
Social anxiety disorder (n=1514)	31%	9%
Panic disorder (n=1663)	21%	14%
Key: ER = extended-release		

d) The discontinuation rate due to nausea for venlafaxine extended-release was 2% to 8% compared wi release oral capsules, 2008).

e) Although venlafaxine is a highly effective antidepressant, up to one- third of patients develop nausea. However, in others, reduction of the dose or discontinuation of the drug is required. For this group, cisap treatment with venlafaxine. Other alternatives to reduce nausea include: (1) administration of venlafaxine (3) counseling patients about possible nausea with reassurance that it will decrease over time (Amchin & induced nausea and vomiting is increased serotonin levels within the chemoreceptor trigger zone and ar and vomiting (McManis & Talley, 1997).

3.3.4.A.7 Summary

a) Adverse effects which commonly occurred during clinical trials of venlafaxine and venlafaxine extend Rare cases of gastrointestinal hemorrhage have been reported rarely (defined as occurring in fewer thar hydrochloride (HCl). Additionally, hemorrhage, including gastrointestinal bleeding, has been associated definitively established (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended

3.3.4.A.8 Vomiting

a) Incidence: 3% to 7.9% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) exten

b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 3 was 6% compared to 2% in patients receiving placebo (n=609) (Prod Info EFFEXOR(R) oral tablets, 200

c) During a dose comparison trial involving 358 patients, the incidence of vomiting was 1.1% for placeb milligrams/day, respectively (Prod Info EFFEXOR(R) oral tablets, 2008).

The table below provides the incidence rates of vomiting during clinical trials of extended-release ve

Studies	Percent of patients with vomiting	
	Venlafaxine ER	Placebo
Major depressive disorder (n=642)	4%	2%
Generalized anxiety disorder (n=1936)	5%	3%
Social anxiety disorder (n=1514)	3%	2%
Key: ER = extended-release		

d) The proposed mechanism for selective serotonin reuptake inhibitor-induced nausea and vomiting is i brainstem, the primary areas within the brain associated with nausea and vomiting (McManis & Talley, 1 (Klamerus et al, 1992b; Saletu et al, 1992b; Schweizer et al, 1988; Schweizer et al, 1991).

3.3.4.A.9 Xerostomia

a) Incidence: 12% to 22% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) exten

b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 3

was 22% compared to 11% in patients receiving placebo (n=609) (Prod Info EFFEXOR(R) oral tablets, 2
c) Dry mouth occurred in 12% to 17% of patients on extended-release venlafaxine compared with 4% to
extended-release capsules, 2006).

The table below provides the incidence rates of dry mouth during clinical trials of extended-release v

Studies	Percent of patients with dry mouth	
	Venlafaxine ER	Placebo
Major depressive disorder (n=642)	12%	6%
Generalized anxiety disorder (n=1936)	16%	6%
Social anxiety disorder (n=1514)	17%	4%
Panic disorder (n=1663)	12%	6%
Key: ER = extended-release		

3.3.5 Hematologic Effects

3.3.5.A Venlafaxine Hydrochloride

Agranulocytosis

Bleeding, Abnormal

Ecchymosis

3.3.5.A.1 Agranulocytosis

a) Approximately 3 weeks after discontinuing mianserin therapy and 5 days after beginning venlafaxine
58/microliter; total WBC count, 2,900). The patient completely recovered following the discontinuation of
(Lucht et al, 2000).

3.3.5.A.2 Bleeding, Abnormal

a) In case reports and epidemiological studies, drugs which interfere with serotonin reuptake (e.g., selec
(SNRIs)) have been associated with an increased incidence of gastrointestinal hemorrhage. Bleeding ev
gastrointestinal bleeding, and life-threatening hemorrhages have been reported with SSRI and SNRI use
affect coagulation (e.g., NSAIDs, aspirin, warfarin), use caution when these agents are co-administered
therapy should be monitored when venlafaxine is started or discontinued (Prod Info EFFEXOR(R) oral ta
b) A 19-year-old woman developed easy and spontaneous bruising on her arms one week after beginni
studies were within normal limits; bleeding time was not evaluated. Ten days after stopping venlafaxine,
possible. She was initially treated with sertraline 50 mg daily, but due to intolerable diarrhea, it was stopp
are an interaction between venlafaxine and sertraline or a change in platelet serotonin transporter which

3.3.5.A.3 Ecchymosis

a) Incidence: 1% or greater (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) exte
b) Ecchymosis has been reported frequently (defined as occurring on one or more occasions in at least
hydrochloride (HCl). Because the risk of bleeding may be increased by the concomitant use of drugs tha
administered with venlafaxine HCl. Additionally, patients receiving concurrent warfarin therapy should be
tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008).

3.3.6 Hepatic Effects

3.3.6.A Venlafaxine Hydrochloride

3.3.6.A.1 Hepatitis

a) Incidence: rare (Horsmans et al, 1999; Cardona et al, 2000)
b) LITERATURE REPORTS
1) Venlafaxine 150 milligrams/day for six months was associated with acute hepatitis in a 44-year-o
venlafaxine was started. Due to severe asthenia, LFTs were repeated with the following results: alar
tests for hepatitis were negative, and abdominal ultrasonography was normal; however, a liver biops
stopped, LFTs returned to normal. This patient received lormetazepam and trazodone before venlaf
2) A 78-year-old man with a past history of Parkinson disease and a major depression episode dev
returned to normal after venlafaxine therapy was progressively discontinued (Cardona et al, 2000).

3.3.8 Musculoskeletal Effects

3.3.8.A Venlafaxine Hydrochloride

3.3.8.A.1 Rhabdomyolysis

a) A 38-year-old male developed rhabdomyolysis after ingesting venlafaxine and lamotrigine (Peano et

3.3.9 Neurologic Effects

3.3.9.A Venlafaxine Hydrochloride

Asthenia

Dizziness

Dream disorder

Headache

Insomnia

Restless legs syndrome

Seizure

Somnolence

Summary

Tremor

3.3.9.A.1 Asthenia

a) Incidence: 8% to 19% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extend

b) Immediate-release

1) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 (n=1033) was 12% compared to 6% in patients receiving placebo (n=609) (Prod Info EFFEXOR(R)

2) During a dose comparison trial involving 358 patients, the incidence of asthenia was 3.3% for pla and 375 milligrams/day, respectively (Prod Info EFFEXOR(R) oral tablets, 2008).

c) Extended-release

1) Asthenia led to discontinuation in 1% to 3% of patients on extended release venlafaxine and 0% incidence rates of asthenia during clinical trials of extended-release venlafaxine (Prod Info EFFEXO

Studies	Percent of patients with asthenia	
	Venlafaxine ER	Placebo
Major depressive disorder (n=642)	8%	7%
Generalized anxiety disorder (n=1936)	12%	8%
Social anxiety disorder (n=1514)	19%	9%
Panic disorder (n=1663)	10%	8%
Key: ER = extended-release		

3.3.9.A.2 Dizziness

a) Incidence: 11% to 23.9% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) exte

b) Immediate-release

1) Dizziness is a relatively common side effect with venlafaxine, usually occurring at higher doses. EFFEXOR(R) oral tablets, 2008; Klamerus et al, 1992b; Saletu et al, 1992b).

2) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 (n=1033) was 19% compared to 7% in patients receiving placebo (n=609) (Prod Info EFFEXOR(R)

3) During a dose comparison trial involving 358 patients, the incidence of dizziness was 4.3% for pl and 375 milligrams/day, respectively (Prod Info EFFEXOR(R) oral tablets, 2008).

c) Extended-release

1) The table below provides the incidence rates of dizziness associated with extended-release venl release oral capsules, 2008):

Studies	Percent of patients with dizziness	
	Venlafaxine ER	Placebo
Major depressive disorder (n=642)	20%	9%

Generalized anxiety disorder (n=1936)	16%	11%
Social anxiety disorder (n=1514)	16%	8%
Panic disorder (n=1663)	11%	10%
Key: ER = extended-release		

3.3.9.A.3 Dream disorder

a) Incidence: 3% to 7% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extende

b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 3 (n=1033) was 4% compared to 3% in patients receiving placebo (n=609) (Prod Info EFFEXOR(R) oral ta

c) The table below provides the incidence rates of abnormal dreams, primarily described as "vivid drean venlafaxine (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008):

Studies	Percent of patients with abnormal dreams	
	Venlafaxine ER	Placebo
Major depressive disorder (n=642)	7%	2%
Generalized anxiety disorder (n=1936)	3%	2%
Social anxiety disorder (n=1514)	3%	less than 1%
Key: ER = extended-release		

3.3.9.A.4 Headache

a) Incidence: 25% to 38% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) exten

b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 3 was 25% compared to 24% in patients receiving placebo (n=609) (Prod Info EFFEXOR(R) oral tablets, 2

c) In short-term, placebo-controlled clinical trials involving patients with social anxiety disorder (n=1514) patients experienced headache (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008)

d) Headache and fatigue are frequently reported side effects and have occurred with higher single dose 1992b; Saletu et al, 1992b).

3.3.9.A.5 Insomnia

a) Incidence: 14% to 24% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR(R) XR oral e

b) Immediate-release

1) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 (n=1033) was 18% compared to 10% in patients receiving placebo (n=609). Insomnia led to drug dis depression studies (Prod Info EFFEXOR(R) oral tablets, 2008).

2) During a dose comparison trial involving 358 patients, the incidence of insomnia was 9.8% for pl and 375 milligrams/day, respectively (Prod Info EFFEXOR(R) oral tablets, 2008).

c) Extended-release

1) The table below provides the incidence rates of insomnia during clinical trials of extended-releas

Studies	Percent of patients with insomnia	
	Venlafaxine ER	Placebo
Major depressive disorder (n=642)	17%	11%
Generalized anxiety disorder (n=1936)	15%	10%
Social anxiety disorder (n=1514)	24%	8%
Panic disorder (n=1663)	17%	9%
Key: ER = extended-release		

The discontinuation rates due to insomnia were 1% to 3% of patients on extended-release venl EFFEXOR XR(R) extended-release oral capsules, 2008).

3.3.9.A.6 Restless legs syndrome

a) In a prospective, naturalistic study of patients (median age, 46 years; range, 18 to 87 years) treated v syndrome (RLS) or worsening of preexisting RLS as a side effect related to treatment. Antidepressants i duloxetine, reboxetine, and mirtazapine. Mirtazapine led to a marked decline of RLS in 28% of subjects symptoms (newly occurred or deteriorated) at the rate of 5% to 10%. Subjects stated symptoms occurre

3.3.9.A.7 Seizure

a) Incidence: 0.3% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-rel

b) During premarketing studies of immediate-release venlafaxine, seizures occurred in 8 out of 3082 (0. 5 occurred in patients receiving doses of 150 milligrams daily or less. During premarketing studies of ext extended-release venlafaxine. Venlafaxine should be cautiously used in patients with a history of seizure when venlafaxine and monamine oxidase inhibitor (MAOI) therapy were started or stopped within close p venlafaxine started after a recent discontinuation of an MAOI) (Prod Info EFFEXOR(R) oral tablets, 2008

3.3.9.A.8 Somnolence

a) Incidence: 14% to 26% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) exten

b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 37
was 23% compared to 9% in patients receiving placebo (n=609) (Prod Info EFFEXOR(R) oral tablets, 20
c) During a dose comparison trial involving 358 patients, the incidence of somnolence was 4.3% for plac
375 milligrams/day, respectively (Prod Info EFFEXOR(R) oral tablets, 2008).
d) The table below provides the incidence rates of somnolence during clinical trials of extended-release

Studies	Percent of patients with somnolence	
	Venlafaxine ER	Placebo
Major depressive disorder (n=642)	17%	8%
Generalized anxiety disorder (n=1936)	14%	8%
Social anxiety disorder (n=1514)	20%	8%
Panic disorder (n=1663)	12%	6%
Key: ER = extended-release		

e) The discontinuation rates due to somnolence were 0% to 3% in patients on extended-release venlafa
Info EFFEXOR XR(R) extended-release oral capsules, 2008).

3.3.9.A.9 Summary

a) Asthenia, dizziness, headache), insomnia, drowsiness, tremor , and abnormal dreams have common
(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008). Serious side e
syndrome. Features resembling neuroleptic malignant syndrome have occurred when venlafaxine and m
of each other (MAOI started after a recent discontinuation of venlafaxine or venlafaxine started after a re
EFFEXOR XR(R) extended-release oral capsules, 2008).

3.3.9.A.10 Tremor

a) Incidence: 1.1% to 10.2% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR(R) XR ora
b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 37
5% compared to 1% in patients receiving placebo (n=609) (Prod Info EFFEXOR(R) oral tablets, 2008).
c) During a dose comparison trial involving 358 patients, the incidence of tremor was 0% for placebo co
milligrams/day, respectively (Prod Info EFFEXOR(R) oral tablets, 2008).
d) The table below provides the incidence rates of tremor during clinical trials of extended-release venla

Studies	Percent of patients with tremor	
	Venlafaxine ER	Placebo
Major depressive disorder (n=642)	5%	2%
Generalized anxiety disorder (n=1936)	4%	less than 1%
Social anxiety disorder (n=1514)	2%	2%
Panic disorder (n=1663)	5%	2%
Key: ER = extended-release		

3.3.10 Ophthalmic Effects

3.3.10.A Venlafaxine Hydrochloride

Blurred vision

Disorder of accommodation

Glaucoma

Mydriasis

3.3.10.A.1 Blurred vision

a) Incidence: 4% to 6% (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008; Prod Info EF
b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 37
(n=1033) was 6% compared to 2% in patients receiving placebo (n=609) (Prod Info EFFEXOR(R) oral ta
c) The table below provides the incidence rates of abnormal vision during clinical trials of extended-relea

Studies	Venlafaxine ER	Placebo
Major depressive disorder (n=642)	4%*	less than 1%
Generalized anxiety disorder (n=1936)	5%*	less than 1%
Social anxiety disorder (n=1514)	4%**	2%
Key: ER = extended-release; * mostly described as blurred vision and difficulty focusing eyes; **		

mostly described as blurred vision

3.3.10.A.2 Disorder of accommodation

a) Incidence: 5.6% to 9.1% (Prod Info EFFEXOR(R) oral tablets, 2008)

b) During a dose comparison trial involving 358 patients, the incidence of abnormality of accommodatio venlafaxine 75, 225, and 375 milligrams/day, respectively (Prod Info EFFEXOR(R) oral tablets, 2008).

3.3.10.A.3 Glaucoma

a) A 45-year-old woman with bipolar disorder developed bilateral acute angle closure glaucoma when sl 150 mg daily). At admission, she was taking sodium valproate 1500 mg per day and slow-release lithium nausea and vomiting, and subsequent swelling and drooping of the left upper eyelid and a dilated and fix intraocular pressure was elevated (50 mmHg). Treatment with intravenous mannitol, topical apraclonidin to 35 mmHg. Laser iridotomy was done repeatedly until successful. Eight days after starting venlafaxine, Venlafaxine was discontinued and successful laser iridotomy was performed. After 8 weeks, her intraocu

3.3.10.A.4 Mydriasis

a) Incidence: 2% (Prod Info EFFEXOR(R) oral tablets, 2008)

b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 3 was 2% compared to less than 1% in patients receiving placebo (n=609). As mydriasis has been reporte angle glaucoma require monitoring during therapy (Prod Info EFFEXOR(R) oral tablets, 2008).

3.3.12 Psychiatric Effects

3.3.12.A Venlafaxine Hydrochloride

Anxiety

Depression, exacerbation

Feeling nervous

Hallucinations

Hypomania

Mania

Paranoid delusion

Suicidal thoughts

Summary

3.3.12.A.1 Anxiety

a) Incidence: 5% to 11.2% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) exter

b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 3 6% compared to 3% in patients receiving placebo (n=609). Anxiety led to drug discontinuation in 2% of p EFFEXOR(R) oral tablets, 2008).

c) During a dose comparison trial involving 358 patients, the incidence of anxiety was 4.3% for placebo milligrams/day, respectively (Prod Info EFFEXOR(R) oral tablets, 2008).

d) Anxiety was experienced in 5% of extended-release venlafaxine treated patients and 4% of placebo-t Info EFFEXOR XR(R) extended-release oral capsules, 2008).

3.3.12.A.2 Depression, exacerbation

a) Incidence: rare (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-rele

b) Adult and pediatric patients being treated with antidepressants for major depressive disorder who exp aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, or other unusual l antidepressant treatment and when the dose is adjusted. Symptoms such as these indicate the need for to treating patients with other psychiatric and nonpsychiatric disorders. If these symptoms are observed, symptoms are severe, sudden in onset, or were not part of the patient's initial symptoms. Patients and th (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules,

3.3.12.A.3 Feeling nervous

a) Incidence: 4% to 21.3% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) exter

b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 37 (n=1033) was 13% compared to 6% in patients receiving placebo (n=609). Nervousness led to drug disc depression studies (Prod Info EFFEXOR(R) oral tablets, 2008).

c) During a dose comparison trial involving 358 patients, the incidence of anxiety was 4.3% for placebo 375 milligrams/day, respectively (Prod Info EFFEXOR(R) oral tablets, 2008).

d) The table below provides the incidence rates of nervousness during clinical trials of extended-release

Studies	Percent of patients with nervousness	
	Venlafaxine ER	Placebo
Major depressive disorder (n=642)	10%	5%
Generalized anxiety disorder (n=1936)	6%	4%
Social anxiety disorder (n=1514)	10%	5%
Panic Disorder (n=1663)	4%	6%
Key: ER = extended-release		

The discontinuation rates due to nervousness were 0.1% to 3% of patients on extended-release ver 2008).

3.3.12.A.4 Hallucinations

a) In a case report, a 17-year-old male exhibited visual and tactile hallucinations following a dose increa headaches. The patient had a family history of anxiety (maternal) and a personal history of DSM-IV mod disorder. He also had a history of drug reactions which included delirium following anesthesia, and visua psychiatric systems were normal. Upon presentation, he had a 6- to 7-month escalation of depression ar anxiety. Concomitant drugs included lamotrigine, eletriptan (once a week), hydrocodone/acetaminophen treatment with venlafaxine immediate release 37.5 mg once daily, the patient's symptoms persisted and dose he experienced visual and tactile hallucinations of crawling bugs and became disoriented 1 hour la delirium. Venlafaxine treatment was suspended until the next morning. On the second day, the patient w morning dose, the patient again experienced visual and tactile hallucinations and within 30 to 60 minutes to the emergency department the patient's symptoms resolved overnight 16 to 20 hours following his las and his anxiety has begun to improve with cognitive-behavioral therapy (Jacob & Ash, 2009).

3.3.12.A.5 Hypomania

a) During Phase 2 and Phase 3 trials with immediate-release venlafaxine, mania or hypomania occurred hypomania occurred in 0.3% of patients receiving venlafaxine extended-release compared with 0% of pla anxiety disorder studies was 0% and 0.2% for venlafaxine extended-release and placebo, respectively, v respectively. During panic disorder trials, the incidence of mania or hypomania was 0.1% and 0% in patie be used cautiously in patients with a history of mania (Prod Info EFFEXOR(R) oral tablets, 2008; Prod In

b) Two women with bipolar affective disorder developed hypomania after starting venlafaxine (Wilson & antidepressants during a two year period of depression. Venlafaxine 75 mg titrated to 225 mg daily resul of venlafaxine. After beginning venlafaxine 75 mg titrated to 150 mg, the second patient became hypoma 5 cases of mania associated with venlafaxine were reported to the United Kingdom's Committee on Safe venlafaxine in patients with bipolar disorder (Wilson & Jenkins, 1997).

3.3.12.A.6 Mania

a) During Phase 2 and Phase 3 trials with immediate-release venlafaxine, mania or hypomania occurred hypomania occurred in 0.3% of patients receiving venlafaxine extended-release compared with 0% of pla anxiety disorder studies was 0% and 0.2% for venlafaxine extended-release and placebo, respectively, v respectively. During panic disorder trials, the incidence of mania or hypomania was 0.1% and 0% in patie be used cautiously in patients with a history of mania (Prod Info EFFEXOR(R) oral tablets, 2008; Prod In

b) A 17-year-old female diagnosed with severe major depressive disorder per DSM-IV criteria experienc She started venlafaxine 37.5 mg/day, which was then gradually increased to 150 mg/day over a 2-week elated moods, increased energy levels, increased speech output, decreased need for sleep, increased g behavior which warranted hospital admission; and she met DSM-IV criteria for mania. Venlafaxine was d and valproate 750 mg/day (subsequently increased to 1500 mg/day) were initiated. The patient reached weeks and the patient remained euthymic during the last 6 month of valproate treatment. Since the patie venlafaxine treatment, the authors suspected venlafaxine-induced mania (Raman et al, 2007).

c) Three patients with no history of mania or hypomania developed mania when they were treated for de months (Shulman et al, 2001)

d) A 63-year-old man with bipolar disorder developed mania six days after venlafaxine was increased to daily and nefazodone but depressive symptoms had not improved after eight months of treatment with n Behavioral symptoms included verbal agitation, hyperactivity, grandiose ideas, thoughts of persecution, i fluphenazine 10 mg at bedtime and an increase in the divalproex sodium dose. Two weeks after stoppin weeks. This patient had been hospitalized several times for manic behavior, and this episode may have temporal relationship to initiation and discontinuation of venlafaxine suggests that venlafaxine may have

3.3.12.A.7 Paranoid delusion

a) Paranoid delusion developed in an 85-year-old Caucasian man following administration of venlafaxin dose from 75 milligrams (mg) daily to 150 mg daily for increasing depression, he began having paranoid the dose to 75 mg/day. Venlafaxine was withdrawn and symptoms resolved within 48 hours. Treatment v symptoms resolved again with the withdrawal of the drug. Sertraline therapy was initiated and no further

3.3.12.A.8 Suicidal thoughts

a) Incidence: rare (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-rele
b) Adult and pediatric patients being treated with antidepressants for major depressive disorder who exp aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, or other unusual during early antidepressant treatment and when the dose is adjusted. Symptoms such as these indicate concern applies to treating patients with other psychiatric and nonpsychiatric disorders. If these symptom medications when symptoms are severe, sudden in onset, or were not part of the patient's initial symptor available for this drug (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-
c) A causal role for antidepressants in inducing suicidality has been established in pediatric patients. An with the clinical need. In pooled analyses of 24 short-term, placebo-controlled trials of nine antidepressar nefazodone, and venlafaxine extended-release) including over 4400 pediatric patients with major depres greater risk of suicidal behavior or ideation during the first few months of therapy was demonstrated in pa risk of suicidality was most consistently observed in the trials that included patients with major depressiv such as obsessive compulsive disorder and social anxiety disorder. No suicides occurred in these trials. patients is not known. It is also unknown whether this risk extends to adult patients (Anon, 2004). :
d) Pooled analyses of short-term placebo-controlled trials of antidepressants indicated that treatment wi adolescents and young adults with major depressive disorder and other psychiatric disorders. The poole (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, bupropion, mirtazapine, nefazodone, and ver disorder (MDD), obsessive compulsive disorder, or other psychiatric disorders, as well as 295 trials (with MDD or other psychiatric disorders. There was a tendency toward an increase in the risk of suicidality in was highest in patients with MDD. The risk differences between drug versus placebo are provided below oral capsules, 2008):

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 100 Patients Treated
Less than 18 years	14 Additional Cases
18 to 24 years	5 Additional Cases
25 to 64 years	1 Fewer Case
65 years and older	6 Fewer Cases

3.3.12.A.9 Summary

a) Anxiety, mania/hypomania, nervousness, and suicidal ideation/worsening of depression (rare) have b discontinuation of venlafaxine during clinical trials. Adult and pediatric patients being treated with antidep panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restless of their depression and/or suicidality, especially during early antidepressant treatment and when the dos possible changes in the medication (Prod Info EFFEXOR(R) oral tablets, 2008). Two women with bipolar 1997).

3.3.13 Renal Effects

3.3.13.A Venlafaxine Hydrochloride

Difficulty passing urine

Finding of frequency of urination

3.3.13.A.1 Difficulty passing urine

a) Incidence: 2% (Prod Info EFFEXOR(R) oral tablets, 2008)
b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 37 (n=1033) was 2% compared to less than 1% in patients receiving placebo (n=609) (Prod Info EFFEXOR

3.3.13.A.2 Finding of frequency of urination

a) Incidence: 3% (Prod Info EFFEXOR(R) oral tablets, 2008)
b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 37 (n=1033) was 3% compared to 2% in patients receiving placebo (n=609) (Prod Info EFFEXOR(R) oral ta

3.3.14 Reproductive Effects

Venlafaxine

Venlafaxine Hydrochloride

3.3.14.A Venlafaxine

3.3.14.A.1 Sexual dysfunction

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

3.3.14.B Venlafaxine Hydrochloride

Abnormal ejaculation

Impotence

Orgasm disorder

Priapism

Reduced libido

3.3.14.B.1 Abnormal ejaculation

a) Incidence: 2.2% to 19% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) exter
b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 3
receiving venlafaxine was 12% compared to less than 1% in patients receiving placebo (Prod Info EFFE
c) During a dose comparison trial involving 358 patients, the incidence of abnormal ejaculation/orgasm
venlafaxine 75, 225, and 375 milligrams/day, respectively (Prod Info EFFEXOR(R) oral tablets, 2008).
d) The table below provides the incidence rates of abnormal ejaculation in males on venlafaxine extend
oral capsules, 2008):

Studies	Percent of males with abnormal ejaculation	
	Venlafaxine ER	Placebo
Major depressive disorder *	16%	less than 1%
Generalized anxiety disorder (n=745) **	11%	less than 1%
Social anxiety disorder (n=811) **	19%	less than 1%
Panic disorder (n=573) ***	8%	less than 1%
Key: ER = extended-release; * = mostly delayed ejaculation; ** = includes delayed ejaculation and anorgasmia; *** = includes delayed or retarded ejaculation and anorgasmia		

3.3.14.B.2 Impotence

a) Incidence: 2.1% to 6% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) exten
b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 3
6% compared to less than 1% in patients receiving placebo (Prod Info EFFEXOR(R) oral tablets, 2008).
c) During a dose comparison trial involving 219 male patients, the incidence of impotence was 0% for pl
375 milligrams/day, respectively (Prod Info EFFEXOR(R) oral tablets, 2008).
d) The table below provides the incidence rates of impotence in males on venlafaxine extended-release
capsules, 2008):

Studies	Percent of males with impotence	
	Venlafaxine ER	Placebo
Major depressive disorder	4%	less than 1%
Generalized anxiety disorder (n=745)	5%	less than 1%
Social anxiety disorder (n=811)	6%	less than 1%
Panic disorder (n=573)	4%	less than 1%
Key: ER = extended-release		

3.3.14.B.3 Orgasm disorder

a) Incidence: 2% to 5% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extende
b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 3
venlafaxine was 2% compared to less than 1% in patients receiving placebo (Prod Info EFFEXOR(R) ora

c) The table below provides the incidence rates of anorgasmia, delayed orgasm, or abnormal orgasm in EFFEXOR XR(R) extended-release oral capsules, 2008):

Studies	Percent of females with anorgasmia, delayed orgasm, or abnormal orgasm	
	Venlafaxine ER	Placebo
Major depressive disorder *	3%	less than 1%
Generalized anxiety disorder (n=1191) **	2%	0%
Social anxiety disorder (n=703) ***	5%	less than 1%
Panic disorder (n=1090) *	2%	less than 1%
Key: ER = extended-release; * = mostly delayed orgasm or anorgasmia; ** = includes delayed orgasm, abnormal orgasm and anorgasmia; *** = includes abnormal orgasm and anorgasmia		

3.3.14.B.4 Priapism

a) A 16-year-old boy developed priapism while being treated with venlafaxine (37.5 mg/day, titrated to 1 He had no problem with libido, erection, or ejaculation; however, after ejaculation, his erection persisted venlafaxine and experienced only one more episode of priapism, approximately three weeks after discor

3.3.14.B.5 Reduced libido

a) Incidence: 1.1% to 8% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extenc
b) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 37 (n=1033) was 2% compared to less than 1% in patients receiving placebo (n=609) (Prod Info EFFEXOR
c) During a dose comparison trial involving 358 patients, the incidence of reduced libido was 1.1% for pl 375 milligrams/day, respectively (Prod Info EFFEXOR(R) oral tablets, 2008).
d) The table below provides the incidence rates of decreased libido during clinical trials of extended-rele

Studies	Incidence of Decreased Libido	
	Venlafaxine ER	Placebo
Major depressive disorder (n=642)	3%	less than 1%
Generalized anxiety disorder (n=1936)	4%	2%
Social anxiety disorder (n=1514)	8%	2%
Panic disorder (n=1663)	4%	2%
Key: ER = extended-release		

3.3.15 Respiratory Effects

3.3.15.A Venlafaxine Hydrochloride

Interstitial pneumonia

Simple pulmonary eosinophilia

Yawning

3.3.15.A.1 Interstitial pneumonia

a) Two cases of interstitial pneumonia with heart failure have been reported following the use of venlafa month) in combination with steroid treatment led to a complete recovery in a 21-year-old woman. Howev multiple-organ failure and died despite attempts at treatment (Drent et al, 2003). The possibility of interst progressive dyspnea, cough or chest discomfort. In these cases, prompt medical evaluation is necessary tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008).

3.3.15.A.2 Simple pulmonary eosinophilia

a) Acute eosinophilic pneumonia developed in a man treated with venlafaxine for 17 days. On admissio crackles and rales; the oxygen saturation was 89.4%. The white blood cell count was elevated with 32.5 transbronchial biopsies showed accumulation of eosinophils and neutrophils within alveolar vessels. He methylprednisolone 1 gram daily for three days followed by tapering doses of prednisone for four weeks. within five days of beginning corticosteroids. All potential infectious causes were excluded with appropria pneumonia that resolved rapidly after starting corticosteroids (Fleisch et al, 2000). The possibility of eosi progressive dyspnea, cough or chest discomfort. In these cases, prompt medical evaluation is necessary tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008).

3.3.15.A.3 Yawning

a) Incidence: 3% to 8% (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extende

b) A dose increase of venlafaxine extended release (XR) led to excessive yawning in a patient who was or psychiatric disorders, suffered for 8 weeks from dysphoric mood, difficulty in concentration, loss of inte depressive disorder and prescribed venlafaxine XR 75 mg/day for 4 weeks. Due to an inadequate respo improved after 2 weeks of the dose increase. Excessive yawning not associated with drowsiness was nc occurrences of yawning per day, frequently in the morning, that interfered with his normal daily activities the patient's request, and the yawning completely disappeared 3 days after the dose decrease with no fu mechanism of excessive yawning was not clear, noradrenergic and dopaminergic mechanisms may play effect appeared to be dose-dependent (Chen & Lu, 2009).

c) During 4- to 8-week placebo-controlled trials of venlafaxine hydrochloride (dose ranging from 75 to 37 was 3% compared to less than 1% in patients receiving placebo (n=609) (Prod Info EFFEXOR(R) oral ta

d) During a dose comparison trial involving 358 patients, the incidence of yawning was 0% for placebo c milligrams/day, respectively (Prod Info EFFEXOR(R) oral tablets, 2008).

e) The table below provides the incidence rates of yawning during clinical trials of extended-release ven

Studies	Venlafaxine ER	Placebo
Major depressive disorder (n=642)	3%	0%
Generalized anxiety disorder (n=1936)	3%	less than 1%
Social anxiety disorder (n=1514)	5%	less than 1%
Key: ER = extended-release		

3.3.16 Other

Venlafaxine

Venlafaxine Hydrochloride

3.3.16.A Venlafaxine

3.3.16.A.1 Drug withdrawal

See Drug Consult reference: WITHDRAWAL SYNDROME OF SELECTIVE SEROTONIN REUPTAKE IN

3.3.16.B Venlafaxine Hydrochloride

Neuroleptic malignant syndrome

Serotonin syndrome

Withdrawal sign or symptom

3.3.16.B.1 Neuroleptic malignant syndrome

a) Neuroleptic malignant syndrome developed 12 hours after adding venlafaxine 75 mg daily to trifluope effects. The patient presented with profound anxiety, malaise, rigidity, tremor, and severe diaphoresis. O pulse was 163 beats per minute, temperature 38.3 degrees C, and respiratory rate 25 breaths/minute. Al concentration (11,320 international units/L)) and white blood cell count 23.5 x 10(9)/L. Treatment consist hours. Vital signs were normal 24 hours after admission, and trifluoperazine was restarted without proble

3.3.16.B.2 Serotonin syndrome

a) Serotonin syndrome, including life-threatening cases, or neuroleptic malignant syndrome (NMS)-like r serotonin syndrome include mental status changes (eg, agitation, hallucination, coma), autonomic instab hyperreflexia, incoordination) and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). Severe rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Se including triptans, with drugs that impair metabolism of serotonin, including MAOIs, or with antipsychotics 2009; Prod Info Effexor(R) oral tablets, 2009).

b) Despite compliance with the recommended two week washout period, three patients were diagnosed after stopping treatment with phenelzine, a 25-year-old woman started venlafaxine 37.5 mg/day. Followi legs, shakiness, sweating, tachycardia, tachypnea, fever, and increased blood pressure. The woman wa hours later with no residual problems. A 49-year-old woman also started venlafaxine 14 days after disco The woman's symptoms subsided 3 hours later without treatment. Fourteen days after terminating phene tightness, anxiety, and emesis. Symptoms subsided without medical treatment. Finally, a 29-year-old fer

after ingestion of venlafaxine, the woman experienced shakiness, stomach pain, facial flushing, crying, d successfully treated with cyproheptadine and lorazepam and had no residual problems. A longer waiting (Diamond et al, 1998b).

c) A 44-year-old woman experienced serotonin syndrome after accidentally ingesting two 15 mg phenel anxious 30 minutes after ingesting the medications. Forty-five minutes later she experienced lower extre arrival had an elevated blood pressure, heart rate, respiratory rate, and temperature. The patient also ex was given 50 grams of charcoal with sorbitol, hydration therapy, benzodiazepines for muscle rigidity, anc woman showed improvements and an additional six days later was discharged from the hospital with no

d) A 60-year-old female presented to the emergency department obtunded, tachycardic, hyperthermic, h dose of venlafaxine while on maintenance tranylcypromine therapy. The patient recovered following supp

3.3.16.B.3 Withdrawal sign or symptom

a) Withdrawal symptoms such as agitation, anorexia, anxiety, confusion, impaired coordination and bala hypomania, insomnia, nausea, nervousness, nightmares, sensory disturbances (including shock-like ele with abrupt discontinuation or dose reduction of venlafaxine at various doses. The frequency of these eff EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008).

b) A 45-year-old man and a 36-year-old woman reported electric shock-like sensations of the head shor experienced severe sensations of shock in his head and radiating to his back and arms on two occasions daily to 75 mg at bedtime and 150 mg at bedtime, respectively. The female patient was taking venlafaxin when trying to stop the medication on several occasions. Her dose was tapered to 37.5 mg three times a objects in her field of vision) when the medicine was withdrawn. For both patients, the sensations resolve

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 Effexor XR(R) extended-rele

a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) 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: B2(Australian Drug Evaluation Committee, 1999)

a) Drugs which have been taken by only a limited number of pregnant women and women of childbearing ag effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but a

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Unknown

4) Clinical Management

a) Due to the lack of adequate, well-controlled studies in pregnant women, it is recommended that venlafaxir release oral capsules, 2009; Prod Info Effexor(R) oral tablets, 2009; Ferreira et al, 2007). Because adverse s the third trimester, the potential risks and benefits of venlafaxine therapy during this time should be taken into trimester (Prod Info Effexor XR(R) extended-release oral capsules, 2009; Prod Info Effexor(R) oral tablets, 20

5) Literature Reports

a) Neonates exposed to venlafaxine or other serotonin and norepinephrine reuptake inhibitors (SNRIs) or SS hospitalizations, respiratory support and tube feeding. These complications can occur immediately upon deliv difficulty, vomiting, hypoglycemia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying or a drug discontinuation syndrome. In some cases, clinical findings have been consistent with serotonin syn (R) oral tablets, 2009).

b) A multicenter, prospective, controlled study comparing the results of pregnant women who called into the trimester and who were being treated with venlafaxine (n=150), an SSRI (n=150), or a nonteratogenic drug (r patients taking venlafaxine. Of the 150 patients in the venlafaxine group, all were treated with venlafaxine in t pregnancy. Of the patients treated with venlafaxine, 105 patients took 75 mg/day of the immediate-release fo (hypospadias and neural tube defect with club foot) reported in the venlafaxine group (1.6%), compared with not a significant difference in pregnancy outcomes among the three groups. An increase in spontaneous abo and the nonteratogenic drugs group (7.3%), but it did not reach statistical significance (Einarson et al, 2001).

c) Seventy-nine neonates of mothers treated with SSRIs or venlafaxine (n=76) during the third trimester exhi mothers (n=90). Treatment included paroxetine 5 to 40 mg (n=46), fluoxetine 10 to 40 mg (n=10), venlafaxine fluvoxamine 50 to 150 mg (n=2) with a mean duration of 32 months for SSRI use. In the treated group, 1 pati gestational age was reported in exposed infants (38.3 weeks) compared with 39.7 weeks; p less than 0.001). spasms, hypotonia, irritability, sleep disturbances, apnea/bradycardia and tachypnea. Respiratory effects, inc neonates. Exposed neonates also had a longer median length of hospitalization compared with unexposed ir were hospitalized nearly 4 times longer than unexposed infants (14.5 days vs 3.7 days; p less than 0.001). Et potential risks and benefits in continuing SSRI or venlafaxine treatment during pregnancy on an individual ba

d) A study of prospectively collected data suggests antenatal use of SSRI antidepressants is associated with 2005, researchers compared 52 neonates exposed to SSRI antidepressants (paroxetine (n=25), citalopram (antenatal period to 52 matched neonates with no exposure. Prolonged QTc is defined as an interval of greate pediatric cardiology and neonatology). A pediatric cardiologist, blinded to drug exposure, interpreted all electr markedly prolonged mean QTc intervals in exposed neonates compared to unexposed neonates (mean; 409 longer among exposed neonates (mean; 280 +/- 31 msec vs 261 +/- 25 msec, p less than 0.001). Ten percer than 460 msec) compared to none of the unexposed neonates. The longest QTc interval observed was 543 r

e) Two cases of seizures were reported in neonates born to mothers using venlafaxine during pregnancy. Se found in either case. Both children had subsequently normal growth and development at one year follow-up (

f) A case report described development of necrotizing enterocolitis in dichorial, diamniotic, twin infants on the

throughout pregnancy until delivery. The mother, who experienced uneventful first and second trimesters, wa
was diagnosed for which she received azithromycin for 4 days. She received betamethasone 12 g twice in 24
section at 33+2 weeks. Twin A and B weighed 1700 g and 1980 g, respectively, with Apgar scores of 6, 7, an
intubated on day 1 of life. Twin A was successfully extubated on day 2. On day 6, signs of necrotizing enteroc
observed in the infants. Subsequently, oral feeding was withheld and IV amikacin and amoxicillin were given
continued to deteriorate and underwent surgery on day 10. Bowel necrosis was observed. Therefore, termina
was performed. He underwent a second surgery for stomal stenosis on day 22 of life. At 5 months of age, the
the remaining transverse colon and the proximal section of the descending colon for which an intestinal anas
2009).

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 risks before prescribing this drug during breastfeeding.

2) Clinical Management

a) Venlafaxine is excreted in human breast milk. Because of the potential for serious adverse effects in nursi
nursing, taking into consideration the importance of the drug to the mother (Prod Info Effexor XR(R) extended
administered to a nursing woman, the nursing infant should be monitored closely for adverse effects (Ilett et a

3) Literature Reports

a) A study of 78 breast-feeding mothers treated with antidepressants (3 took venlafaxine at a dose of 162.5 r
venlafaxine. The mean weights of all infants exposed to antidepressants in the study were 7.26 +/- 0.71 kg fo
normative growth data and remained similar in separate analyses of each antidepressant. However, infants o
months or more) despite antidepressant treatment weighed significantly less at 6 months (p=0.002) when cor
infants born to mothers who did not relapse to depression. The small venlafaxine sample size, maternal use
took psychotropics such as benzodiazepines or tricyclic antidepressants during the study), and absence of a

b) A study describing 3 lactating women treated with venlafaxine and their nursing infants found infant mean
concentrations for the sum of venlafaxine plus O-desmethylvenlafaxine (ODV). The maternal drug dose was
the mothers. The authors suggest that breast-feeding should generally not be discouraged in mothers treatec

c) Venlafaxine and its metabolite, O-desmethylvenlafaxine (ODV) were detected in six infant blood samples
venlafaxine dose of 255 mg/day in a study of 6 women taking venlafaxine and their 7 nursing infants (mean a
concentration of 5 mcg/L, while ODV was present in four infants in concentrations ranging from 3 to 38 mcg/r
2.74 (range 2.3 to 3.2), respectively. Although no adverse effects were noted in the infants, the authors recor
the potential risks and benefits of breast-feeding during venlafaxine therapy (Ilett et al, 2002).

d) Detectable levels of the metabolite O-desmethylvenlafaxine (ODV) were reported in three infants exposec
milk (milk-to-plasma concentration ratio of 4:1 and 3:1, respectively). Total infant exposure was 7.6% of the w
(Ilett et al, 1998).

4) Drug Levels in Breastmilk

a) Venlafaxine Hydrochloride

1) Parent Drug

a) Percent Adult Dose in Breastmilk

1) 7.6% (Ilett et al, 1998)

2) Active Metabolites

a) O-desmethylvenlafaxine (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R)

1) Milk to Maternal Plasma Ratio

a) 3.06 +/- 0.08 (Ilett et al, 1998)

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Food Combinations

3.5.1 Drug-Drug Combinations

Aceclofenac

Acemetacin

Acenocoumarol

Alclofenac

Almotriptan

Amitriptyline

Amoxapine

Amoxicillin

Anagrelide

Ancrod

Anisindione

Antithrombin III Human

Aspirin

Atazanavir

Benoxaprofen

Bivalirudin

Bromfenac

Bufexamac

Cannabis

Carprofen

Celecoxib

Cilostazol

Cimetidine

Clarithromycin

Clomipramine

Clonixin

Clopidogrel

Clozapine

Danaparoid

Defibrotide

Dermatan Sulfate

Desipramine

Desirudin

Desvenlafaxine

Dexfenfluramine

Dexketoprofen

Dextroamphetamine

Dibenzepin

Diclofenac

Dicumarol

Diflunisal

Dipyridamole

Dipyrone

Dothiepin

Doxepin

Droxicam

Duloxetine

Entacapone

Epoprostenol

Eptifibatide

Etodolac

Etofenamate

Etoricoxib

Felbinac

Fenbufen

Fenfluramine

Fenoprofen

Fentiazac

Floctafenine

Flufenamic Acid

Fluoxetine

Flurbiprofen

Fondaparinux

Frovatriptan

Furazolidone

Ginkgo

Haloperidol

Heparin

Ibuprofen

Iloprost

Imipramine

Indinavir

Indomethacin

Indoprofen

Iproniazid

Isocarboxazid

Isoxicam

Itraconazole

Jujube

Ketoconazole

Ketoprofen

Ketorolac

Lamifiban

Lexipafant

Linezolid

Lornoxicam

Meclofenamate

Mefenamic Acid

Meloxicam

Metoclopramide

Metoprolol

Mirtazapine

Moclobemide

Morniflumate

Nabumetone

Naproxen

Naratriptan

Nefazodone

Nelfinavir

Nialamide

Niflumic Acid

Nimesulide

Nortriptyline

Oxaprozin

Parecoxib

Pargyline

Pentosan Polysulfate Sodium

Phenelzine

Phenindione

Phenprocoumon

Phenylbutazone

Pirazolac

Piroxicam

Pirprofen

Procarbazine

Propyphenazone

Proquazone

Protriptyline

Rasagiline

Ritonavir

Rizatriptan

Rofecoxib

Saquinavir

Selegiline

Sibrafiban

Sibutramine

St John's Wort

Sulfinpyrazone

Sulindac

Sulodexide

Sumatriptan

Suprofen

Tapentadol

Telithromycin

Tenidap

Tenoxicam

Tiaprofenic Acid

Ticlopidine

Tirofiban

Tolmetin

Toloxatone

Tramadol

Tranylcypromine

Trazodone

Trifluoperazine

Trimipramine

Valdecoxib

Vasopressin

Warfarin

Xemilofiban

Zolmitriptan

Zolpidem

Zomepirac

3.5.1.A Aceclofenac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.B Acemetacin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.C Acenocoumarol

1) Interaction Effect: an increased risk of bleeding
2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake
venlafaxine, is associated with gastrointestinal bleeding. Bleeding events with SSRIs and SNRIs included cas
have also occurred. Coadministration with warfarin or other anticoagulants may potentiate the risk of bleedinç
phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased ris
Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was
with warfarin or other drugs affecting coagulation should be undertaken with caution. Whenever venlafaxine i
coagulation parameters is recommended (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with warfarin or other drugs af
or discontinued in patients receiving anticoagulants, such as warfarin (Prod Info EFFEXOR XR(R) extended-
7) Probable Mechanism: additive adverse events
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit
abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duratic
showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95
(adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

3.5.1.D Alclofenac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.E Almotriptan

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Concomitant use of almotriptan and selective serotonin reuptake inhibitors (SSRI's) has been r Concurrent use of a triptan and an SSRI may result in serotonin syndrome which may be life-threatening. Sy coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive refl commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physicia combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administratic
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of a triptan, such as almotriptan, and an SSRI may result in a life- used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordinatic
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) Concomitant administration of fluoxetine and almotriptan is well tolerated and fluoxetine has only a m pharmacokinetics are not significantly affected. A randomized, open-label, two-way crossover study invo treatments with a minimum 3-week washout between periods: (1) three 20 mg fluoxetine capsules on da on day 8 with no treatment on days 1 through 7. Peak almotriptan concentrations were 18% higher follov This difference was statistically significant (p equal 0.023). Mean almotriptan area under the concentratic treatment groups. Mean half-life was not statistically different between the treatment groups. During fluox almotriptan may have been increased by fluoxetine. The author concludes that based on the results of th and fluoxetine can be safely used concomitantly in migraine management (Fleishaker et al, 2001).

3.5.1.F Amitriptyline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Tricyclic antidepressants (TCAs) and venlafaxine have been shown to prolong the QTc interval 1982). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antide recommended (Prod Info Elavil(R), 1999). In addition, venlafaxine and tricyclic antidepressants (TCAs) may c (Perry, 2000; Prod Info Effexor(R) XR, 2003; Ellingrod & Perry, 1994a). Venlafaxine increased the AUC, Cma increased by 2.5 and 4.5 fold when administered with venlafaxine 37.5 mg and 75 mg every 12 hours, respec affected (Prod Info venlafaxine extended release oral tablets, 2008).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administra
7) Probable Mechanism: decreased TCA and venlafaxine metabolism; additive effects on QT prolongation
8) Literature Reports
a) When administered with imipramine, the pharmacokinetics of imipramine and the 2-hydroxy metaboli (AUC), maximum concentration (Cmax), and minimum concentration (Cmin) of desipramine by approxim 12 hours) and by 4.5-fold (venlafaxine 75 mg every 12 hours). The clinical significance of this finding is u

3.5.1.G Amoxapine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Tricyclic antidepressants (TCAs) and venlafaxine have been shown to prolong the QTc interval 1982). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antide recommended (Prod Info Elavil(R), 1999). In addition, venlafaxine and tricyclic antidepressants (TCAs) may c (Perry, 2000; Prod Info Effexor(R) XR, 2003; Ellingrod & Perry, 1994a). Venlafaxine increased the AUC, Cma increased by 2.5 and 4.5 fold when administered with venlafaxine 37.5 mg and 75 mg every 12 hours, respec affected (Prod Info venlafaxine extended release oral tablets, 2008).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administra
7) Probable Mechanism: decreased TCA and venlafaxine metabolism; additive effects on QT prolongation
8) Literature Reports
a) When administered with imipramine, the pharmacokinetics of imipramine and the 2-hydroxy metaboli

(AUC), maximum concentration (Cmax), and minimum concentration (Cmin) of desipramine by approxim
12 hours) and by 4.5-fold (venlafaxine 75 mg every 12 hours). The clinical significance of this finding is u

3.5.1.H Amoxicillin

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: A 56-year-old male on venlafaxine experienced serotonin syndrome within 3 hours of taking an amoxicillin/clavulanate and venlafaxine are used concomitantly, monitor closely for symptoms of serotonin sy supportive care and other therapy as necessary (Boyer & Shannon, 2005).

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: A case of serotonin syndrome was reported with coadministration of amoxicillin/clav amoxicillin/clavulanate and venlafaxine are used concomitantly, monitor closely for symptoms of serotonin sy rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including tachycardia, mydri changes (including agitation and delirium). Serotonin syndrome can be life-threatening. If serotonin syndrome therapy as necessary (Boyer & Shannon, 2005).

7) Probable Mechanism: unknown

8) Literature Reports

a) A 56-year-old male on venlafaxine experienced serotonin syndrome within 3 hours of taking amoxicill mg twice daily for 10 months for depression. He experienced tingling in the tip of his tongue, intense para uncontrollable shivering and tremor, agitation, and he was frightened but not confused 2 hours after takir symptoms resolved after 6 hours and then he slept a further 8 hours. No further amoxicillin/clavulanate d same symptoms after the first dose. The patient continued on venlafaxine without further episodes. His r without any events (Connor, 2003).

3.5.1.I Anagrelide

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case reports and (SSRIs) and serotonin-norephinephrine reuptake inhibitors (SNRIs), including venlafaxine, is associated with ecchymoses, hematomas, epistaxis, and petechiae; life-threatening hemorrhages have also occurred. Coadr the risk of bleeding (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when venlafaxine is used concomitantly with antiplatelet agents. Close patients receiving antiplatelet agents concomitantly (Prod Info EFFEXOR XR(R) extended-release oral capsu

7) Probable Mechanism: unknown

3.5.1.J Ancrod

1) Interaction Effect: an increased risk of bleeding

2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake venlafaxine, is associated with gastrointestinal bleeding. Bleeding events with SSRIs and SNRIs included cas have also occurred. Coadministration with warfarin or other anticoagulants may potentiate the risk of bleeding phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased ris Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was with warfarin or other drugs affecting coagulation should be undertaken with caution. Whenever venlafaxine i coagulation parameters is recommended (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when venlafaxine is used concomitantly with warfarin or other drugs af or discontinued in patients receiving anticoagulants, such as warfarin (Prod Info EFFEXOR XR(R) extended-

7) Probable Mechanism: additive adverse events

8) Literature Reports

a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duratic showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95 (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

3.5.1.K Anisindione

1) Interaction Effect: an increased risk of bleeding

2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake venlafaxine, is associated with gastrointestinal bleeding. Bleeding events with SSRIs and SNRIs included cas have also occurred. Coadministration with warfarin or other anticoagulants may potentiate the risk of bleeding phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased ris Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was with warfarin or other drugs affecting coagulation should be undertaken with caution. Whenever venlafaxine i

coagulation parameters is recommended (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with warfarin or other drugs af
or discontinued in patients receiving anticoagulants, such as warfarin (Prod Info EFFEXOR XR(R) extended-
7) Probable Mechanism: additive adverse events
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit
abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duratic
showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95
(adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

3.5.1.L Antithrombin III Human
1) Interaction Effect: an increased risk of bleeding
2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake
venlafaxine, is associated with gastrointestinal bleeding. Bleeding events with SSRIs and SNRIs included cas
have also occurred. Coadministration with warfarin or other anticoagulants may potentiate the risk of bleedin
phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased ris
Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was
with warfarin or other drugs affecting coagulation should be undertaken with caution. Whenever venlafaxine i
coagulation parameters is recommended (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with warfarin or other drugs af
or discontinued in patients receiving anticoagulants, such as warfarin (Prod Info EFFEXOR XR(R) extended-
7) Probable Mechanism: additive adverse events
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit
abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duratic
showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95
(adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

3.5.1.M Aspirin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case reports and
(SSRIs) and serotonin-norephinephrine reuptake inhibitors (SNRIs), including venlafaxine, is associated with
ecchymoses, hematomas, epistaxis, and petechiae; life-threatening hemorrhages have also occurred. Coadr
the risk of bleeding (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with antiplatelet agents. Close
patients receiving antiplatelet agents concomitantly (Prod Info EFFEXOR XR(R) extended-release oral capsu
7) Probable Mechanism: unknown

3.5.1.N Atazanavir
1) Interaction Effect: increased plasma concentrations of venlafaxine
2) Summary: Caution is advised if a CYP3A4 inhibitor is administered with venlafaxine due to the possible in
(Prod Info venlafaxine extended release oral tablets, 2008). Patients should be monitored for venlafaxine toxi
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Patients should be monitored for signs of venlafaxine toxicity such as nausea, drow
7) Probable Mechanism: decreased venlafaxine clearance
8) Literature Reports
a) Caution is warranted with the concurrent use of CYP3A4 inhibitors, such as atazanavir, and venlafaxi
desvenlafaxine (ODV) (Prod Info venlafaxine extended release oral tablets, 2008).

3.5.1.O Benoxaprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate

4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.P Bivalirudin
1) Interaction Effect: an increased risk of bleeding
2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake
venlafaxine, is associated with gastrointestinal bleeding. Bleeding events with SSRIs and SNRIs included cas
have also occurred. Coadministration with warfarin or other anticoagulants may potentiate the risk of bleedin
phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased ris
Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was
with warfarin or other drugs affecting coagulation should be undertaken with caution. Whenever venlafaxine i
coagulation parameters is recommended (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with warfarin or other drugs af
or discontinued in patients receiving anticoagulants, such as warfarin (Prod Info EFFEXOR XR(R) extended-
7) Probable Mechanism: additive adverse events
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit
abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duratio
showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95
(adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

3.5.1.Q Bromfenac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.R Bufexamac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.S Cannabis
1) Interaction Effect: manic symptoms
2) Summary: One case of mania following use of marijuana with fluoxetine therapy has been reported (Stoll
symptoms could have resulted from the fluoxetine or marijuana alone. Caution is advised for patients using m
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Caution patients taking selective serotonin reuptake inhibitors to avoid concomitant
7) Probable Mechanism: additive serotonergic stimulation
8) Literature Reports
a) A 21-year-old female presented with mania, agitation, and grandiose delusions following use of mariju
reported smoking 2 "joints" during a 36-hour period. Over the next 24 hours, she developed increased en
perphenazine were given for agitation and excitement which gradually resolved over 4 days. She remain
prior to discharge. One week after discharge, she discontinued fluoxetine due to insomnia and feeling "h
rapid switch to mania after smoking marijuana with fluoxetine, the manic symptoms were associated with
from either fluoxetine or marijuana alone (Stoll et al, 1991).

3.5.1.T Carprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.U Celecoxib

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.V Cilostazol

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case reports anc (SSRIs) and serotonin-norephinephrine reuptake inhibitors (SNRIs), including venlafaxine, is associated with ecchymoses, hematomas, epistaxis, and petechiae; life-threatening hemorrhages have also occurred. Coadr the risk of bleeding (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with antiplatelet agents. Close patients receiving antiplatelet agents concomitantly (Prod Info EFFEXOR XR(R) extended-release oral capsu
7) Probable Mechanism: unknown

3.5.1.W Cimetidine

1) Interaction Effect: an increased risk of venlafaxine toxicity (nausea, drowsiness, dizziness, ejaculatory dis
2) Summary: Concurrent administration of cimetidine and venlafaxine (both at steady state) resulted in a 43 concentration of venlafaxine (Prod Info venlafaxine extended release oral tablets, 2008). The major metabolit amounts in the circulation than the parent drug. Because of this, it is unlikely that a clinically significant intera in patients with preexisting hepatic or renal dysfunction (Troy et al, 1998a). Therefore, caution is advised whe hepatic or renal function (Prod Info venlafaxine extended release oral tablets, 2008).
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of cimetidine and venlafaxine may result in decreased venlafaxine as nausea, drowsiness, and dizziness; a decrease in dosage may be required with concomitant therapy. An a such as ranitidine or famotidine, may be an alternative.
7) Probable Mechanism: decreased venlafaxine clearance
8) Literature Reports
a) Eighteen healthy volunteers received venlafaxine 50 mg three times daily for five days alone and in c pharmacokinetics of venlafaxine. Venlafaxine has pharmacologic activity, and the metabolite O-desmeth cimetidine was coadministered, the average steady-state concentration of venlafaxine increased from a desmethylvenlafaxine did not change in the presence of cimetidine (388 ng/mL vs. 387 ng/mL). Therefor increased by an average of 13%. This increase is not expected to produce clinically significant alteration (Troy et al, 1998).

3.5.1.X Clarithromycin

1) Interaction Effect: increased plasma concentrations of venlafaxine
2) Summary: Caution is advised if a CYP3A4 inhibitor is administered with venlafaxine, due to the possible i (Prod Info venlafaxine extended release oral tablets, 2008). Patients should be monitored for venlafaxine toxi
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Patients should be monitored for signs of venlafaxine toxicity such as nausea, drow

7) Probable Mechanism: decreased venlafaxine clearance
8) Literature Reports
a) Caution is warranted with the concurrent use of CYP3A4 inhibitors, such as clarithromycin, and venla desvenlafaxine (ODV) (Prod Info venlafaxine extended release oral tablets, 2008).

3.5.1.Y Clomipramine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and venlafaxine have been shown to prolong the QTc interval 1982). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antide recommended (Prod Info Elavil(R), 1999). In addition, venlafaxine and tricyclic antidepressants (TCAs) may c (Perry, 2000; Prod Info Effexor(R) XR, 2003; Ellingrod & Perry, 1994a). Venlafaxine increased the AUC, Cma increased by 2.5 and 4.5 fold when administered with venlafaxine 37.5 mg and 75 mg every 12 hours, respec affected (Prod Info venlafaxine extended release oral tablets, 2008).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administra
7) Probable Mechanism: decreased TCA and venlafaxine metabolism; additive effects on QT prolongation
8) Literature Reports
a) When administered with imipramine, the pharmacokinetics of imipramine and the 2-hydroxy metaboli (AUC), maximum concentration (Cmax), and minimum concentration (Cmin) of desipramine by approxim 12 hours) and by 4.5-fold (venlafaxine 75 mg every 12 hours). The clinical significance of this finding is u

3.5.1.Z Clonixin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrently 2008).
7) Probable Mechanism: unknown

3.5.1.AA Clopidogrel
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case reports and (SSRIs) and serotonin-norephinephrine reuptake inhibitors (SNRIs), including venlafaxine, is associated with ecchymoses, hematomas, epistaxis, and petechiae; life-threatening hemorrhages have also occurred. Coadr the risk of bleeding (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with antiplatelet agents. Close patients receiving antiplatelet agents concomitantly (Prod Info EFFEXOR XR(R) extended-release oral capsu
7) Probable Mechanism: unknown

3.5.1.AB Clozapine
1) Interaction Effect: increased serum concentrations of clozapine and venlafaxine
2) Summary: Coadministration of clozapine with other drugs that are metabolized by cytochrome P450 2D6, The hepatic P450IID6 isoenzyme is apparently involved with clozapine metabolism. Venlafaxine is a weak inl (Prod Info Effexor(R) XR, 1999c; Ellingrod & Perry, 1994b). With clozapine-venlafaxine coadministration, botl concentrations of both. Controlled studies are needed to validate these expectations and to document the cli
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Monitor patients receiving concurrent clozapine and venlafaxine for signs of clozapi venlafaxine toxicity (somnolence). Doses of either or both medications may need to be reduced.
7) Probable Mechanism: decreased clozapine and venlafaxine metabolism

3.5.1.AC Danaparoid
1) Interaction Effect: an increased risk of bleeding
2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake venlafaxine, is associated with gastrointestinal bleeding. Bleeding events with SSRIs and SNRIs included cas have also occurred. Coadministration with warfarin or other anticoagulants may potentiate the risk of bleeding phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased ris Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was

with warfarin or other drugs affecting coagulation should be undertaken with caution. Whenever venlafaxine i
coagulation parameters is recommended (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with warfarin or other drugs af
or discontinued in patients receiving anticoagulants, such as warfarin (Prod Info EFFEXOR XR(R) extended-
7) Probable Mechanism: additive adverse events
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit
abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duratic
showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95
(adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

3.5.1.AD Defibrotide
1) Interaction Effect: an increased risk of bleeding
2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake
venlafaxine, is associated with gastrointestinal bleeding. Bleeding events with SSRIs and SNRIs included cas
have also occurred. Coadministration with warfarin or other anticoagulants may potentiate the risk of bleedin
phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased ris
Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was
with warfarin or other drugs affecting coagulation should be undertaken with caution. Whenever venlafaxine i
coagulation parameters is recommended (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with warfarin or other drugs af
or discontinued in patients receiving anticoagulants, such as warfarin (Prod Info EFFEXOR XR(R) extended-
7) Probable Mechanism: additive adverse events
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit
abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duratic
showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95
(adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

3.5.1.AE Dermatan Sulfate
1) Interaction Effect: an increased risk of bleeding
2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake
venlafaxine, is associated with gastrointestinal bleeding. Bleeding events with SSRIs and SNRIs included cas
have also occurred. Coadministration with warfarin or other anticoagulants may potentiate the risk of bleedin
phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased ris
Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was
with warfarin or other drugs affecting coagulation should be undertaken with caution. Whenever venlafaxine i
coagulation parameters is recommended (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with warfarin or other drugs af
or discontinued in patients receiving anticoagulants, such as warfarin (Prod Info EFFEXOR XR(R) extended-
7) Probable Mechanism: additive adverse events
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit
abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duratic
showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95
(adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

3.5.1.AF Desipramine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Tricyclic antidepressants (TCAs) and venlafaxine have been shown to prolong the QTc interval
1982). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antide
recommended (Prod Info Elavil(R), 1999). In addition, venlafaxine and tricyclic antidepressants (TCAs) may c
(Perry, 2000; Prod Info Effexor(R) XR, 2003; Ellingrod & Perry, 1994a). Venlafaxine increased the AUC, Cma
increased by 2.5 and 4.5 fold when administered with venlafaxine 37.5 mg and 75 mg every 12 hours, respec
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 administr
7) Probable Mechanism: decreased TCA and venlafaxine metabolism; additive effects on QT prolongation
8) Literature Reports
a) When administered with imipramine, the pharmacokinetics of imipramine and the 2-hydroxy metaboli
(AUC), maximum concentration (Cmax), and minimum concentration (Cmin) of desipramine by approxim
12 hours) and by 4.5-fold (venlafaxine 75 mg every 12 hours). The clinical significance of this finding is u

3.5.1.AG Desirudin
1) Interaction Effect: an increased risk of bleeding
2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake
venlafaxine, is associated with gastrointestinal bleeding. Bleeding events with SSRIs and SNRIs included cas
have also occurred. Coadministration with warfarin or other anticoagulants may potentiate the risk of bleedin
phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased ris
Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was
with warfarin or other drugs affecting coagulation should be undertaken with caution. Whenever venlafaxine i
coagulation parameters is recommended (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with warfarin or other drugs af
or discontinued in patients receiving anticoagulants, such as warfarin (Prod Info EFFEXOR XR(R) extended-
7) Probable Mechanism: additive adverse events
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit
abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duratic
showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95
(adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

3.5.1.AH Desvenlafaxine
1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental s
2) Summary: Desvenlafaxine is the major active metabolite of venlafaxine, and these agents should not be u
norepinephrine reuptake inhibitors, and their concomitant use may result in serotonin syndrome, which may b
hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body tempera
extended-release tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of of desvenlafaxine and venlafaxine should be avoided, as desve
and norepinephrine reuptake inhibitors, and concomitant use increases the risk of serotonin syndrome (Prod
7) Probable Mechanism: additive serotonergic effect

3.5.1.AI Dexfenfluramine
1) Interaction Effect: serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Dexfenfluramine is a nonspecific serotonin agonist that both enhances the release of serotonin
selective serotonin reuptake inhibitor, such as venlafaxine, has the potential to cause serotonin syndrome (S
characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaph
(Sternbach, 1991k). Dexfenfluramine should not be used in combination with venlafaxine (Prod Info Redux(R
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of dexfenfluramine and venlafaxine may result in an additive increa
syndrome (hypertension, hyperthermia, myoclonus, mental status changes). Dexfenfluramine should not be u
7) Probable Mechanism: additive serotonergic effects

3.5.1.AJ Dexketoprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.AK Dextroamphetamine

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: Two weeks of concurrent use of dextroamphetamine and venlafaxine resulted in symptoms of s venlafaxine are used concomitantly, monitor closely for symptoms of serotonin syndrome. Serotonin syndrom agents and provide supportive care and other therapy as necessary (Boyer & Shannon, 2005).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: A case of serotonin syndrome was reported with coadministration of dextroamphetа concomitantly, monitor closely for symptoms of serotonin syndrome such as neuromuscular abnormalities (in shivering), autonomic hyperactivity (including tachycardia, mydriasis, diaphoresis, the presence of bowel sou Serotonin syndrome can be life-threatening. If serotonin syndrome develops, discontinue the offending agent

7) Probable Mechanism: additive pharmacologic effects

8) Literature Reports

a) A 32-year-old male on dextroamphetamine experienced serotonin syndrome approximately 2 weeks attention deficit hyperactivity disorder. He started 75 mg a day of venlafaxine for 1 week then the dose w experienced marked agitation, anxiety, shivering, and tremor. On admission he was alert and oriented. H per minute, blood pressure was 142/93 mmHg, and temperature was 37.3 degrees Celsius. No nystagm generalized hypertonia, hyperreflexia, inducible ankle clonus, frequent myoclonic jerking, and unilateral-t sinus tachycardia with a baseline tremor. Dextroamphetamine and venlafaxine were discontinued and cy and he was discharged the following morning. Dextroamphetamine was restarted 3 days later. Four days symptoms as he did with dextroamphetamine and venlafaxine. Agitation, nausea, diarrhea, and teeth cle cyproheptadine were given and within 2 days he was asymptomatic (Prior et al, 2002).

3.5.1.AL Dibenzepin

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

2) Summary: Tricyclic antidepressants (TCAs) and venlafaxine have been shown to prolong the QTc interval 1982). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antid recommended (Prod Info Elavil(R), 1999). In addition, venlafaxine and tricyclic antidepressants (TCAs) may c (Perry, 2000; Prod Info Effexor(R) XR, 2003; Ellingrod & Perry, 1994a). Venlafaxine increased the AUC, Cma increased by 2.5 and 4.5 fold when administered with venlafaxine 37.5 mg and 75 mg every 12 hours, respec affected (Prod Info venlafaxine extended release oral tablets, 2008).

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administra

7) Probable Mechanism: decreased TCA and venlafaxine metabolism; additive effects on QT prolongation

8) Literature Reports

a) When administered with imipramine, the pharmacokinetics of imipramine and the 2-hydroxy metaboli (AUC), maximum concentration (Cmax), and minimum concentration (Cmin) of desipramine by approxim 12 hours) and by 4.5-fold (venlafaxine 75 mg every 12 hours). The clinical significance of this finding is u

3.5.1.AM Diclofenac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).

7) Probable Mechanism: unknown

3.5.1.AN Dicumarol

1) Interaction Effect: an increased risk of bleeding

2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake venlafaxine, is associated with gastrointestinal bleeding. Bleeding events with SSRIs and SNRIs included cas have also occurred. Coadministration with warfarin or other anticoagulants may potentiate the risk of bleeding phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased ris Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was with warfarin or other drugs affecting coagulation should be undertaken with caution. Whenever venlafaxine i coagulation parameters is recommended (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when venlafaxine is used concomitantly with warfarin or other drugs af

or discontinued in patients receiving anticoagulants, such as warfarin (Prod Info EFFEXOR XR(R) extended-
7) Probable Mechanism: additive adverse events
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duratic showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95 (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

3.5.1.AO Diflunisal
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.AP Dipyridamole
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case reports anc (SSRIs) and serotonin-norephinephrine reuptake inhibitors (SNRIs), including venlafaxine, is associated with ecchymoses, hematomas, epistaxis, and petechiae; life-threatening hemorrhages have also occurred. Coadr the risk of bleeding (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with antiplatelet agents. Close patients receiving antiplatelet agents concomitantly (Prod Info EFFEXOR XR(R) extended-release oral capsu
7) Probable Mechanism: unknown

3.5.1.AQ Dipyrone
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.AR Dothiepin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Tricyclic antidepressants (TCAs) and venlafaxine have been shown to prolong the QTc interval 1982). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antid recommended (Prod Info Elavil(R), 1999). In addition, venlafaxine and tricyclic antidepressants (TCAs) may c (Perry, 2000; Prod Info Effexor(R) XR, 2003; Ellingrod & Perry, 1994a). Venlafaxine increased the AUC, Cma increased by 2.5 and 4.5 fold when administered with venlafaxine 37.5 mg and 75 mg every 12 hours, respec 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 administr
7) Probable Mechanism: decreased TCA and venlafaxine metabolism; additive effects on QT prolongation
8) Literature Reports
a) When administered with imipramine, the pharmacokinetics of imipramine and the 2-hydroxy metaboli (AUC), maximum concentration (Cmax), and minimum concentration (Cmin) of desipramine by approxim 12 hours) and by 4.5-fold (venlafaxine 75 mg every 12 hours). The clinical significance of this finding is u

3.5.1.AS Doxepin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Tricyclic antidepressants (TCAs) and venlafaxine have been shown to prolong the QTc interval 1982). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antid

recommended (Prod Info Elavil(R), 1999). In addition, venlafaxine and tricyclic antidepressants (TCAs) may c
(Perry, 2000; Prod Info Effexor(R) XR, 2003; Ellingrod & Perry, 1994a). Venlafaxine increased the AUC, Cma
increased by 2.5 and 4.5 fold when administered with venlafaxine 37.5 mg and 75 mg every 12 hours, respec
affected (Prod Info venlafaxine extended release oral tablets, 2008).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administra
7) Probable Mechanism: decreased TCA and venlafaxine metabolism; additive effects on QT prolongation
8) Literature Reports
a) When administered with imipramine, the pharmacokinetics of imipramine and the 2-hydroxy metaboli
(AUC), maximum concentration (Cmax), and minimum concentration (Cmin) of desipramine by approxim
12 hours) and by 4.5-fold (venlafaxine 75 mg every 12 hours). The clinical significance of this finding is u

3.5.1.AT Droxicam
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrently
2008).
7) Probable Mechanism: unknown

3.5.1.AU Duloxetine
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor. The concomitant use
inhibitor, is not recommended due to the potential for serotonin syndrome (Prod Info CYMBALTA(R) delayed-
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concomitant use of duloxetine and venlafaxine is not recommended due to the
release oral capsules, 2008).
7) Probable Mechanism: additive serotonergic effects

3.5.1.AV Entacapone
1) Interaction Effect: an increased risk of tachycardia, hypertension, and arrhythmias
2) Summary: Entacapone is an inhibitor of catechol-o-methyltransferase (COMT), and inhibits the metabolisr
inhibitor; the concurrent administration of entacapone and venlafaxine may theoretically provoke a suprathera
cardiovascular adverse events (Prod Info Comtan(R), 2000; Prod Info Comtan(R), 2004).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Coadministration of entacapone with venlafaxine is not recommended. Caution sho
be monitored for excessively increased heart rate, increased blood pressure, and cardiac arrhythmias.
7) Probable Mechanism: augmented inhibition of norepinephrine metabolism and clearance

3.5.1.AW Epoprostenol
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case reports anc
(SSRIs) and serotonin-norephinephrine reuptake inhibitors (SNRIs), including venlafaxine, is associated with
ecchymoses, hematomas, epistaxis, and petechiae; life-threatening hemorrhages have also occurred. Coadr
the risk of bleeding (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with antiplatelet agents. Close
patients receiving antiplatelet agents concomitantly (Prod Info EFFEXOR XR(R) extended-release oral capsu
7) Probable Mechanism: unknown

3.5.1.AX Eptifibatide
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case reports anc
(SSRIs) and serotonin-norephinephrine reuptake inhibitors (SNRIs), including venlafaxine, is associated with
ecchymoses, hematomas, epistaxis, and petechiae; life-threatening hemorrhages have also occurred. Coadr
the risk of bleeding (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a).

3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with antiplatelet agents. Close patients receiving antiplatelet agents concomitantly (Prod Info EFFEXOR XR(R) extended-release oral capsu
7) Probable Mechanism: unknown

3.5.1.AY Etodolac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.AZ Etofenamate
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.BA Etoricoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.BB Felbinac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.BC Fenbufen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.BD Fenfluramine

1) Interaction Effect: serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Fenfluramine is a nonspecific serotonin agonist that both enhances the release of serotonin an serotonin reuptake inhibitor, such as venlafaxine, has the potential to cause serotonin syndrome (Schenck & symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, more data are available, fenfluramine should not be used in combination with venlafaxine.
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of fenfluramine and venlafaxine may result in an additive increase i (hypertension, hyperthermia, myoclonus, mental status changes). Fenfluramine should not be used in combi
7) Probable Mechanism: additive serotonergic effects

3.5.1.BE Fenoprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.BF Fentiazac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.BG Floctafenine
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.BH Flufenamic Acid
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.BI Fluoxetine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest mental status changes)
2) Summary: Venlafaxine and fluoxetine have been shown to prolong the QTc interval at the recommended though no formal drug interaction studies have been done, the coadministration of drugs known to prolong th fluoxetine may result in serotonin syndrome (Chan et al, 1998a).
3) Severity: major
4) Onset: rapid

5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of venlafaxine and fluoxetine is not recommended.
7) Probable Mechanism: additive effects on QT prolongation; additive serotonergic effect

3.5.1.BJ Flurbiprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.BK Fondaparinux
1) Interaction Effect: an increased risk of bleeding
2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake venlafaxine, is associated with gastrointestinal bleeding. Bleeding events with SSRIs and SNRIs included cas have also occurred. Coadministration with warfarin or other anticoagulants may potentiate the risk of bleedin phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased ris Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was with warfarin or other drugs affecting coagulation should be undertaken with caution. Whenever venlafaxine i coagulation parameters is recommended (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with warfarin or other drugs af or discontinued in patients receiving anticoagulants, such as warfarin (Prod Info EFFEXOR XR(R) extended-
7) Probable Mechanism: additive adverse events
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duratic showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95 (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

3.5.1.BL Frovatriptan
1) Interaction Effect: increased risk of serotonin syndrome
2) Summary: A life-threatening condition known as serotonin syndrome may occur when triptans, such as fro (SNRI), such as venlafaxine. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans r prescribed by a different physician. Discuss the risks of serotonin syndrome with patients who are prescribed and Drug Administration, 2006).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of a triptan, such as frovatriptan, and an SNRI, such as venlafaxir triptans may be commonly used intermittently and that either the triptan or the SNRI may be prescribed by a syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hypertherr
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.BM Furazolidone
1) Interaction Effect: weakness, hyperreflexia, and incoordination
2) Summary: Although not its primary mechanism of action, furazolidone has monoamine oxidase inhibitor a receiving selective serotonin reuptake inhibitors (SSRI) in combination with monoamine oxidase inhibitors (M fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium a SSRI, or within a minimum of 14 days of discontinuing therapy with a MAOI (Prod Info Furoxone(R), 1999).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If concurrent therapy with furazolidone and a selective serotonin reuptake inhibitor excess (mental status changes, diaphoresis, fever, weakness, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.BN Ginkgo
1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental s

2) Summary: The addition of Ginkgo biloba and/or St. John's Wort to therapy with buspirone and fluoxetine r
is unclear if Ginkgo or St. John's Wort, the combination of both, or other patient factors, contributed to the eff
selective serotonin reuptake inhibitors (SSRIs). Caution is advised, especially when ginkgo is taken to counte
(Sloley et al, 2000; White et al, 1996), and has demonstrated serotonergic activity in animals (Ramassamy et
with SSRIs. The potential MAO inhibitory activity of ginkgo is questionable. A human study did not show MAC
extract inhibited MAO-A/MAO-B in the rat brain in vitro (Sloley et al, 2000; White et al, 1996) and MAO-B in h
following oral consumption (Porsolt et al, 2000).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients closely for symptoms of serotonin syndrome if ginkgo is combined
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) A 42-year-old female experienced symptoms consistent with a mixed hypomanic episode following cc
symptoms resolved following discontinuation of Ginkgo and St. John's Wort. The patient was being treat
twice daily and buspirone 15 mg twice daily. Several weeks prior to presentation, buspirone was increas
melatonin, and St. John's Wort in unspecified doses. Melatonin was considered unlikely to have contribu
since they may potentiate antidepressants, and considering the temporal relationship between the use o
symptoms. However, the brain injury was considered a possible contributor (Spinella & Eaton, 2002).

3.5.1.BO Haloperidol
1) Interaction Effect: increased haloperidol serum concentrations and an increased risk of cardiotoxicity (QT
2) Summary: Venlafaxine may inhibit haloperidol metabolism (Prod Info Effexor(R) XR, 2003c). Haloperidol i
Prod Info Haldol(R), 2001). Venlafaxine has been shown to prolong the QTc interval at the recommended the
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The concurrent administration of haloperidol and venlafaxine is not recommended.
7) Probable Mechanism: decreased haloperidol metabolism; theoretical additive effect on QT prolongation
8) Literature Reports
a) Under steady-state conditions, venlafaxine 150 mg daily decreased the total oral clearance of a singl
in the haloperidol area under the concentration-time curve (AUC). The haloperidol maximum concentrati
elimination half-life of haloperidol was not affected. The mechanism behind this interaction is not known
b) Numerous case reports have described significant QTc prolongation and torsades de pointes (TdP) a
ventricular fibrillation, asystole, and death have been reported. The risk of TdP appears to be greater wit
increases with doses greater than 35 milligrams (mg) over 24 hours, although TdP has been associated
haloperidol-induced TdP, screen patients for a history of dilated cardiomyopathy or alcohol abuse, testin
throughout therapy, and monitoring potassium, magnesium, and calcium. In patients with a baseline QTc
alternative agent should be used. Discontinue haloperidol if the QTc increases more than 25% from base
2003).

3.5.1.BP Heparin
1) Interaction Effect: an increased risk of bleeding
2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake
venlafaxine, is associated with gastrointestinal bleeding. Bleeding events with SSRIs and SNRIs included cas
have also occurred. Coadministration with warfarin or other anticoagulants may potentiate the risk of bleedin
phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased ris
Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was
with warfarin or other drugs affecting coagulation should be undertaken with caution. Whenever venlafaxine i
coagulation parameters is recommended (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with warfarin or other drugs af
or discontinued in patients receiving anticoagulants, such as warfarin (Prod Info EFFEXOR XR(R) extended-
7) Probable Mechanism: additive adverse events
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit
abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duratic
showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95
(adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

3.5.1.BQ Ibuprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).

3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrently 2008).
7) Probable Mechanism: unknown

3.5.1.BR Iloprost
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case reports and (SSRIs) and serotonin-norephinephrine reuptake inhibitors (SNRIs), including venlafaxine, is associated with ecchymoses, hematomas, epistaxis, and petechiae; life-threatening hemorrhages have also occurred. Coadr the risk of bleeding (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with antiplatelet agents. Close patients receiving antiplatelet agents concomitantly (Prod Info EFFEXOR XR(R) extended-release oral capsu
7) Probable Mechanism: unknown

3.5.1.BS Imipramine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Tricyclic antidepressants (TCAs) and venlafaxine have been shown to prolong the QTc interval 1982). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antide recommended (Prod Info Elavil(R), 1999). In addition, venlafaxine and tricyclic antidepressants (TCAs) may c (Perry, 2000; Prod Info Effexor(R) XR, 2003; Ellingrod & Perry, 1994a). Venlafaxine increased the AUC, Cma increased by 2.5 and 4.5 fold when administered with venlafaxine 37.5 mg and 75 mg every 12 hours, respec affected (Prod Info venlafaxine extended release oral tablets, 2008).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administra
7) Probable Mechanism: decreased TCA and venlafaxine metabolism; additive effects on QT prolongation
8) Literature Reports
a) When administered with imipramine, the pharmacokinetics of imipramine and the 2-hydroxy metaboli (AUC), maximum concentration (Cmax), and minimum concentration (Cmin) of desipramine by approxim 12 hours) and by 4.5-fold (venlafaxine 75 mg every 12 hours). The clinical significance of this finding is u

3.5.1.BT Indinavir
1) Interaction Effect: decreased indinavir serum concentrations
2) Summary: Venlafaxine 150 mg per day was administered under steady-state conditions to nine healthy vo 28% for a single 800 mg oral dose of indinavir, while the Cmax decreased by 36%. The pharmacokinetics of administration of indinavir. The clinical significance of this has not been determined (Prod Info venlafaxine ex
3) Severity: minor
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Although the clinical significance of this interaction is unknown, monitor patient for a
7) Probable Mechanism: increased indinavir metabolism

3.5.1.BU Indomethacin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrently 2008).
7) Probable Mechanism: unknown

3.5.1.BV Indoprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified

5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrently 2008).
7) Probable Mechanism: unknown

3.5.1.BW Iproniazid

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with venlafaxine and a monoamine oxidase (state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Effexor(R) XR, 1999a 60-year old woman developed a serious case of serotonin syndrome after the inadvertent ingestion of a singl Concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of venlafaxine and a MAO inhibitor is contraindicated. Wait at least at least seven days after discontinuing venlafaxine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports

a) Concomitant use of selective serotonin reuptake inhibitors and monoamine oxidase inhibitors can pro syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, cha not recognized and correctly treated, death can result.

b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for the patient became restless and developed leg twitches. The patients was later admitted to the emergen disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient wa symptoms after the second dose (Lappin & Auchincloss, 1994b).

c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ac taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant sy sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinue 1994b).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close tempora relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

e) A case of a 60-year old female who developed serotonin syndrome after the inadvertent ingestion of Approximately four hours after taking the venlafaxine, the patient became weak, confused, and collapse hyperreflexia, and diaphoresis. After treatment with diazepam, dantrolene, and other supportive therapy,

3.5.1.BX Isocarboxazid

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with venlafaxine and a monoamine oxidase (state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Effexor(R) XR, 2000; Concomitant use is contraindicated (Prod Info Marplan(R), 1998).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of venlafaxine and a MAO inhibitor is contraindicated. Wait at least at least seven days after discontinuing venlafaxine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, cha not recognized and correctly treated, death can result.

b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for the patient became restless and developed leg twitches. The patients was later admitted to the emergen disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient wa symptoms after the second dose (Lappin & Auchincloss, 1994d).

c) A 43-year old man began taking venlafaxine 75 mg after showing only a partial response to isocarbo agitation, hypomania, diaphoresis, shivering, and dilated pupils. The symptoms resolved after discontinu venlafaxine and isocarboxazid. After approximately six weeks of treatment, the patient was admitted to t The following day the patient continued to present with symptoms of serotonin syndrome, such as increa was given every six hours and symptoms slowly resolved over the next six days (Klysner et al, 1995).

d) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ac taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe

Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant sy sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinue 1994d).

e) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky approximately 1 month after adding selegiline to fluoxetine therapy. The patient improved 2 months after involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relat quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.BY Isoxicam

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).

7) Probable Mechanism: unknown

3.5.1.BZ Itraconazole

1) Interaction Effect: increased plasma concentrations of venlafaxine

2) Summary: Caution is advised if a CYP3A4 inhibitor, such as itraconazole, is administered with venlafaxine desvenlafaxine (ODV) (Prod Info venlafaxine extended release oral tablets, 2008). Patients should be monito

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Patients should be monitored for signs of venlafaxine toxicity such as nausea, drow

7) Probable Mechanism: decreased venlafaxine clearance

8) Literature Reports

a) Caution is warranted with the concurrent use of CYP3A4 inhibitors, such as itraconazole, and venlafa desvenlafaxine (ODV) (Prod Info venlafaxine extended release oral tablets, 2008).

3.5.1.CA Jujube

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: Serotonin syndrome developed within one hour in a 40-year-old female, when venlafaxine was nut) (Stewart, 2004). If Ziziphus jujube and venlafaxine are used concomitantly, monitor closely for symptoms syndrome develops, discontinue the offending agents and provide supportive care and other therapy as nece

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: A case of serotonin syndrome was reported with coadministration of Ziziphus jujube therefore, concomitant use is discouraged (Stewart, 2004). If Ziziphus jujube and venlafaxine are used concc abnormalities (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering bowel sounds, and diarrhea), and mental status changes (including agitation and delirium). Serotonin syndro agents and provide supportive care and other therapy as necessary (Boyer & Shannon, 2005).

7) Probable Mechanism: additive pharmacologic effects

8) Literature Reports

a) Serotonin syndrome developed in a 40-year-old female, when venlafaxine was added to Ziziphus juju jujube 500 mg/day for insomnia, fatigue, nervousness, and poor appetite. After several weeks of treatme venlafaxine she experienced restlessness, nausea, dizziness, and ataxia. She then collapsed. She was and shivering. Peripheral pulses were absent but she had a carotid pulse of 50 bpm. Vital signs were 60/ signs were 180/100 mmHg, 80 beats/minute, and 14 breaths/minute. Vital signs and mental status norm venlafaxine at 150 mg/day, but did not restart jujube, and 1 month later remained stable (Stewart, 2004).

3.5.1.CB Ketoconazole

1) Interaction Effect: an increased risk of venlafaxine toxicity (nausea, drowsiness, dizziness, ejaculatory dis

2) Summary: Caution is advised if ketoconazole, a CYP3A4 inhibitor, is administered with venlafaxine. A pha the O-desvenlafaxine active metabolite with concomitant use (Prod Info EFFEXOR(R) oral tablets, 2008; Pro

3) Severity: minor

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Patients should be monitored for signs of venlafaxine toxicity such as nausea, drow

7) Probable Mechanism: decreased venlafaxine clearance

8) Literature Reports

a) Higher plasma concentrations of both venlafaxine and the active metabolite O-desvenlafaxine (ODV) dose of venlafaxine (50 mg to 14 extensive metabolizers (EM) and 25 mg to 6 poor metabolizers (PM)).

metabolizers. Cmax of ODV increased by 29% in PM and 14% in EM subjects. Venlafaxine AUC increas
increased by 141% and 23% in PM and EM subjects, respectively, and the combined AUCs of venlafaxi
oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008).

3.5.1.CC Ketoprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.CD Ketorolac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.CE Lamifiban

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case reports anc
(SSRIs) and serotonin-norephinephrine reuptake inhibitors (SNRIs), including venlafaxine, is associated with
ecchymoses, hematomas, epistaxis, and petechiae; life-threatening hemorrhages have also occurred. Coadr
the risk of bleeding (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with antiplatelet agents. Close
patients receiving antiplatelet agents concomitantly (Prod Info EFFEXOR XR(R) extended-release oral capsu
7) Probable Mechanism: unknown

3.5.1.CF Lexipafant

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case reports anc
(SSRIs) and serotonin-norephinephrine reuptake inhibitors (SNRIs), including venlafaxine, is associated with
ecchymoses, hematomas, epistaxis, and petechiae; life-threatening hemorrhages have also occurred. Coadr
the risk of bleeding (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with antiplatelet agents. Close
patients receiving antiplatelet agents concomitantly (Prod Info EFFEXOR XR(R) extended-release oral capsu
7) Probable Mechanism: unknown

3.5.1.CG Linezolid

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Linezolid is a reversible, nonselective inhibitor of monoamine oxidase (MAO). Concurrent admi
toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, r
Serious, even fatal, reactions have been reported(Prod Info ZYVOX(R) IV injection, oral tablets, oral suspens
syndrome has been reported in 6 cases including 5 women (30, 36, 38, 58, and 81 years of age) and 1 man (
case, symptoms of serotonin syndrome abated when linezolid, venlafaxine, or both were discontinued (Maso
Berman, 2007; Jones et al, 2004). When concomitant use is warranted, monitoring the patient for serotonin s
both of the drugs should be considered (Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension, 2008
waiting period of 14 days between administration of these drugs may be considered (Packer & Berman, 2007
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of linezolid and venlafaxine may result in serotonin syndrome. Mon

blushing, diaphoresis, and hyperpyrexia (Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension, 2008
consider a waiting period of 14 days between administration of these drugs (Packer & Berman, 2007). If the u
symptoms of serotonin syndrome such as neuromuscular abnormalities (including hyper-reflexia, tremor, mus
(including tachycardia, mydriasis, diaphoresis, and diarrhea), and mental status changes (including agitation
develops, discontinue the offending agents and provide supportive care and other therapy as necessary (Boy
7) Probable Mechanism: inhibition of monamine oxidase-mediated serotonin metabolism
8) Literature Reports
a) A case report described serotonin toxicity in a 58-year-old woman following concomitant use of linezo
resection for transitional cell carcinoma 18 years earlier and had undergone a bilateral total hip arthropla
episodes of self-harm. She presented with symptoms of systemic infection. Increased activity at the site
Subsequently, the patient was initiated on vancomycin and rifampicin intravenously. A 2-stage revision T
antibiotic administration, her regimen was changed to oral linezolid and oral rifampicin 2 weeks postoper
examination and CT scan of the head did not reveal any abnormal findings or autonomic dysfunction. Ov
venlafaxine were stopped due to possible serotonin toxicity. The patient's condition normalized 48 hours
b) A case report described serotonin syndrome in a 36-year-old woman following the concomitant use o
regimen included lithium, venlafaxine, and imipramine for bipolar disorder, depression, and headaches, r
presenting to the ER, the patient received vancomycin for treatment of methicillin-resistant Staphylococc
before her ER visit. At presentation, she had a blood pressure (BP) of 234/196 mmHg, a heart rate of 16
with slow reaction to light and she was unresponsive to verbal instructions. The patient was intubated an
BP to 150/85 mmHg. Her serum lithium level was 1.2 mEq/L and there were no electrolyte abnormalities
patient was extubated. While both imipramine and venlafaxine were withheld, lithium was continued and
alert and oriented over the following days and had reduced anxiety. Three weeks following discharge, th
was postulated that her 3 chronic serotonergic medications led to a baseline hyperserotonergic state, wh
c) In one case report, a 30-year-old woman experienced symptoms of serotonin syndrome after concom
age of 15 years for depression, social anxiety, bulimia, and alcohol/benzodiazepine abuse, she had becc
After two weeks of treatment with linezolid, the patient complained of dizziness, syncope, and ataxia. At
discontinued and intensive therapy was instituted. Although her neurological symptoms dissipated, she c
quetiapine 25 mg 3 times daily was prescribed. Two weeks later, venlafaxine was gradually reinitiated (F
d) A retrospective chart review identified one highly probable case of serotonin syndrome in a patient wh
Charts of 72 inpatients who received linezolid and an SSRI or venlafaxine within 14 days of each other w
Hunter Serotonin Toxicity criteria. Of these patients, 52 (72%) were treated concomitantly with linezolid a
probability of SS. Of these, one case involved an 81-year-old woman who was diagnosed with a high pro
citalopram. Linezolid was given for a vancomycin-resistant Enterococcus urinary tract infection. When th
shouting. Although she appeared to have met 6 of the Sternbach criteria and 4 of the Hunter criteria for S
Hg with a heart rate of 120 beats/min, and a respiratory rate of 50 breaths/min. The following day, she ba
twitching and jerking, eyes rolled back in her head, and labored breathing. Linezolid was discontinued, a
after linezolid was stopped, she was extubated and had returned to baseline mental status with the abilit
e) A case report described serotonin toxicity in a 38-year-old woman following the concomitant administ
recent rib fracture was admitted after 3 weeks of coughing, progressive dyspnea, and green-colored spu
gabapentin 100 mg 3 times daily for one year, and hydromorphone 1 mg every 4 hours as needed for the
linezolid 600 mg IV every 12 hours for confirmed methicillin-resistant Staphylococcus aureus infection. F
hot flashes, dyspnea, and tiredness. Eight days following linezolid initiation, the venlafaxine dose was re
reported nervousness, muscle rigidity of the mouth, fine tremors (fingers), and involuntary arm, trunk, an
her BP normalized to 142/84 mmHg; other symptoms dissipated the next day. Upon discharge on day 10
150 mg once daily. In the subsequent 2-year period, the patient received two 10-day courses of linezolid
serotonin toxicity (Bergeron et al, 2005).
f) Serotonin syndrome was reported in the case of an 85-year-old man who was receiving venlafaxine 1
rifampicin for a closed wound due to the removal of a chronically infected hip prothesis. His medical histo
permanent pacemaker. After 20 days of receiving oral antibiotic therapy, the patient was reportedly confu
scan and serum chemistries were all normal with no evidence of sepsis; vital signs were also within norm
hospital due to drowsiness. He had a fever of 37.6 degrees Celsius and a decreased level of consciousn
venlafaxine were discontinued due to a suspected drug interaction. Within 2 days, the patient's mental st

3.5.1.CH Lornoxicam
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrently
2008).
7) Probable Mechanism: unknown

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

NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.CJ Mefenamic Acid
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.CK Meloxicam
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.CL Metoclopramide
1) Interaction Effect: an increased risk of developing extrapyramidal symptoms
2) Summary: A risk of serotonin syndrome with serious extrapyramidal reactions may occur with concomitan
developed extrapyramidal symptoms after metoclopramide was added to a regimen of venlafaxine (Fisher &
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Clinicians should be alerted to the possibility that patients may have an increased ri
metoclopramide. Close patient monitoring is warranted.
7) Probable Mechanism: synergistic dopaminergic inhibition
8) Literature Reports
a) Metoclopramide interacts with venlafaxine resulting in serotonin syndrome with serious dystonic-dysk
hospital after falling. She had been treated with venlafaxine 150 mg am and 75 mg pm for 3 years. The p
and clenching of the teeth after receiving metoclopramide intravenously. She was unresponsive for less
later, the patient developed mycolonic jerks and muscle rigidity and she became diaphoretic, confused a
and dilated pupils. Her temperature rose to 37.9 degrees Celsius, heart rate was 115 beats/min, respirat
values were normal. There was improvement in symptoms after intravenous diazepam was administered
increased muscle rigidity with intermittent forceful extensions of her legs and jerking of her arms. Two or
resolution of symptoms occurred on hospital day 3. Venlafaxine was reinstated without problems. Accord
was considered a probable cause of serotonin syndrome (Fisher & David, 2002).

3.5.1.CM Metoprolol
1) Interaction Effect: increased metoprolol plasma concentrations, but decreased metoprolol efficacy in lowe
2) Summary: Concomitant use of metoprolol and venlafaxine extended-release tablets may reduce the effica
administration. Some patients treated with venlafaxine have experienced dose-related increases in blood pre
extended-release tablets concomitantly (Prod Info Effexor XR(R) extended-release oral capsules, 2009).
3) Severity: major
4) Onset: unspecified
5) Substantiation: established
6) Clinical Management: Concurrent administration of metoprolol and venlafaxine extended-release tablets c
should be controlled before treatment with venlafaxine. Regularly monitor blood pressure in patients receiving
capsules, 2009).
7) Probable Mechanism: unknown
8) Literature Reports
a) In an interaction study of 18 healthy males, concomitant administration of metoprolol (100 mg every 2

increase in metoprolol plasma concentrations by approximately 30 to 40% without altering the plasma cc pharmacokinetic profile of venlafaxine or its O-desmethylvenlafaxine metabolite. It appeared that venlafa finding for hypertensive patients is unknown (Prod Info Effexor XR(R) extended-release oral capsules, 2(

3.5.1.CN Mirtazapine

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: Concurrent use of mirtazapine and venlafaxine resulted in symptoms of serotonin syndrome in limbs, diaphoresis, hyperreflexia, tachycardia (greater than 100 beats per minute), and increased blood press symptoms of serotonin syndrome. Serotonin syndrome can be life-threatening. If serotonin syndrome develop necessary (Boyer & Shannon, 2005).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: A case of serotonin syndrome was reported with concomitant use of mirtazapine ar mirtazapine and venlafaxine are used together, monitor closely for symptoms of serotonin syndrome such as peripheral hypertonicity, and shivering), autonomic hyperactivity (including tachycardia, mydriasis, diaphoresi agitation and delirium). Serotonin syndrome can be life-threatening. If serotonin syndrome develops, disconti (Boyer & Shannon, 2005).

7) Probable Mechanism: additive serotonergic pharmacologic effects

8) Literature Reports

a) A 31-year-old female on mirtazapine experienced serotonin syndrome after venlafaxine was added. S decided to slowly discontinue mirtazapine, with 30 mg/day, and start venlafaxine extended-release 75 m gross tremor of the upper limbs, diaphoresis, hyperreflexia, tachycardia (greater than 100 beats per minu tomography. Mirtazapine and venlafaxine were discontinued and she was administered oral lorazepam a resolved 24 hours later (Dimellis, 2002).

3.5.1.CO Moclobemide

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

2) Summary: Concurrent administration or overlapping therapy with venlafaxine and a monoamine oxidase (state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Effexor(R) XR, 2000b & de Vries, 1990i). Concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of venlafaxine and a MAO inhibitor is contraindicated. Wait at least at least seven days after discontinuing venlafaxine before initiating therapy with a MAO inhibitor.

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

8) Literature Reports

a) Concomitant use of selective serotonin reuptake inhibitors and monoamine oxidase inhibitors can pro syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, cha not recognized and correctly treated, death can result.

b) Two cases suggestive of an interaction between fluoxetine and selegiline, a selective monoamine oxi involved a first episode of mania being observed approximately one month after adding selegiline to fluo no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with

c) Five fatal overdose cases due to serotonin syndrome have been reported (Neuvonen et al, 1993). In moclobemide, a selective monoamine oxidase inhibitor, and citalopram. Of the three patients, blood conc therapeutic level, and citalopram concentrations ranged from normal therapeutic levels to five times the t

d) A 34-year-old man experienced serotonin syndrome after ingesting venlafaxine 2.625 g and moclobe beats/min), tachypnea (26 breaths/min), altered mental status, hypertonia, and had a creatine phosphoki may act like an irreversible MAOI with large doses, increasing the level of serotonin in the synaptic cleft

e) A 32-year-old man taking moclobemide 20 mg twice daily and diazepam 15 mg daily was given venla vomiting, diaphoresis, hallucination and agitation. He also demonstrated muscle rigidity and ocular oscill mg and chlorpromazine 12.5 mg and his condition improved significantly (Chan et al, 1998).

3.5.1.CP Morniflumate

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).

7) Probable Mechanism: unknown

3.5.1.CQ Nabumetone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.CR Naproxen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.CS Naratriptan

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Rare incidences of weakness, hyperreflexia, and incoordination have been reported with the co 1 (5HT-1) agonist (Prod Info Amerge(TM), 2002). Concurrent use of a triptan and an SSRI may result in sero include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, inc Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the syndrome with patients who are prescribed this combination and monitor them closely for symptoms of seroto
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as naratriptan, and an SSRI may result in a life-t used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordinatic
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.CT Nefazodone

1) Interaction Effect: increased plasma concentrations of venlafaxine
2) Summary: Caution is advised if a CYP3A4 inhibitor, such as nefazodone, is administered with venlafaxine desvenlafaxine (ODV) (Prod Info venlafaxine extended release oral tablets, 2008). Patients should be monito
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Patients should be monitored for signs of venlafaxine toxicity such as nausea, drow
7) Probable Mechanism: decreased venlafaxine clearance
8) Literature Reports
  a) Caution is warranted with the concurrent use of CYP3A4 inhibitors, such as nefazodone, and venlafa desvenlafaxine (ODV) (Prod Info venlafaxine extended release oral tablets, 2008).

3.5.1.CU Nelfinavir

1) Interaction Effect: increased plasma concentrations of venlafaxine
2) Summary: Caution is advised if a CYP3A4 inhibitor, such as nelfinavir, is administered with venlafaxine, d desvenlafaxine (ODV) (Prod Info venlafaxine extended release oral tablets, 2008). Patients should be monito
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Patients should be monitored for signs of venlafaxine toxicity such as nausea, drow
7) Probable Mechanism: decreased venlafaxine clearance
8) Literature Reports
  a) Caution is warranted with the concurrent use of CYP3A4 inhibitors, such as nelfinavir, and venlafaxin desvenlafaxine (ODV) (Prod Info venlafaxine extended release oral tablets, 2008).

3.5.1.CV Nialamide

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental st
2) Summary: Concurrent administration or overlapping therapy with venlafaxine and a monoamine oxidase (

state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Effexor(R) XR, 1999b year old woman developed a serious case of serotonin syndrome after the inadvertent ingestion of a single d Concomitant use is contraindicated.

3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of venlafaxine and a MAO inhibitor is contraindicated. Wait at least at least seven days after discontinuing venlafaxine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports

a) Concomitant use of selective serotonin reuptake inhibitors and monoamine oxidase inhibitors can pro syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, cha not recognized and correctly treated, death can result.

b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for the patient became restless and developed leg twitches. The patients was later admitted to the emergen disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient wa symptoms after the second dose (Lappin & Auchincloss, 1994h).

c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ac taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant sy sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinue 1994i).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close tempora relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

e) A case of a 60-year old female who developed serotonin syndrome after the inadvertent ingestion of Approximately four hours after taking the venlafaxine, the patient became weak, confused, and collapse hyperreflexia, and diaphoresis. After treatment with diazepam, dantrolene, and other supportive therapy,

3.5.1.CW Niflumic Acid

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.CX Nimesulide

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.CY Nortriptyline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Tricyclic antidepressants (TCAs) and venlafaxine have been shown to prolong the QTc interval 1982). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antid recommended (Prod Info Elavil(R), 1999). In addition, venlafaxine and tricyclic antidepressants (TCAs) may c (Perry, 2000; Prod Info Effexor(R) XR, 2003; Ellingrod & Perry, 1994a). Venlafaxine increased the AUC, Cma increased by 2.5 and 4.5 fold when administered with venlafaxine 37.5 mg and 75 mg every 12 hours, respec 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 administr

7) Probable Mechanism: decreased TCA and venlafaxine metabolism; additive effects on QT prolongation
8) Literature Reports
a) When administered with imipramine, the pharmacokinetics of imipramine and the 2-hydroxy metaboli (AUC), maximum concentration (Cmax), and minimum concentration (Cmin) of desipramine by approxim 12 hours) and by 4.5-fold (venlafaxine 75 mg every 12 hours). The clinical significance of this finding is u

3.5.1.CZ Oxaprozin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.DA Parecoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.DB Pargyline
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental st
2) Summary: Concurrent administration or overlapping therapy with venlafaxine and a monoamine oxidase (state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Effexor(R) XR, 1999; 60-year old woman developed a serious case of serotonin syndrome after the inadvertent ingestion of a singl Concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of venlafaxine and a MAO inhibitor is contraindicated. Wait at least at least seven days after discontinuing venlafaxine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of selective serotonin reuptake inhibitors and monoamine oxidase inhibitors can pro syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, cha not recognized and correctly treated, death can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for the patient became restless and developed leg twitches. The patients was later admitted to the emergen disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient wa symptoms after the second dose (Lappin & Auchincloss, 1994).
c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ac taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant sy sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinue 1994).
d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close tempora relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.
e) A case of a 60-year old female who developed serotonin syndrome after the inadvertent ingestion of Approximately four hours after taking the venlafaxine, the patient became weak, confused, and collapse hyperreflexia, and diaphoresis. After treatment with diazepam, dantrolene, and other supportive therapy,

3.5.1.DC Pentosan Polysulfate Sodium
1) Interaction Effect: an increased risk of bleeding
2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake

venlafaxine, is associated with gastrointestinal bleeding. Bleeding events with SSRIs and SNRIs included cas have also occurred. Coadministration with warfarin or other anticoagulants may potentiate the risk of bleeding phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased ris Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was with warfarin or other drugs affecting coagulation should be undertaken with caution. Whenever venlafaxine i coagulation parameters is recommended (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a

3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with warfarin or other drugs af or discontinued in patients receiving anticoagulants, such as warfarin (Prod Info EFFEXOR XR(R) extended-
7) Probable Mechanism: additive adverse events
8) Literature Reports

a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duratic showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95 (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

3.5.1.DD Phenelzine

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Serious, sometimes fatal, reactions have been seen with the combination of venlafaxine and m Effexor(R) XR, 2000c). Reports of adverse effects have included hyperthermia, rigidity, myoclonus, instability MAOIs and venlafaxine has also been reported to result in a condition termed serotonin syndrome (Klysner e potentially fatal condition of serotonergic hyperstimulation characterized by changes in mental status, restless one case serotonin syndrome occurred with initiation of venlafaxine therapy 16 days after discontinuation of p another report, two additional patients were started on venlafaxine at least 14 days after discontinuation of ph 1998a).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of venlafaxine and a MAO inhibitor is contraindicated. Wait at least at least seven days after discontinuing venlafaxine before initiating therapy with a MAO inhibitor. Even if initia for development of serotonin syndrome.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, cha not recognized and correctly treated, death can result.

b) A 46-year old man with depression was taking a regimen of phenelzine 30 mg three times daily and c initiating therapy with venlafaxine. The exact tapering regimen was not available. One day after the patie 60 minutes, the patient was confused, twitching, and had a full body tremor. The patient was also having propranolol, diphenhydramine, and lorazepam in the emergency room, with subsequent improvement in the intensive care unit with resolution of symptoms over the next day without further complications (Heisl

c) A 39-year old woman developed symptoms similar to serotonin syndrome due to an interaction betwe phenelzine 45 mg daily seven days earlier, took a single 37.5 mg dose of venlafaxine. The patient then e creatinine kinase level. After treatment with lorazepam and other supportive therapy, the patient's sympt dose (Phillips & Ringo, 1995).

d) A case of serotonin syndrome was reported in a 34-year old man due to an interaction between venla discontinued 16 days before the initiation of therapy with venlafaxine. Shortly after the first venlafaxine d tachycardia, and muscular rigidity. The patient had a temperature of 98.1 degrees F, a pulse of 115, and rigidity, and myoclonus in both feet, the patient was diagnosed with serotonin syndrome. The patient's sy three times daily for two days upon discharge. This case may be of major importance since phenelzine h venlafaxine. A longer washout period may be necessary (Kolecki, 1997).

e) A 44-year-old female was stabilized on phenelzine 30 mg twice daily and alprazolam 0.5 mg three tim phenelzine and alprazolam. Within 45 minutes she began to experience extremity shaking and rapid resp increased muscle tone, and diminished verbal responsiveness. Vital signs included blood pressure of 13 degrees Celsius. The diagnosis of serotonin syndrome was made. Following intubation and seven days i (Weiner et al, 1998).

f) In a case report on four patients, symptoms of serotonin syndrome were noted, even in two cases wh patients ranged in age from 25 to 49 years, and all had been on phenelzine for co-existing migraine and of the four patients had been advised to wait 14 days after stopping phenelzine to start taking venlafaxin experienced symptoms including agitation, shaking, diaphoresis, hyperthermia, slight hypertension, dizzi one hour of administration of venlafaxine, and all the patients were returned to baseline within 24 hours c

3.5.1.DE Phenindione

1) Interaction Effect: an increased risk of bleeding
2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake

venlafaxine, is associated with gastrointestinal bleeding. Bleeding events with SSRIs and SNRIs included cas
have also occurred. Coadministration with warfarin or other anticoagulants may potentiate the risk of bleedinç
phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased ris
Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was
with warfarin or other drugs affecting coagulation should be undertaken with caution. Whenever venlafaxine i
coagulation parameters is recommended (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with warfarin or other drugs af
or discontinued in patients receiving anticoagulants, such as warfarin (Prod Info EFFEXOR XR(R) extended-
7) Probable Mechanism: additive adverse events
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit
abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duratic
showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95
(adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

3.5.1.DF Phenprocoumon

1) Interaction Effect: an increased risk of bleeding
2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake
venlafaxine, is associated with gastrointestinal bleeding. Bleeding events with SSRIs and SNRIs included cas
have also occurred. Coadministration with warfarin or other anticoagulants may potentiate the risk of bleedinç
phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased ris
Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was
with warfarin or other drugs affecting coagulation should be undertaken with caution. Whenever venlafaxine i
coagulation parameters is recommended (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with warfarin or other drugs af
or discontinued in patients receiving anticoagulants, such as warfarin (Prod Info EFFEXOR XR(R) extended-
7) Probable Mechanism: additive adverse events
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit
abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duratic
showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95
(adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

3.5.1.DG Phenylbutazone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.DH Pirazolac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.DI Piroxicam

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

NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.DJ Pirprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.DK Procarbazine
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental st
2) Summary: Concurrent administration or overlapping therapy with venlafaxine and a monoamine oxidase (
state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia,
concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Effexor(R) XR, 1999d
60-year old woman developed a serious case of serotonin syndrome after the inadvertent ingestion of a singl
Concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of venlafaxine and a MAO inhibitor is contraindicated. Wait at least
at least seven days after discontinuing venlafaxine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of selective serotonin reuptake inhibitors and monoamine oxidase inhibitors can pro
syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, cha
not recognized and correctly treated, death can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for
the patient became restless and developed leg twitches. The patients was later admitted to the emergen
disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient wa
symptoms after the second dose (Lappin & Auchincloss, 1994j).
c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ac
taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe
Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant sy
sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should
serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinue
1994k).
d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky
approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months
case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close tempora
relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.
e) A case of a 60-year old female who developed serotonin syndrome after the inadvertent ingestion of
Approximately four hours after taking the venlafaxine, the patient became weak, confused, and collapsed
hyperreflexia, and diaphoresis. After treatment with diazepam, dantrolene, and other supportive therapy,

3.5.1.DL Propyphenazone
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.DM Proquazone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.DN Protriptyline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Tricyclic antidepressants (TCAs) and venlafaxine have been shown to prolong the QTc interval 1982). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antid recommended (Prod Info Elavil(R), 1999). In addition, venlafaxine and tricyclic antidepressants (TCAs) may c (Perry, 2000; Prod Info Effexor(R) XR, 2003; Ellingrod & Perry, 1994a). Venlafaxine increased the AUC, Cma increased by 2.5 and 4.5 fold when administered with venlafaxine 37.5 mg and 75 mg every 12 hours, respec 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 administr
7) Probable Mechanism: decreased TCA and venlafaxine metabolism; additive effects on QT prolongation
8) Literature Reports
a) When administered with imipramine, the pharmacokinetics of imipramine and the 2-hydroxy metaboli (AUC), maximum concentration (Cmax), and minimum concentration (Cmin) of desipramine by approxim 12 hours) and by 4.5-fold (venlafaxine 75 mg every 12 hours). The clinical significance of this finding is u

3.5.1.DO Rasagiline

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental st
2) Summary: Concomitant use of rasagiline and venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SSRIs and non-selective MAOIs has been reported to cause serious, sometimes fatal reactions. Signs and s sign fluctuations, and mental status changes progressing to extreme agitation, delirium, and coma. Similar re elapse after discontinuing rasagiline before initiating venlafaxine therapy (Prod Info AZILECT(R) oral tablets, therapy with rasagiline (Prod Info EFFEXOR(R) oral tablets, 2007).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of rasagiline and venlafaxine is not recommended. Wait at least 14 least 7 days after discontinuing venlafaxine before initiating therapy with rasagiline (Prod Info AZILECT(R) or
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase

3.5.1.DP Ritonavir

1) Interaction Effect: increased plasma concentrations of venlafaxine
2) Summary: Caution is advised if a CYP3A4 inhibitor, such as ritonavir, is administered with venlafaxine, du desvenlafaxine (ODV) (Prod Info venlafaxine extended release oral tablets, 2008). Patients should be monito
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Patients should be monitored for signs of venlafaxine toxicity such as nausea, drow
7) Probable Mechanism: decreased venlafaxine clearance
8) Literature Reports
a) Caution is warranted with the concurrent use of CYP3A4 inhibitors, such as ritonavir, and venlafaxine desvenlafaxine (ODV) (Prod Info venlafaxine extended release oral tablets, 2008).

3.5.1.DQ Rizatriptan

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concon specific reuptake inhibitor (SSRI) (Prod Info Imitrex(R), 1998). Because rizatriptan is a 5HT 1B/1D receptor a 1998a). Concurrent use of a triptan and an SSRI may result in serotonin syndrome which may be life-threate coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive refl commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physicia combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administratic
3) Severity: major
4) Onset: delayed

5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as rizatriptan, and an SSRI may result in a life-th used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordinatic
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) Twelve healthy volunteers received paroxetine 20 mg daily for two weeks and a single dose of rizatrip paroxetine (Prod Info Maxalt(R), 1998).

3.5.1.DR Rofecoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.DS Saquinavir
1) Interaction Effect: increased plasma concentrations of venlafaxine
2) Summary: Caution is advised if a CYP3A4 inhibitor, such as saquinavir, is administered with venlafaxine. desvenlafaxine (ODV) (Prod Info venlafaxine extended release oral tablets, 2008). Patients should be monito
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Patients should be monitored for signs of venlafaxine toxicity such as nausea, drow
7) Probable Mechanism: decreased venlafaxine clearance
8) Literature Reports
a) Caution is warranted with the concurrent use of CYP3A4 inhibitors, such as saquinavir, and venlafaxi desvenlafaxine (ODV) (Prod Info venlafaxine extended release oral tablets, 2008).

3.5.1.DT Selegiline
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with venlafaxine and a monoamine oxidase (state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Effexor(R) XR, 2000f; Concomitant administration of venlafaxine and selegiline is contraindicated, and a minimum of 14 days shoul minimum of 7 days should elapse after discontinuing venlafaxine before initiating therapy with selegiline (Pro reported 15 days after discontinuation of selegiline therapy and initiation of venlafaxine therapy, indicating tha
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of venlafaxine and selegiline is contraindicated. Wait at least 14 da seven days after discontinuing venlafaxine before initiating therapy with selegiline.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, cha not recognized and correctly treated, death can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for the patient became restless and developed leg twitches. The patient was later admitted to the emergenc disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient wa symptoms after the second dose (Lappin & Auchincloss, 1994n).
c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ac taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant sy sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinue 1994o).
d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close tempora relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.
e) Although it has been suggested that MAOIs be discontinued for at least 14 days before the initiation c venlafaxine 15 days after cessation of selegiline. The patient had been treated previously with multiple a

50 mg. All medications were discontinued due to poor response and venlafaxine 37.5 mg was started 15 including profound anxiety, diarrhea, myoclonic jerks, shivering, tremor, and diaphoresis. These symptor further complications. The authors suggested that some patients may need a longer washout period betv

3.5.1.DU Sibrafiban

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case reports anc (SSRIs) and serotonin-norephinephrine reuptake inhibitors (SNRIs), including venlafaxine, is associated with ecchymoses, hematomas, epistaxis, and petechiae; life-threatening hemorrhages have also occurred. Coadr the risk of bleeding (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with antiplatelet agents. Close patients receiving antiplatelet agents concomitantly (Prod Info EFFEXOR XR(R) extended-release oral capsu
7) Probable Mechanism: unknown

3.5.1.DV Sibutramine

1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, ment
2) Summary: Sibutramine inhibits the reuptake of norepinephrine, dopamine, and serotonin. In addition, the t neurotransmitters. A hyperserotonergic state, termed serotonin syndrome, may result if sibutramine is given c and selective serotonin reuptake inhibitors is not recommended (Prod Info Meridia(R), 1997).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Sibutramine should not be administered with serotonergic agents, including selectiv
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, m the syndrome is not recognized and correctly treated, death can result (Sternbach, 1991a).

3.5.1.DW St John's Wort

1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, ment
2) Summary: One case of serotonin syndrome likely resulting from concomitant use of St. John's Wort and v of serotonin syndrome-like symptoms following the addition of St. John's Wort to sertraline or nefazodone the have mild monoamine oxidase inhibitory activity (Singer et al, 1999; Thiede & Walper, 1994), which when adc syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes Wort was initially characterized as a monoamine oxidase inhibitor (MAOI), it is now believed that insufficient I (Muller et al, 1997). It remains possible that the mild MAOI property of St. John's Wort may contribute to an ir (Demisch et al, 1989). Concomitant administration of monoamine oxidase inhibitors (MAOIs) with SSRIs has manufacturers. This contraindication may be extended to venlafaxine which, though not an SSRI, inhibits ser discontinuing St. John's Wort before starting a SSRI (Gordon, 1998), and may be applied to venlafaxine as w
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Avoid concomitant use. Given the half-life of venlafaxine of up to 11 hours, St. Johr discontinuation. A two-week washout period is suggested after discontinuing St. John's Wort before starting a
7) Probable Mechanism: additive serotonergic effect
8) Literature Reports
a) A 32-year-old male experienced symptoms of serotonin syndrome (malaise, anxiety, diaphoresis, trer and St. John's Wort tincture 200 drops three times daily (usual dose stated as 160 drops daily). The pati St. John's Wort after hearing of its benefits. St. John's Wort was discontinued on day 4 while venlafaxine

3.5.1.DX Sulfinpyrazone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case reports anc (SSRIs) and serotonin-norephinephrine reuptake inhibitors (SNRIs), including venlafaxine, is associated with ecchymoses, hematomas, epistaxis, and petechiae; life-threatening hemorrhages have also occurred. Coadr the risk of bleeding (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with antiplatelet agents. Close patients receiving antiplatelet agents concomitantly (Prod Info EFFEXOR XR(R) extended-release oral capsu
7) Probable Mechanism: unknown

3.5.1.DY Sulindac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.DZ Sulodexide
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case reports anc
(SSRIs) and serotonin-norephinephrine reuptake inhibitors (SNRIs), including venlafaxine, is associated with
ecchymoses, hematomas, epistaxis, and petechiae; life-threatening hemorrhages have also occurred. Coadr
the risk of bleeding (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with antiplatelet agents. Close
patients receiving antiplatelet agents concomitantly (Prod Info EFFEXOR XR(R) extended-release oral capsu
7) Probable Mechanism: unknown

3.5.1.EA Sumatriptan
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Concurrent use of a serotonin norepinephrine reuptake inhibitor, such as venlafaxine, and sum
serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid char
vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and tha
risks of serotonin syndrome with patients who are prescribed this combination and monitor them closely for s
EFFEXOR XR(R) extended-release oral capsules, 2008; Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of a triptan, such as sumatriptan, and a serotonergic agent, such
aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be presc
serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, I
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.EB Suprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl
2008).
7) Probable Mechanism: unknown

3.5.1.EC Tapentadol
1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental s
2) Summary: Concurrent use of tapentadol and venlafaxine may result in serotonin syndrome, which may be
hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body tempera
immediate release oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of tapentadol and venlafaxine may result in a life-threatening conc
closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination), espe
release oral tablets, 2008).
7) Probable Mechanism: additive serotonergic effect

3.5.1.ED Telithromycin
1) Interaction Effect: increased plasma concentrations of venlafaxine
2) Summary: Caution is advised if a CYP3A4 inhibitor, such as telithromycin, is administered with venlafaxin
desvenlafaxine (ODV) (Prod Info venlafaxine extended release oral tablets, 2008). Patients should be monito
3) Severity: major

4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Patients should be monitored for signs of venlafaxine toxicity such as nausea, drow
7) Probable Mechanism: decreased venlafaxine clearance
8) Literature Reports
a) Caution is warranted with the concurrent use of CYP3A4 inhibitors, such as telithromycin, and venlafa desvenlafaxine (ODV) (Prod Info venlafaxine extended release oral tablets, 2008).

3.5.1.EE Tenidap
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.EF Tenoxicam
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.EG Tiaprofenic Acid
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.EH Ticlopidine
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case reports anc (SSRIs) and serotonin-norephinephrine reuptake inhibitors (SNRIs), including venlafaxine, is associated with ecchymoses, hematomas, epistaxis, and petechiae; life-threatening hemorrhages have also occurred. Coadr the risk of bleeding (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with antiplatelet agents. Close patients receiving antiplatelet agents concomitantly (Prod Info EFFEXOR XR(R) extended-release oral capsu
7) Probable Mechanism: unknown

3.5.1.EI Tirofiban
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case reports anc (SSRIs) and serotonin-norephinephrine reuptake inhibitors (SNRIs), including venlafaxine, is associated with ecchymoses, hematomas, epistaxis, and petechiae; life-threatening hemorrhages have also occurred. Coadr the risk of bleeding (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with antiplatelet agents. Close patients receiving antiplatelet agents concomitantly (Prod Info EFFEXOR XR(R) extended-release oral capsu

7) Probable Mechanism: unknown

3.5.1.EJ Tolmetin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrentl 2008).
7) Probable Mechanism: unknown

3.5.1.EK Toloxatone

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental st
2) Summary: Concurrent administration or overlapping therapy with venlafaxine and a monoamine oxidase (state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Effexor(R) XR, 1999e 60-year old woman developed a serious case of serotonin syndrome after the inadvertent ingestion of a singl As a reversible and selective monoamine oxidase inhibitor, toloxatone may not potentiate the effects of selec with other MAOIs. However, until further studies confirm the safety and efficacy of this combined therapy, cor
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of venlafaxine and a MAO inhibitor is contraindicated. Wait at least at least seven days after discontinuing venlafaxine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of selective serotonin reuptake inhibitors and monoamine oxidase inhibitors can pro syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, cha not recognized and correctly treated, death can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for the patient became restless and developed leg twitches. The patients was later admitted to the emergen disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient wa symptoms after the second dose (Lappin & Auchincloss, 1994l).
c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ac taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant sy sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinue 1994m).
d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close tempora relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.
e) A case of a 60-year old female who developed serotonin syndrome after the inadvertent ingestion of Approximately four hours after taking the venlafaxine, the patient became weak, confused, and collapse hyperreflexia, and diaphoresis. After treatment with diazepam, dantrolene, and other supportive therapy,

3.5.1.EL Tramadol

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: The use of tramadol concurrently with other serotonergic drugs may result in serotonin syndror tramadol with mirtazapine and venlafaxine resulted in symptoms of serotonin syndrome in 47-year-old male. hyperreflexia, and mydriasis (Houlihan, 2004). If tramadol is used concomitantly with venlafaxine, monitor clo serotonin syndrome develops, discontinue the offending agents and provide supportive care and other therap
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: There is potential for serotonin syndrome with the concomitant use of tramadol and release tablets, 2008). A case of serotonin syndrome was reported with coadministration of tramadol with ver If the use of tramadol concomitantly with venlafaxine is clinically warranted, monitor closely for symptoms of s muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including tachycardi changes (including agitation and delirium). Serotonin syndrome can be life-threatening. If serotonin syndrome therapy as necessary (Boyer & Shannon, 2005).
7) Probable Mechanism: additive serotonergic pharmacologic effects
8) Literature Reports
a) Serotonin syndrome developed in a 47-year-old male when tramadol was added to a regimen of venl

and mirtazapine 30 mg/day for 4 months. Tramadol was added and over 4 weeks the dose was titrated u
mg/day of tramadol, he experienced agitation, confusion, severe shivering, diaphoresis, myoclonus, hype
the next 4 hours, tachycardia and a fever (39.2 degrees Celsius) developed. Intravenous fluids were adn
were restarted with dose titrations to original doses over 1 week without any recurrence of serotonin syn

3.5.1.EM Tranylcypromine

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with venlafaxine and a monoamine oxidase (
state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia,
concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Effexor(R) XR, 2000a
60-year old woman developed a serious case of serotonin syndrome after the inadvertent ingestion of a singl
Concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of venlafaxine and a MAO inhibitor is contraindicated. Wait at least
at least seven days after discontinuing venlafaxine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod
syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, cha
not recognized and correctly treated, death can result.

b) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ac
taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe
Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant sy
sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should
serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinue
1994f).

c) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky
approximately one month after adding selegiline to fluoxetine therapy. The patient improved two months
case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close tempora
relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

d) A case of a 60-year old female who developed serotonin syndrome after the inadvertent ingestion of
Approximately four hours after taking the venlafaxine, the patient became weak, confused, and collapsed
hyperreflexia, and diaphoresis. After treatment with diazepam, dantrolene, and other supportive therapy,

3.5.1.EN Trazodone

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Concurrent use of trazodone and venlafaxine resulted in symptoms of serotonin syndrome in a
and venlafaxine are used concomitantly, monitor closely for symptoms of serotonin syn
agents and provide supportive care and other therapy as necessary (Boyer & Shannon, 2005).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: A case of serotonin syndrome was reported with coadministration of trazodone and
concomitantly, monitor closely for symptoms of serotonin syndrome such as neuromuscular abnormalities (in
shivering), autonomic hyperactivity (including tachycardia, mydriasis, diaphoresis, the presence of bowel sou
Serotonin syndrome can be life-threatening. If serotonin syndrome develops, discontinue the offending agent
7) Probable Mechanism: additive pharmacologic effects
8) Literature Reports

a) A 50-year-old male experienced serotonin syndrome 18 days after starting venlafaxine and trazodone
opioid dependence, and docusate were started after he was admitted to the hospital for depressed mood
increased over 7 days to 225 mg/day. Eighteen days after hospitalization, he became disoriented, restles
afebrile. His other vital signs were unremarkable. All his drugs were discontinued because his symptoms
within 24 hours. Methadone and docusate were restarted and mirtazapine was started. He experienced
inhibitors (SSRIs) while on methadone, without any similar symptoms (McCue & Joseph, 2001).

3.5.1.EO Trifluoperazine

1) Interaction Effect: an increased risk of neuroleptic malignant syndrome and an increased risk of cardiotoxi
2) Summary: Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Stel
that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R),
interval at the recommended therapeutic dose (Prod Info Effexor(R) XR, 2003a). In addition, concomitant use
(Nimmagadda et al, 2000a).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The concurrent administration of venlafaxine and trifluoperazine is contraindicated.

7) Probable Mechanism: dopamine-inhibition effect of venlafaxine augments dopamine-receptor inhibition by
8) Literature Reports
a) A 44-year-old male who had been receiving trifluoperazine 1 mg three times daily for ten years as an following his first dose, he presented with profound sweating, anxiety, tremor, and rigidity. Vital signs rev beats per minute. Urine and blood panels were within normal limits, with the exception of an elevated cre Neuroleptic malignant syndrome was diagnosed, and the patient was treated with dantrolene and bromo reintroduced without complications. Neuroleptic malignant syndrome may have developed in this patient venlafaxine which augmented dopamine-receptor inhibition by trifluoperazine (Nimmagadda et al, 2000).

3.5.1.EP Trimipramine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and venlafaxine have been shown to prolong the QTc interval 1982). Even though no formal drug interaction studies have been done, the coadministration of tricyclic antide recommended (Prod Info Elavil(R), 1999). In addition, venlafaxine and tricyclic antidepressants (TCAs) may c (Perry, 2000; Prod Info Effexor(R) XR, 2003; Ellingrod & Perry, 1994a). Venlafaxine increased the AUC, Cma increased by 2.5 and 4.5 fold when administered with venlafaxine 37.5 mg and 75 mg every 12 hours, respec affected (Prod Info venlafaxine extended release oral tablets, 2008).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administra
7) Probable Mechanism: decreased TCA and venlafaxine metabolism; additive effects on QT prolongation
8) Literature Reports
a) When administered with imipramine, the pharmacokinetics of imipramine and the 2-hydroxy metaboli (AUC), maximum concentration (Cmax), and minimum concentration (Cmin) of desipramine by approxim 12 hours) and by 4.5-fold (venlafaxine 75 mg every 12 hours). The clinical significance of this finding is u

3.5.1.EQ Valdecoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec (R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrently 2008).
7) Probable Mechanism: unknown

3.5.1.ER Vasopressin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Venlafaxine and vasopressin have been shown to prolong the QTc interval at the recommende though no formal drug interaction studies have been done, the coadministration of drugs known to prolong th
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of venlafaxine and vasopressin is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.ES Warfarin
1) Interaction Effect: an increased risk of bleeding
2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake venlafaxine, is associated with gastrointestinal bleeding. Bleeding events with SSRIs and SNRIs included cas have also occurred. Coadministration with warfarin or other anticoagulants may potentiate the risk of bleeding phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased ris Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was with warfarin or other drugs affecting coagulation should be undertaken with caution. Whenever venlafaxine i coagulation parameters is recommended (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with warfarin or other drugs af or discontinued in patients receiving anticoagulants, such as warfarin (Prod Info EFFEXOR XR(R) extended-
7) Probable Mechanism: additive adverse events
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duratio

showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95
(adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

3.5.1.ET Xemilofiban

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case reports anc
(SSRIs) and serotonin-norephinephrine reuptake inhibitors (SNRIs), including venlafaxine, is associated with
ecchymoses, hematomas, epistaxis, and petechiae; life-threatening hemorrhages have also occurred. Coadr
the risk of bleeding (Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when venlafaxine is used concomitantly with antiplatelet agents. Close
patients receiving antiplatelet agents concomitantly (Prod Info EFFEXOR XR(R) extended-release oral capsu
7) Probable Mechanism: unknown

3.5.1.EU Zolmitriptan

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Concurrent use of a serotonin norepinephrine reuptake inhibitor, such as venlafaxine, and zoln
serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid char
vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and tha
risks of serotonin syndrome with patients who are prescribed this combination and monitor them closely for s
EFFEXOR XR(R) extended-release oral capsules, 2008; Prod Info EFFEXOR(R) oral tablets, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of a triptan, such as zolmitriptan, and a serotonergic agent, such a
aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be presc
serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, l
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.EV Zolpidem

1) Interaction Effect: an increased risk of hallucinations
2) Summary: The publication of five case reports from the Washington Poison Center elucidates potential int
reported hallucinations after concurrent use of zolpidem and antidepressant medication. The hallucination ep
1998a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Observe patients for hallucinatory activity. Alternative anti-insomnia medication may
7) Probable Mechanism: unknown
8) Literature Reports
a) The Washington Poison Center reports that they received five different calls from patients experienci
the five reports came from patients taking serotonin-reuptake inhibitors in addition to zolpidem. The antic
and bupropion. In each case, the hallucinatory activity lasted longer than one hour, but the patients' sym
which zolpidem might cause hallucinations has not been firmly established (Elko et al, 1998).

3.5.1.EW Zomepirac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ec
(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammatory agent are given concurrently
2008).
7) Probable Mechanism: unknown

3.5.2 Drug-Food Combinations

3.5.2.A Ethanol

1) Interaction Effect: an increased risk of CNS effects
2) Summary: Concomitant use of venlafaxine and ethanol did not potentiate psychomotor or psychometric ef
However, the manufacturer of venlafaxine recommends that patients be advised to avoid alcohol while using
3) Severity: minor
4) Onset: rapid
5) Substantiation: theoretical

6) Clinical Management: Patients receiving venlafaxine should be advised to avoid the use of alcohol.
7) Probable Mechanism: unknown
8) Literature Reports
a) The pharmacokinetic and pharmacodynamic effect of venlafaxine was tested in 16 healthy volunteers every eight hours for seven days. Ethanol or placebo was given on day 5 or 7 of venlafaxine administrati pharmacokinetics of venlafaxine when given with ethanol or placebo. In addition, no significant difference ethanol or placebo. It is not known if repeated administration of ethanol would have had a significant effe

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) Venlafaxine Hydrochloride
1) Therapeutic
a) Physical Findings
1) Measures such as the Hamilton Depression Rating Scale, Hamilton depressed mood item, MADRS t Improvement item may be used to assess efficacy in patients receiving venlafaxine for major depressive extended-release oral capsules, 2008).
2) The Hamilton Rating Scale for Anxiety (HAM-A) total score, the HAM-A anxiety and tension items, an of venlafaxine extended-release in generalized anxiety disorder (Prod Info EFFEXOR XR(R) extended-re
3) The Liebowitz Social Anxiety Scale (LSAS) may be used to assess therapeutic efficacy of venlafaxine release oral capsules, 2008).
4) The Panic and Anticipatory Anxiety Scale (PAAS), Panic Disorder Severity Scale (PDSS) total score, therapeutic efficacy of venlafaxine extended-release in panic disorder (Prod Info EFFEXOR XR(R) exten
2) Toxic
a) Laboratory Parameters
1) Measurement of serum cholesterol levels should be considered during long-term treatment as clinical venlafaxine for at least 3 months during placebo-controlled trials (Prod Info EFFEXOR(R) oral tablets, 20
2) Hyponatremia may occur as a result of treatment with SSRIs and serotonine-norepinephrine reuptake diuretics. Consider monitoring serum sodium levels in these patients (Prod Info EFFEXOR(R) oral tablet
3) Liver function should be monitored as dosage adjustments are necessary in cases of cirrhosis of the release oral capsules, 2008).
4) Patients receiving warfarin therapy should be carefully monitored when venlafaxine is initiated or disc reported when SSRIs and serotonine-norepinephrine reuptake inhibitors were co-administered with warf release oral capsules, 2008).
5) Renal function should be monitored, particularly in the elderly, as dosage adjustments are necessary oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008).
b) Physical Findings
1) Cough, progressive dyspnea, or chest discomfort may be indicative of interstitial lung disease and eo symptoms are observed, prompt medical evaluation and possible discontinuation of venlafaxine therapy extended-release oral capsules, 2008).
2) Increases in blood pressure have been reported in patients receiving venlafaxine. Preexisting hyperte monitoring of blood pressure should occur in patients receiving venlafaxine. Dose-reduction or discontinu pressure (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral c
3) Observe patients for discontinuation symptoms such as dysphoric mood, irritability, agitation, dizzines insomnia, hypomania, tinnitus, and seizures. Avoid abrupt discontinuation or dose-reduction of venlafaxi release oral capsules, 2008).
4) Observe patients (particularly the elderly, volume-depleted, and those receiving diuretics) for signs ar impairment, confusion, weakness, and unsteadiness. More severe and/or acute cases may lead to hallu oral tablets, 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008).
5) Observe patients for signs and symptoms of serotonin syndrome. Symptoms may include mental stat blood pressure, hyperthermia), neuromuscular aberrations (hyperreflexia, incoordination), and/or gastroi 2008; Prod Info EFFEXOR XR(R) extended-release oral capsules, 2008).

6) Patients with depressive symptoms should be screened prior to initiating treatment with an antidepres
detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression (Prod In
capsules, 2008).
7) Patients receiving antidepressants should be monitored for worsening of depression, suicidality, or ur
increases or decreases. Such monitoring should include at least weekly face-to-face contact with patient
every other week for the next 4 weeks, then at 12 weeks, and then as clinically indicated beyond 12 wee
observation) of patients and communication with the prescriber (Prod Info EFFEXOR(R) oral tablets, 200
2004).
8) Patients who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility,
for worsening depression or suicidality. If these symptoms are observed, therapy should be re-evaluated
in onset, or were not part of the patient's initial symptoms (Anon, 2004; Anon, 2004; Prod Info EFFEXOF
9) Patients with raised ocular pressure or at risk of acute narrow angle glaucoma should have ocular pre
Info EFFEXOR XR(R) extended-release oral capsules, 2008).

4.2 Patient Instructions

A) Venlafaxine (By mouth)

Venlafaxine

Treats depression. Effexor XR® also treats panic disorder, social anxiety disorder, and generalized anxiety disorc

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to venlafaxine, or if you have used an MAO
days.

How to Use This Medicine:
Long Acting Capsule, Long Acting Tablet, Tablet
Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed
use it more often than your doctor tells you to.
It is best to take this medicine with food or milk.
Swallow the extended-release capsule whole. Do not crush, break, or chew it.
If you cannot swallow the extended-release capsule, you may open it and pour the medicine into a small amo
it without chewing.
It is best to take this medicine at the same time each day.
This medicine should come with a Medication Guide. Read and follow these instructions carefully. Ask your d
Guide if you do not have one. Your doctor might ask you to sign some forms to show that you understand this

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
medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after
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 using an MAO inhibitor (such as isocarboxazid, phenelzine, selegilin
inhibitor within the last 14 days. Using these medicines with venlafaxine could cause serious health problems
Tell your doctor if you are also using St. John's Wort, tryptophan supplements, cimetidine (Tagamet®), halop
(Lithane®, Lithobid®, Eskalith®), or tramadol (Ultram®). Make sure your doctor knows if you are also using n
depression (such as desipramine, fluoxetine, paroxetine, Celexa®, Lexapro™, Norpramin®, Paxil®, Zoloft®),
for pain or arthritis, also called "NSAIDs" (such as aspirin, celecoxib, ibuprofen, Advil®, Aleve®, Celebrex®, E
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and a
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant, trying to become pregnant, or breastfeeding.
Make sure your doctor knows if you have liver disease, kidney disease, heart disease, had a recent heart atta
high cholesterol in the blood, or a mineral imbalance (such as low sodium in the blood). Tell your doctor if you
For some children, teenagers, and young adults, this medicine can increase thoughts of suicide. Tell your do
have thoughts about hurting yourselves. Report any unusual thoughts or behaviors that trouble you or your c
you or your child have trouble sleeping, get upset easily, have a big increase in energy, or start to act reckles
nervous, angry, restless, violent, or scared. Let the doctor know if you, your child, or anyone in your family ha
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that cou
Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to ke
Do not stop using this medicine suddenly without asking your doctor. You may need to slowly decrease your

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
Change in how much or how often you urinate.
Chest pain.
Fast or uneven heartbeat.
Feeling confused, nervous, restless, or clumsy.
Feeling more excited or energetic than usual.
Fever, chills, cough, sore throat, and body aches.
Lightheadedness, dizziness, or fainting.
Muscle spasms, twitching, or stiffness.
Seizures or tremors.
Severe nausea or diarrhea.
Unexplained fever, sweating, or shivering.
Unusual behavior or thoughts of hurting yourself or others.
Unusual bleeding or bruising.
Unusual tiredness or weakness.

If you notice these less serious side effects, talk with your doctor:
Anxiety, trouble sleeping, or unusual dreams.
Blurred vision.
Constipation or dry mouth.
Headache.
Mild nausea, vomiting, loss of appetite, or weight loss.
Problems with sex.
Sleepiness.
Warmth or redness in your face, neck, arms, or upper chest.

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

4.3 Place In Therapy

A) Venlafaxine Hydrochloride

1) Like the SSRIs, venlafaxine does not cause the anticholinergic, sedative, or cardiovascular adverse effects typ activating effect, at least with acute administration. Although its clinical significance is unclear, it inhibits synaptos patients with previous experience with tricyclic antidepressants indicate that venlafaxine has a different adverse e

2) Despite availability of newer antidepressants, 30% to 40% of patients with severe depression fail to achieve co limited clinical trials, venlafaxine was comparable to tricyclic antidepressants and superior to selective serotonin r response rates may result from the dual action of venlafaxine on the norepinephrine and serotonin system. Furthe Venlafaxine extended-release was superior to placebo in the prevention of recurrent episodes of depression in pa maintenance phase trials (Kocsis et al, 2007; Keller et al, 2007).

3) One potential advantage of venlafaxine is its apparent rapid onset of action; significant improvement of depres 2 weeks of therapy. However, it has not been established that venlafaxine clearly works faster than other antidepr trials, rather than a distinguishing characteristic of this drug. If additional research including comparative trials sup should be considered.

4) Preliminary data suggest that venlafaxine may be useful in the treatment of obsessive-compulsive disorder an these disorders.

4.4 Mechanism of Action / Pharmacology

A) Venlafaxine Hydrochloride

1) MECHANISM OF ACTION

a) Venlafaxine hydrochloride is an antidepressant agent that potentiates the neurotransmitter activity in the c norepinephrine and dopamine reuptake. Venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV slightly less potent inhibitors of neuronal norepinephrine reuptake, and weak inhibitors of neuronal dopamine serotonin reuptake inhibitors (Prod Info EFFEXOR(R) oral tablets, 2008; Prod Info EFFEXOR XR(R) extende Perry, 1994; Saletu et al, 1992; Muth et al, 1991; Fabre & Putmann, 1987).

b) Venlafaxine is a bicyclic antidepressant that has been referred to as an atypical or "second-generation" ar dopamine in order of decreasing potency. It does not inhibit monoamine oxidase, and does not show the deg antidepressants have been shown to exhibit. No affinity for central muscarinic-cholinergic, dopaminergic, hist demonstrated for venlafaxine or its major active metabolite, O-desmethylvenlafaxine. In animal studies, venla Other antidepressant properties include its ability to reverse reserpine hypothermia and to cause pineal beta- Saletu et al, 1992a; Yardley et al, 1990).

c) Venlafaxine is a racemic mixture; while the pharmacologic profile of the levo(-) isomer is similar to that of 1992).

2) ELECTROENCEPHALOGRAPHIC EFFECTS

a) Electroencephalographic (EEG) analysis in patients receiving venlafaxine has shown that it exerts signific compared with placebo, alpha power is decreased, relative delta/theta and beta powers are increased, and th antidepressants such as imipramine (Saletu et al, 1992a).

3) NEUROPSYCHIATRIC EFFECTS
- **a)** Administration of venlafaxine has been shown to cause significant improvement in attention, concentratio to placebo in healthy volunteers. This is thought to be due to activation of all 3 neurotransmitter systems (i.e., with higher doses, most likely due to the drug's serotonergic activity (Saletu et al, 1992a).

4) REVIEW ARTICLES
- **a)** Two reviews provide a discussion of the efficacy of selective serotonin reuptake inhibitors and other antid
- **b)** The efficacy of antidepressants in reducing panic attack frequency, symptoms of depression, social avoid
- **c)** A review article discussed the rational treatment of depression and included a discussion of each class of
- **d)** The pharmacology and therapeutic potential of venlafaxine has been reviewed (Holliday & Benfield, 1995
- **e)** Drug-interactions of antidepressants are reviewed in German language (Zapotoczky & Simhandl, 1995).

4.5 Therapeutic Uses

4.5.A Venlafaxine Hydrochloride

Antineoplastic adverse reaction - Neurotoxicity

Attention deficit hyperactivity disorder

Binging - Eating disorder

Bipolar disorder, depressed phase

Cancer pain

Cerebrovascular accident - Depression

Depression - Perimenopausal disorder

Diabetic neuropathy

Dysthymia

Generalized anxiety disorder

Hot sweats, Breast cancer-related

Major depressive disorder

Menopausal flushing

Obsessive-compulsive disorder

Panic disorder, With or without agoraphobia

Posttraumatic stress disorder

Premenstrual dysphoric disorder

Recurrent major depressive episodes; Prophylaxis

Severe major depression with psychotic features

Social phobia

Tension-type headache; Prophylaxis

4.5.A.1 Antineoplastic adverse reaction - Neurotoxicity

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:

Venlafaxine extended-release completely resolved paclitaxel-neurosensory toxicity in a 69-year-old

c) Adult:

1) In a single case report, venlafaxine hydrochloride extended-release (XR) completely resolved paclitax milligrams (mg)/m(2) and carboplatin for ovarian cancer. After failure of clonazepam 1.5 mg, venlafaxine resolved pin-pricks and parerethises in both her hands and wrists (Durand & Goldwasser, 2002).

4.5.A.2 Attention deficit hyperactivity disorder

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Results of a prospective, 6-week, open-label trial (n=13) demonstrate that venlafaxine therapy impro Abali, 2004).

c) Pediatric:

1) Symptoms of attention deficit hyperactivity disorder (ADHD) improved following venlafaxine treatment 6 to 15 years of age (mean age, 9.9 years) with ADHD and without comorbid depression received venlaf dose, 40.38 mg/day) for 6 weeks. No other psychotropic medications were allowed during the study. Res Clinical Global Impression (CGI)-Improvement scale. The total mean score of the Connor Parent Index w including significant improvement in individual index items such as "short attention span", "easily distract CGI-Severity rating was also significantly improved from baseline to endpoint (p less than 0.05) and ther who did not respond to venlafaxine treatment had comorbid conditions, including tic disorder or oppositic complicated by venlafaxine therapy. Transient adverse effects included stomachache (n=2), somnolence (56.25 mg/day) and one patient, with a comorbid tic disorder, experienced behavioral activation and wors safety and efficacy of venlafaxine in the treatment of ADHD in pediatric patients (Mukaddes & Abali, 200

4.5.A.3 Binging - Eating 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:

Results of a retrospective study (n=35) indicate venlafaxine may be an effective treatment for binge-

c) Adult:

1) The results of a small, retrospective study indicate that venlafaxine may be an effective treatment for eating disorder (n=35) received venlafaxine alone (n=29) or as an adjunctive therapy (n=6) at a mean do (range, 28 to 300 days). Some patients also received behavioral dietary counseling (91%), formal psych amitriptyline, bupropion, paroxetine, or sertraline. Patients on single or combination venlafaxine therapy frequency, Clinical Global Impressions-Severity of Illness (CGI-S) scale scores for binge eating and depr 0.0001). Fifteen (43%) patients lost at least 5% of their baseline weight and 7 (20%) patients lost at least sexual dysfunction (14%), insomnia (14%), nausea (11%), and blood pressure changes (46%). A small i

4.5.A.4 Bipolar disorder, depressed phase

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:

No significant difference between adjunctive bupropion, sertraline or venlafaxine was revealed amor risk of switching into (hypo)mania was significantly higher with venlafaxine in a randomized, double- Venlafaxine monotherapy was more effective than lithium for the initial treatment of bipolar II major d randomized, open-label, clinical trial (n=83) (Amsterdam & Shults, 2008).

Venlafaxine and paroxetine were both significantly effective adjunctive treatments for breakthrough d observed with venlafaxine in a single-blind, randomized, comparative trial (n=60) (Vieta et al, 2002).

c) Adult:

1) General Information

a) The incidence of bipolar disorder is reported to occur in 1% to 3% of the population. Most importa comparison to (hypo)manic episodes and have a 10% to 20% lifetime risk of death by suicide (Post for reduction of morbidity and mortality in patients with bipolar affective disorder. However, practice inadequate. The American Psychiatric Association recommends that initial treatment of bipolar II ma stabilizer and the lowest-effective dose, short-term antidepressant therapy (Amsterdam & Shults, 20 antidepressant monotherapy may be considered in bipolar II major depressive episode in patients w mood stabilizer monotherapy for mild to moderate bipolar II depression and combination mood stabi treatment completely (Amsterdam & Shults, 2008). Historical studies have provided evidence that a (eg, venlafaxine, tricyclic antidepressants) may increase the risk of switch into a hypomanic or mani no significant differences between adjunctive bupropion, sertraline, or venlafaxine among response mania switch was significantly higher with venlafaxine compared with bupropion and sertraline (Pos treatment with venlafaxine or paroxetine were both significantly effective for the treatment of breakth or manic switch was observed with venlafaxine (Vieta et al, 2002). In contrast, venlafaxine monothe major depressive episode with low occurrence of hypomanic switch in a prospective, randomized tri sizes, distinguishing between inclusions of bipolar I or bipolar II patients, a clear definition of switch, would be beneficial for consistent and effective control of major depressive episode and minimizatio Shults, 2008; Vieta et al, 2002).

2) Clinical Trials

a) No significant difference between adjunctive bupropion, sertraline or venlafaxine was revealed a the risk of switching into (hypo)mania was significantly higher with venlafaxine compared with bupro (n=174). All patients were currently treated with at least 1 mood stabilizer or antimanic agent. Subje (n=51), sertraline 50 to 200 mg/day (n=58), or venlafaxine 37.5 to 375 mg/day (n=65) for 10 weeks. the study. Symptoms were assessed using the Inventory of Depression Symptomatology (IDS), the Disorder (CGI-BP). The outcome measures included antidepressant response (defined as either a 5 depression score), antidepressant remission (defined as an IDS score less than 12 and/or a CGI-BP hypomania (defined as either an increase of 2 points on the CGI-BP manic severity score during an at any time point). At week 10, the response rates for bupropion, sertraline and venlafaxine were 49 differences were not statistically significant between groups and controlling for lithium use did not alt venlafaxine. Based on at least a 2-point increase on the CGI-BP score, (hypo)manic switching occu respectively. When these data were analyzed using survival analysis in order to control for the effec treatment groups was significant (p=0.002), and controlling for lithium demonstrated similar results (the significant difference in the risk of switching-time between venlafaxine and sertraline (p=0.01, ac lithium), while there was no significant difference between sertraline and bupropion (p=0.9). The risk score (greater than 13) was analyzed. By study endpoint, 4%, 7%, and 15% of patients switched in for lithium did not change the results. The difference between venlafaxine, bupropion and sertraline mania of at least 3 or YMRS greater than 13 criteria were used (p=0.03 without controlling for lithium cycling was lower with bupropion when compared with venlafaxine (p less than 0.01) but there was venlafaxine. The percentages of patients who discontinued the study prematurely for any reason we Withdrawal for adverse events did not vary between the 3 groups. Limitations of the study include n

b) Venlafaxine monotherapy was more effective than lithium for the initial treatment of bipolar II ma randomized, open-label, clinical trial (n=83). DSM-IV bipolar II adult patients with an ongoing acute included in the trial. All patients had a baseline, 17-item Hamilton Depression Rating Scale (HAM-D psychosis in the preceding 3 months or if they were nonresponsive to venlafaxine or lithium during t neuroleptics, tranquilizers or over-the-counter antidepressant agents were not allowed. Any previous Concomitant zolpidem, zaleplon or trazodone was allowed for severe insomnia. Eligible patients age (n=40) for 12 weeks. Venlafaxine was initiated at 37.5 milligrams (mg)/day, increased to 75 mg/day mg/day by week 4. The highest tolerated dose was maintained for an additional 8 weeks. Lithium wa required serum lithium level of 0.5 millimoles (mmol)/L during week 2. Lithium dose was optimized t maintained for an additional 8 weeks. At baseline, study subjects had a history of bipolar II for 18.5 - 18.7 +/- 8.7 years and first hypomanic episode at age 20.7 +/- 8.2. The mean baseline HAM-D 28 sc group. At the end of the study, 79.1% of patients in the venlafaxine group and 37.5% of patients in t was a greater reduction in HAM-D 28 (primary endpoint) with venlafaxine monotherapy compared w (95% CI, -11.97 to -1.18; p=0.017). Venlafaxine monotherapy yielded a greater number of responde 20%; p less than 0.0005). The proportion of remitters (final HAM-D 28 score of 8 or less) was also s 0.0005). There was no significant difference between treatment groups in the mean Young Mania R each, experienced subsyndromal hypomanic and hypomanic symptoms (2.4% vs 2.6%; p=0.99). Or patient in the lithium group discontinued due to increasing suicidal ideation. Other common adverse mouth (32.6% vs 10%), somnolence (30.2% vs 22.5%) and difficulty thinking (16.3% vs 32.5%) in th of a placebo/control group, short treatment duration and small sample population size (Amsterdam &

c) Venlafaxine and paroxetine were both significantly effective adjunctive treatments for breakthrou manic switch was observed with venlafaxine in a single(rater)-blind, randomized, comparative trial (episode indicated by a score of greater than 17 on the 17-item Hamilton Rating Scale for Depressio carbamazepine, other) for at least 6 months prior to the current depressive episode, and required to throughout the study period. Recent treatment with antidepressant or antipsychotics during the prev attempt, currently abusing alcohol or other psychotropics, using concomitant anxiolytics, had previou Scale (YMRS). Eligible patients were randomly assigned to either venlafaxine (n=30; age 45.5 years

6 weeks. Based on response and tolerability, the venlafaxine group received 37.5 milligrams (mg) tv trial was 179.2 +/- 91 mg/day. The paroxetine group received 20 mg/day titrated by 10-mg/day incre modified intent-to-treat population, defined as all patients who took at least 1 dose of study medicati significant improvement in HAM-D 28 scores from baseline to endpoint (primary endpoint). The char to 13.8 +/- 6.7 for paroxetine (both p less than 0.0001). Venlafaxine was numerically superior to parc defined as a reduction in HAM-D 28 score by 50% or more from baseline, was 48% in the venlafaxir HAM-D score of less than 10 and a Clinical Global Impressions (CGI) severity score of 1 was 33% ir occurred in 4 patients (13%) in the venlafaxine group: 2 switched to hypomania (YMRS score = 12 a (3%) in the paroxetine group who switched to hypomania (YMRS score = 17) (p not significant). The treatment and antidepressant discontinuation. One manic episode required hospitalization. Commor vs 7%), headache (3% vs 10%) and insomnia (10% vs 0%) in the venlafaxine and paroxetine groups study design, small sample population size and short follow-up period (Vieta et al, 2002).

4.5.A.5 Cancer pain

See Drug Consult reference: MANAGEMENT OF CANCER-RELATED PAIN IN ADULT PATIENTS

4.5.A.6 Cerebrovascular accident - Depression

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:

During an open study, 12 post-stroke patients benefited from venlafaxine treatment administered wi

c) Adult:

1) Twelve patients who received venlafaxine within 2 weeks of a stroke showed a decrease in depressiv (mg) daily with an increase to 150 mg daily after 2 days. Response was evaluated with the Hamilton Dep (MADRS). After 5 weeks of treatment, the HAM-D score decreased from 24.3 to 7.25, and the MADRS d dose was decreased in 1 patient due to agitation; 3 patients had nausea during initiation of treatment. Ba with depression secondary to stroke (Dahmen et al, 1999).

4.5.A.7 Depression - Perimenopausal disorder

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

In a small, open-label trial, extended-release venlafaxine therapy reduced depressive symptoms and

c) Adult:

1) In a small, 8-week, open-label trial, treatment with extended-release venlafaxine reduced depressive perimenopausal if they reported one or more climacteric symptoms (hot flushes, sweating, vaginal dryne criteria comprised of presence of current depressive disorder confirmed by the DSM-IV Axis I disorders, non-hormonal method of contraception. The study was initiated on day 10, 11, or 12 of the menstrual cyc orally once daily during week 1 and 75 mg daily during week 2. Data collection instruments included the global impression severity (CGI-S), and a standard measure of 4 subscales: psychiatric, somatic, vasom When clinically necessary, dosage was increased in 75-mg increments after the week 2 and week 4 visit observed by week 2 and were sustained through week 8. Antidepressant response (greater than 50% Ha equal to 7) was achieved in 12 subjects (75%) after 8 weeks of venlafaxine therapy (75 to 225 mg/day). 71%, and anxiety subscores reduced by 63%. Vasomotor and sexual dysfunction subscores were not sig vasomotor subscores greater than 0, a 37.5% decline was observed at week 8 (p less than 0.05). Howev vasomotor symptoms observed in women who had baseline vasomotor symptoms and that further studie depression (Ladd et al, 2005).

4.5.A.8 Diabetic neuropathy

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:

Dose-related, clinically significant reductions in pain were demonstrated with venlafaxine extended-r (Rowbotham et al, 2004).
One case report demonstrated the effectiveness of venlafaxine depot combined with gabapentin for Venlafaxine relieved the unremitting pain of diabetic peripheral neuropathy in 8 patients who found r

In a series of 11 patients, venlafaxine relieved the pain associated with diabetic peripheral neuropat

c) Adult:

1) The efficacy of venlafaxine extended-release (XR) for the treatment of painful diabetic neuropathy wa outpatients with metabolically stable type 1 or 2 diabetes and bilateral distal peripheral neuropathy of at l XR at a dose of 75 milligrams (mg) or 150 to 225 mg daily or placebo orally for 6 weeks. Primary efficacy and Pain Relief (VAS-PR) scales. Of the 244 patients randomized, 242 made up the intent-to-treat (ITT) in the venlafaxine XR 75 mg group, 67.3 mm in the venlafaxine XR 150 to 225 mg group, and 68.8 in the reductions in mean adjusted pain intensity scores were 32%, 50%, and 27% for venlafaxine XR 75 mg, v significantly more effective than placebo (p less than 0.001) and venlafaxine XR 75 mg (p =0.006) at wee venlafaxine 150 to 225 mg was significantly more effective than placebo by week 6 (59.9 mm versus 43. placebo (51 mm versus 43.6 mm). The percentages of patients who were considered responders (at leas placebo groups at week 6 (LOCF) were 56% and 34%, respectively (p less than 0.01). The number neec was 4.5 at week 6. The most common treatment-emergent adverse events associated with both venlafax occurred in 6%, 5%, and 1% of the venlafaxine XR 75 mg, venlafaxine XR 150 to 225 mg, and placebo g changes during treatment. Adverse events leading to study withdrawal did not significantly differ betweer

2) The combination of venlafaxine depot (75 milligrams (mg) three times daily) and gabapentin relieved history of type 1 diabetes. The patient developed burning pain and tenderness of the arms and legs and pain was not relieved despite the following treatments: paracetamol and dextropropoxyphene for 7 mont buprenorphine for 3 months; then eight different analgesics. Placing her legs in buckets of cold water for developed orthostatism, preproliferative retinopathy and moderate signs of distal sensory, autonomic, an 75 mg three times daily), and after 7 months was greatly improved with controllable distal pains. Analges

3) Venlafaxine relieved the unremitting pain of diabetic peripheral neuropathy in 8 patients who found nc acetaminophen, carbamazepine, capsaicin, and amitriptyline were not successful, either due to lack of e patients responded to venlafaxine 37.5 milligrams twice daily with dramatic relief in symptoms associatec rapidly without interruption of treatment. No serious side effects were observed (Kiayias et al, 2000).

4) Eleven patients with type 2 diabetes mellitus and painful diabetic neuropathy had a 75% to 100% red patients had been treated unsuccessfully with other medications known to alleviate the pain associated v 75 milligrams/day, all patients noted a 75% to 100% reduction in pain. No adverse effects were reported pain 2 to 3 days later. When venlafaxine was restarted, the pain was relieved promptly. This series sugg

4.5.A.9 Dysthymia

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:

During 9-week, open study, venlafaxine was effective for treating dysthymic disorder in 14 patients (

c) Adult:

1) In a 9-week, open study, 10 and 4 patients showed a complete and modest response, respectively, tc determination of baseline Hamilton Rating Scale for Depression (HAM-D-17) and Beck Depression Inver was titrated to a maximum dose of 225 mg daily. Seven patients improved with venlafaxine 75 mg daily; weeks, and met proposed criteria for remission of dysthymic disorder. This study suggests that venlafaxi are needed.

4.5.A.10 Generalized anxiety disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (extended-release capsule only); Pediatric, no
Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIa; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Venlafaxine extended-release is approved for treating generalized anxiety disorder (GAD), as define 2008).

Extended-release venlafaxine was more effective than placebo for improving the symptoms of depre generalized anxiety disorder; however, time to response was greater in patients with comorbidity tha

Venlafaxine extended-release was safe and effective for long-term treatment (6 months) of generali (n=251) (Gelenberg et al, 2000).

Extended-release venlafaxine was superior to placebo for relieving generalized anxiety disorder in n blind trial (n=349) (Rickels et al, 2000).

In two randomized, placebo-controlled, 8-week studies enrolling children with generalized anxiety di one individual trial and the pooled analysis (Rynn et al, 2007).

c) Adult:

1) Extended release (XR) venlafaxine was more effective than placebo for improving the symptoms of d generalized anxiety disorder (GAD). However, time to response was greater in patients with comorbidity

meeting DSM-IV criteria for major depressive disorder in a double-blind, randomized trial (n=368), results and compared to results of the noncomorbid patients. Patients took once-daily doses of venlafaxine XR increased to a maximum of 225 mg. According to the criteria of more than 50% reduction (from baseline) improvement with venlafaxine was significantly greater (p less than 0.05) than with placebo by 12 weeks however, overall, there was no evident trend for a placebo-drug difference until after the eighth week of t evident as early as week 2. By week 12, response rate was 66% on HAM-D and 59% on HAM-A for thos 2001a).

2) Venlafaxine extended-release (XR) was safe and effective for the long-term treatment of generalized (n=251) who met DSM-IV criteria for GAD without a diagnosis of major depressive disorder were random age, 41 years) or placebo (n=127; mean age, 38 years) for 28 weeks. Primary outcome measures includ HAM-A psychic anxiety factor score, and the Clinical Global Impressions (CGI) scale Severity of Illness a evaluable for the efficacy analysis. The overall dropout rate was 59%, with 60 and 44 patients in the venl observation-carried-forward (LOCF) method, the adjusted mean changes from baseline to week 28 for H changes for HAM-A psychic anxiety score were -7.4 for venlafaxine XR and -4.2 for placebo (p less than 0.001). Significant (p less than 0.01) changes in the HAM-A scores were seen as early as week 1 with ve differences between venlafaxine XR and placebo were maintained throughout the final assessment at we where significant reductions were noted with venlafaxine XR compared with placebo at week 1 (p=0.02) Illness scores for venlafaxine XR compared to placebo became initially noted at week 2, but became mo superior to placebo on the CGI-Global Improvement item at all times assessed beyond week 1. Respons or a CGI-Global Improvement score of 1 or 2) during weeks 6 through 28 were at least 69% in the venlaf most common adverse events occurring with at least twice the frequency with venlafaxine XR were anor sweating. Over time (days 57 to 196), these events subsided with continued therapy (Gelenberg et al, 20

3) Extended-release (XR) venlafaxine was superior to placebo for relieving generalized anxiety disorder double- blind trial, patients were given placebo (n=96) or venlafaxine XR (n=253) at one of 3 dose levels for the first week; during the second week, those assigned to the 150 and 225 mg/day groups were raise the end of week 1 and throughout the 8 weeks of treatment, efficacy measures for all doses of venlafaxir were indistinguishable for the 2 highest doses of venlafaxine, although, according to the Anxiety Subscal mg/day. Most discontinuations (29% of patients) were caused by adverse reactions and occurred within nausea, insomnia, dry mouth, somnolence, dizziness, and asthenia (Rickels et al, 2000).

d) Pediatric:

1) Extended-release venlafaxine may improve generalized anxiety disorder in children as evaluated in tw identical in design and were analyzed separately and in a pooled analysis. Children with generalized anx once daily (n=157) or placebo (n=163) and were titrated up according to body weight for 8 weeks, follow dose was 225 mg/day for children weighing greater than or equal to 50 kilograms (kg). Patients were stra equal to 20 on the severity component of the generalized anxiety section of the Columbia Schedule for A Patients were excluded if they had major depressive disorder, acute suicidality, social anxiety, or other p in the composite score of nine delineated items from the Columbia K-SADS (primary endpoint) was grea 12.4; p less than or equal 0.001); however, there was not a significant difference between treatment grou patients responded (defined as at least a 50% decrease from baseline in the nine-item Columbia K-SAD group (38%) compared to the placebo group (17%; p-value not reported) in the first study, but not in the of nine delineated items from the Columbia K-SADS generalized anxiety disorder section was 17.4 point ($p < 0.001$). In both studies, patients treated with extended-release venlafaxine experienced greater impr most common adverse events in the extended-release venlafaxine group that were twice as frequent as

4.5.A.11 Hot sweats, Breast cancer-related

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

In two randomized, double-blind, crossover trials, treatment with oral extended-release venlafaxine reductions in hot flash frequency, severity, and bother compared to placebo in breast cancer survivo In a randomized, double-blind German study (n=80), treatment with oral venlafaxine was significantl women with primary breast cancer (Loibl et al, 2007).

c) Adult:

1) General Information

a) Practice guidelines and limited clinical trials support short-term efficacy of oral venlafaxine in bre 2007; Loibl et al, 2007; Hickey et al, 2008). In two, 14-week, randomized, double-blind, placebo-con venlafaxine, primarily in Caucasian breast cancer survivors, both doses administered demonstrated physiologically-assessed), severity, and bother compared to placebo (Carpenter et al, 2007). Furthe evident in this study. In another 4-week, randomized, double-blind, controlled study in adult women frequency to a greater extent compared to clonidine (Loibl et al, 2007). Treatment-emergent adverse (Carpenter et al, 2007; Loibl et al, 2007).

2) Clinical Trials

a) Treatment with oral extended-release (ER) venlafaxine 37.5 milligrams (mg; low-dose) or 75 mg flash frequency, severity, and bother compared to placebo in breast cancer survivors in two random

cancer (the use of tamoxifen and/or aromatase inhibitors were not allowed), experiencing 1 or more
two, 14-week crossover trials. In the low-dose trial (n=52; mean age, 50.5 years; 91% Caucasian), p
(n=26) once daily for 6 weeks; subsequently, without a washout period, patients from each arm were
trial (n=18; mean age, 53 years; 90% Caucasian) had a similar design except venlafaxine ER (n=9)
during weeks 2 to 5. Hot flash frequency was evaluated using both a weekly, 24-hour (hr), ambulato
electronic event markers and written diaries that were completed during one 24-hr period each week
using separate 10-point numeric scales; range; 0=not at all and 10=extremely severe or bothersome
Interference Scale). Data for the 2 crossover trials were analyzed separately using mixed linear mod
(n=45 and n=15, respectively) provided 86% and 43% power, respectively (using a two-sided paired
detect a large effect size (equal to 0.78 standard deviation) in the high-dose group. At baseline, mea
study patients (pooled data from both studies) was 7.46 and 6.02, respectively. After 6 weeks of the
(adjusted mean reduction, -1.7) in the low-dose venlafaxine group compared to no change in the pla
(CI), 0.09 to 0.23). In the high-dose trial, venlafaxine-treated patients experienced a 14% (adjusted r
hr compared to a 13% (adjusted mean increase, +0.98) increase in the placebo group (p=0.013) (eff
baseline by 42% and 18% (p less than 0.001) in the venlafaxine ER and placebo groups, respective
(p=0.001), respectively, in the high-dose trial (effect size, 0.24; 95% CI, 0.1 to 0.38). Additionally, bo
vs -5%; p less than 0.001 for both) and bother (low-dose, -4% vs 10%; high-dose, -19% vs +6%; p le
greater improvements from baseline in hot flash interference occurred only in the high-dose venlafax
significant differences between the venlafaxine and placebo groups for secondary outcomes, which
adverse events was similar among venlafaxine- and placebo-treated patients, severe constipation a
compared to placebo. This study was limited by the placebo effect that was evident for self-reported
three-quarters of study patients were able to correctly identify receipt of placebo by study end (Carp
b) Treatment with oral venlafaxine was significantly more effective than clonidine in decreasing the
double-blind German study (n=80). Enrollees, who were required to have bothersome hot flashes at
either venlafaxine 37.5 mg (n=40) or clonidine 0.075 mg (n=40) orally twice daily for 4 weeks. Concu
was allowed provided patients were on it for at least a month and it was continued throughout the st
measure was the patient-recorded hot flash frequency at end of therapy. The hot flash severity scor
endpoint. At baseline 61% of patients in each group were over 50 years of age, with 90% and 82% r
respectively. At baseline, the median daily hot flash frequency was 11 (range, 3 to 23) and 9.7 (rang
flash severity was 1.7 (range, 1 to 3) and 1.8 (range, 1 to 3.1), respectively, and the median daily ho
Among the evaluable population (n=63), the median hot flash frequency decreased from baseline by
clonidine group at week 4 (p=0.025). Additionally, more patients in the venlafaxine group had a 75%
hot flashes occurred only in the venlafaxine group (n=6). The median daily hot flash score decrease
clonidine groups, respectively (p=0.043). Ten patients discontinued treatment due to adverse events
mouth (35.5% vs 51.1%), tiredness (35.5% vs 42.4%), and restless sleep (35.5% vs 51.5%) were th
were not statistically significant (Loibl et al, 2007).

4.5.A.12 Major depressive disorder

FDA Labeled Indication

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

The immediate-release and extended-release formulations of venlafaxine are indicated for the treatr
EFFEXOR XR(R) extended-release oral capsules, 2008; Prod Info venlafaxine extended release ora
Efficacy of venlafaxine immediate- and extended-release tablets for the treatment of major depressi
(Simon et al, 2004; Silverstone & Salinas, 2001a; Rudolph et al, 1998; Amsterdam et al, 1998) and i
Several open-label studies and individual case reports support the usefulness of venlafaxine as a pc
De Montigny et al, 1999; Fatemi et al, 1999; Sharma, 1998; Bader et al, 1998).
Venlafaxine combined with electroconvulsive therapy was efficacious in patients with treatment-resis
patients (Gonzalez-Pinto et al, 2002).
Separate results of 2 similar placebo-controlled, double-blind, randomized trials did not demonstrate
patients with major depressive disorder; pooled results showed greater improvement in adolescents

c) Adult:

1) Clinical Trials

a) Continuation of venlafaxine extended-release (ER) therapy following response to treatment appe
(MDD). In a prospective, multicenter study, patients (n=318) who responded to 8 weeks of open- lab
192 mg/day) entered a 6-month randomized, double-blind, continuation phase in which they either r
191 mg/day). During the 6-month relapse-prevention phase, significantly fewer patients treated with
0.001) and at study endpoint, the cumulative probability of relapse was higher for patients in the pla
of venlafaxine ER as compared with placebo (p less than 0.001) were also observed for secondary
D depressed mood item, Montgomery-Asberg Depression Rating Scale total score, and Clinical Glo
significantly more often with venlafaxine than with placebo included hypertension and sweating (p=0
withdrawn from the study due to increases in blood pressure (Simon et al, 2004).

b) Extended release (XR) venlafaxine was more effective than placebo for improving the symptoms

generalized anxiety disorder (GAD). However, time to response was greater in patients with comorb
criteria for MDD in a double-blind, randomized trial (n=368), results from the subset of patients who
noncomorbid patients. Patients took once-daily doses of venlafaxine XR 75 milligrams (mg), fluoxeti
of 225 mg. According to the criteria of more than 50% reduction (from baseline) in the Hamilton-Dep
was significantly greater (p less than 0.05) than with placebo by 12 weeks of treatment. About one tl
no evident trend for a placebo-drug difference until after the eighth week of treatment. Among patier
By week 12, response rate was 66% on HAM-D and 59% on HAM-A for those taking venlafaxine an
c) Venlafaxine was superior to placebo for treating depression during a 6-week, double-blind trial. F
(mg) daily, 225 mg daily, or 375 mg daily; the dose was titrated over 7 days in the 2 higher dosage g
the Montgomery-Asberg Depression Rating Scale (MADRS) total score, and the Clinical Global Imp
the CGI scale was significantly greater in all venlafaxine groups than the placebo group. Venlafaxine
the MADRS (p=0.005), and the CGI (p=0.0031). Of the 323 patients who began treatment, 194 com
withdrawal in the venlafaxine groups; whereas, failure to return and an unsatisfactory response were
d) In an open, community-based study, venlafaxine effectively treated depression in 62% of patient
149 were family physicians, and 62 were psychiatrists; each physician could enter a maximum of 5 p
scale, patients began treatment with venlafaxine 37.5 milligrams (mg) twice daily for about 2 weeks
patients who withdrew from the study, 134 (15%) withdrew due to adverse effects; whereas, only 17
Clinical Global Impressions (CGI) assessment; 522 (62%) patients achieved this outcome based on
week of treatment but declined over the remainder of the study (Joffe et al, 1998).
e) Once versus twice daily administration of venlafaxine immediate-release resulted in comparable
double-blind, randomized study (n=48), patients received the same dose of venlafaxine once or twic
groups. This dose was continued for 1 week in the once daily group; whereas, patients in the twice d
maximum dose of 225 mg daily was reached. At 2 weeks, a nonsignificant trend for greater improve
Depression Rating scale (MADRS) were observed in the twice daily versus once daily group; howev
were similar between treatments. This study suggests that once daily versus twice daily administrati
inconvenience of more frequent administration (Amsterdam et al, 1998).

2) Treatment-Resistant Depression

a) Nine out of 11 patients experienced a sustained improvement in depression with combined venla
recurrent depression while 1 patient had a severe major depressive episode. Two patients also had
Nine patients had failed fluoxetine or paroxetine therapy, and 9 had failed augmentation with lithium
clomipramine 150 to 375 milligrams (mg)/day, and 3 patients received imipramine 200 to 250 mg/da
daily to 150 mg every 12 hours. Using the Hamilton Rating Scale for Depression (HAM-D), 9 patient
patients with panic- agoraphobic symptoms also showed improvement; however, there was no impr
venlafaxine that allowed for maximum improvement was 75 to 300 mg/day (Gomez & Perramon, 20
b) In an 8-week, open trial (n=159), 58% and 28% of patients achieved a good response and remis
respond to at least 1 other antidepressant; 45% of patients had used 3 or more medications for this
titration to 375 mg/day over 4 weeks, if needed; the mean daily dose was 260 mg/day at 8 weeks. T
Rating Scale, and the Clinical Global Impression Scale scores were significantly lower at 8 weeks (p
Compared to many antidepressant trials, the number of patients who stopped treatment due to adve
c) Combination therapy with venlafaxine and bupropion was effective in a patient with treatment-res
times daily increased to 150 milligrams 3 times daily. Since her depressive symptoms did not respor
symptoms abated. The Beck Depression Inventory score decreased from 28 to 11.6 while the Globa
effects were sweating and a mild increase in heart rate which was controlled with atenolol 25 milligra
23 months (Fatemi et al, 1999).
d) A case report documents intermittent followed by sustained improvement with venlafaxine in a w
Treatment with venlafaxine 262.5 milligrams (mg) daily, in conjunction with several other medication
however, experienced relapse 4 months later. Attempts were made to increase the dose of venlafax
and venlafaxine was restarted. The patient reacted as she had before, with a relapse after 4 months
mg. Her symptoms resolved, and she had been maintained on that dose for 9 months (Sharma, 199
e) A 79-year-old man with several depressive episodes and a poor response to many antidepressa
venlafaxine titrated to 75 milligrams (mg) 3 times daily which increased his appetite but did not chan
morning and 5 mg at noon. Within 5 days, he began attending to activities of daily living; he continue
pressure and heart rate, this man was monitored carefully but therapy had no adverse cardiovascula

1) With Electroconvulsive Therapy

a) Venlafaxine combined with electroconvulsive therapy (ECT) proved to be efficacious in
was asystole in 4 of 13 patients. Mean score on the Hamilton Rating Scale for Depression
treatment (p less than 0.004, posttreatment compared with baseline). Overall, 10 of 13 (76.
improved' on the Clinical Global Impression (CGI) subscale for improvement and a 50% re
doses of venlafaxine were 265.38 milligrams (mg) (range 150 to 375 mg) and were not cha
Related to safety, rapid reduction in heart rate followed by asystole occurred in 4 of 110 se
the 4 affected patients. None of the study subjects had a history of cardiovascular disease.
(mean 337.5 mg, range 300 to 375 mg) compared with subjects in whom asystole did not c
succinylcholine were given immediately before ECT. No complications, such as prolonged
to 225 mg/day) were as responsive to combination venlafaxine-ECT treatment as those wh

d) Pediatric:

1) Separate results from two similar double-blind, randomized controlled trials indicated there was no sig
treatment of major depressive disorder (MDD) in pediatric patients aged 7 to 17 years, while pooled resu
(aged 12 to 17 years) only. After a single-blind, placebo lead-in phase, study participants (mean age, ap

body weight (n=184) or placebo (n=183) for up to 8 weeks. The primary efficacy measure was the chang
weeks. Secondary efficacy measures included the 21-Item Hamilton Rating Scale for Depression (HAM-
Impression-Severity (CGI-S), and CGI-Improvement scales. Efficacy and safety data from both studies w
pooled data from both studies. The combined study discontinuation rates were 27% and 32% for patients
changes from baseline, no statistically significant differences were seen between venlafaxine ER and pla
significant differences in secondary outcome measures or response rates. In the post hoc subgroup anal
groups on any outcome measure. Adolescents aged 12 to 17 years who received venlafaxine XR experi
to 32.5 at week 8 compared to a decrease from 56.9 to 36.9 at week 8 for the placebo group (p=0.022);
Adjusted mean change scores at week 8 also demonstrated greater improvement with venlafaxine XR o
(p=0.022) but not HAM-D-21 total. Additionally, there was a difference in responder rates based on CDR
reported adverse events for venlafaxine XR and placebo were abdominal pain (21% and 10%, respectiv
reported in 7% and 2% of patients receiving venlafaxine XR and placebo, respectively. Of the SAEs, ven
reaction (n=2). There were no completed suicides (Emslie et al, 2007).

4.5.A.13 Menopausal flushing

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

In a randomized, double-blind study (n=80), treatment with oral, extended-release venlafaxine 75 mi
postmenopausal hot flashes as well as improved mental health and vitality outcomes compared to p
Extended-release venlafaxine was effective for treating hot flashes in women with a history of breas
BC during a 4-week, double-blind, randomized, placebo-controlled trial (n=229) (Loprinzi et al, 2000
2002).

During a 4-week, open, pilot study (n=21), venlafaxine was effective in decreasing the incidence of h
1999).

Low-dose venlafaxine was effective in reducing the incidence and severity of hot flashes in women v
therapy (n=5) (Loprinzi et al, 1998).

c) Adult:

1) Treatment with oral, extended-release (ER) venlafaxine 75 milligrams (mg) per day for 12 weeks sign
improved mental health and vitality outcomes compared to placebo in a randomized, double-blind study
than 14 hot flashes per week were included. Women concurrently on antidepressants or chemotherapy v
(n=40; mean age, 52.7 years) or placebo (n=40; mean age, 51.6 years) for 12 weeks, and followed at 4,
for 1 week and then increased to 75 mg/day for the remainder of the study. The patient-perceived hot fla
visits using a 5-point Likert scale. Additionally, patients completed a daily hot flash diary, noting the frequ
majority of patients (approximately 80%) were in natural menopause, the mean patient-perceived hot flas
more common in the venlafaxine group (67.6% vs 36.8%; p=0.008). At the 3-month follow-up, the averag
was 21 points (95% confidence interval (CI), 11 to 32; p less than 0.001). Although reductions in the sco
month 2 visit, with a mean score of 35.3 in the venlafaxine group at month 3 compared with a rebound in
follow-up visits (p=0.01), the estimated treatment effect of venlafaxine remained significant compared to
score compared to a 15% reduction in the placebo group. Based on diary data, hot flash severity and fre
differences. Venlafaxine was associated with a mean reduction of 2.6 points (95% CI, -2.3 to 7.5; p=0.25
Quality of life measures, assessed monthly using a modified Short Form-36 Health Survey mood scale, s
group difference, 8.7; 95% CI, 2.8 to 14.6) and vitality (between-group difference, 8.5; 95% CI, 2.8 to 14.
occurring commonly and more frequently than placebo included dry mouth (81% vs 44%), sleeplessness
from the study (venlafaxine, n=11; placebo, n=8), difficulty sleeping, decreased libido, nausea, and anxie
of the venlafaxine-treated study participants chose to continue venlafaxine treatment following study com
2) Extended-release venlafaxine was effective for the treatment of hot flashes in breast cancer (BC) sur
four-week, double-blind, randomized, placebo-controlled trial. Eligible patients (n=229) were required to h
least 1 month prior to study entry, and a performance status of 0 to 1 on the Eastern Cooperative Oncolo
weeks treatment with placebo (n=56), 2) 4 weeks treatment with 37.5 milligrams (mg) venlafaxine daily (
week of 37.5 mg daily, 1 week of 75 mg daily, and 2 weeks of 150 mg daily (n=54). Use of antiestrogens
initiated 4 weeks prior to study entry and continued during the entire study duration. The primary endpoir
combined score of frequency and severity (range, 1=mild to 4=very severe). At baseline, study patients h
the modified intent-to-treat analysis of 191 evaluable patients at the end of the study, patients receiving v
activity scores at week 4 from baseline (37%, 61%, and 61% reduction in the venlafaxine 37.5 mg, 75 mg
than 0.001 vs placebo). A reduction of more than 50% in hot flash activity occurred in 45%, 63%, and 55
20% in the placebo group. No difference in efficacy was noted between the 75 mg and the 150 mg group
adverse events included dry mouth, nausea, decreased appetite, and constipation, which occurred more
2000).

a) An 8-week, open-label, longitudinal extension of this trial demonstrated that efficacy of venlafaxi
randomized, placebo-controlled trial that entered the open-label continuation phase, 102 patients we
37.5 to 150 milligrams (mg)/day. At 8 weeks, the venlafaxine doses used were 37.5 mg (n=26), 75 m
from baseline (week 1 of placebo-controlled phase) in hot flash frequency was reported at study enc
experienced an additional mean 26% reduction in hot flash scores, the approximate 60% reduction i

phase was maintained during the open-label extension. Common adverse events in the continuatior (Barton et al, 2002).

3) Low-dose venlafaxine decreased hot flash activity by 81% in men receiving androgen deprivation the 12.5 milligrams twice daily for 4 weeks. Using a diary, patients recorded the number and severity of daily daily hot flashes decreased from 10 at baseline to 6 after 4 weeks of treatment. This was accompanied b weeks, 52% of patients wished to continue venlafaxine treatment. Nausea was the primary adverse effec

4) Low-dose venlafaxine was effective in reducing the incidence and severity of hot flashes in women w therapy (n=5). Patients received venlafaxine 25 milligrams (mg) daily for 5 weeks. The average number (54%) patients reported a 50% or greater decrease in the incidence of hot flashes (P less than 0.0002). study were consistent with previous studies (Loprinzi et al, 1998).

4.5.A.14 Obsessive-compulsive disorder

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Venlafaxine extended-release (XR) was as effective as paroxetine in the primary treatment of patier (Denys et al, 2003a).

During a double-blind study (n=150), venlafaxine was effective as a crossover therapy in patients wi al, 2004).

Venlafaxine was effective for the treatment of obsessive compulsive disorder in two separate case s Hollander, 1996; Zajecka et al, 1990).

c) Adult:

1) Primary Therapy

a) Venlafaxine extended-release (XR) was as effective as paroxetine in the treatment of patients wi study, patients (n=150) with OCD and a score of at least 18 (or at least 12, if only obsessions or only received either venlafaxine XR (initial, 75 milligrams (mg)/day, titrated to 300 mg/day by week 7) or Both paroxetine and venlafaxine XR treatments were effective, producing mean reductions of 7.8 ar decrease in the total Y-BOCS score from baseline was seen at week 3 for venlafaxine XR-treated p no significant differences in responder rates between treatment groups. In the venlafaxine XR group Similarly, in the paroxetine group, 44% and 22% of patients were partial responders and full respond treatments with regard to reduction of anxious or depressive symptoms (as measured by the Hamilt treatments, most adverse effects were of mild or moderate severity and included somnolence, swea

2) Crossover Therapy

a) Patients with obsessive-compulsive disorder (OCD) refractory to initial treatment with a selective a double-blind switch study, patients (n=150) with primary OCD received venlafaxine (titrated to 300 responders (n=43) were switched to the opposite therapy (venlafaxine, n=16; paroxetine, n=27) for a was defined as a reduction in the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) below 25%. (week 16) to endpoint, however the score was significantly reduced in paroxetine-treated patients (p statistically superior as compared with venlafaxine (p=0.017). The response rate during phase II of t group and a 56% (15/27) response rate in the paroxetine group (p=0.01). At the end of both phases between treatment groups including somnolence, sweating, headache, constipation, insomnia, naus

b) Venlafaxine was effective in the treatment of obsessive-compulsive disorder in a 28-year-old ma resulted in sedation, nausea, and dry mouth. A 3-week course of paroxetine 20 mg/d was discontinu anxiety, and agitation. Venlafaxine 25 mg 3 times daily was initiated and titrated up to 75 mg 3 times 24 to 7. Ten months later the patient was still responding well.

c) Venlafaxine may be useful in the treatment of obsessive-compulsive disorder. In one case report compulsive disorder refractory to amitriptyline, fluoxetine, and clomipramine was treated with venlafa baseline NIMH Global Obsessive-Compulsive Scale score was 12. At 4 weeks, there was significant dose of venlafaxine was increased to 375 mg/day over the next week; continued improvement in ob weeks (NIMH score=4). At that time, the patient requested discontinuation of venlafaxine due to per NIMH score went back to 12 (Zajecka et al, 1990).

4.5.A.15 Panic disorder, With or without agoraphobia

FDA Labeled Indication

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Venlafaxine hydrochloride extended-release capsules are indicated for the treatment of panic disord extended-release oral capsules, 2008).

Results of a double-blind, randomized, controlled trial (n=664) comparing venlafaxine extended-rele

demonstrated greater improvement with venlafaxine XR and paroxetine than with placebo (Pollack e

c) Adult:

1) Results of a double-blind, randomized, controlled trial which compared venlafaxine extended-release greater improvement with venlafaxine XR and paroxetine than with placebo. Although paroxetine was inc placebo only. Nondepressed outpatients with a diagnosis of panic disorder with or without agoraphobia v median full-symptom panic attacks, 6), venlafaxine XR 150 mg/day (n=168; baseline median full-sympto attacks, 6), or placebo (n=163; baseline median full-symptom panic attacks, 6.1) orally for 12 weeks. The attacks in the last observation carried forward (LOCF) end point analysis, which was assessed using the Panic Disorder Severity Scale, Clinical Global Impressions-Severity (CGI-S) and -Improvement (CGI-I) s (no full-symptom panic attacks on the PAAS and CGI-S scores of 1 (not at all ill) or 2 (borderline ill). Res that patients who received venlafaxine XR or paroxetine experienced significantly greater improvement c groups had a significantly higher percentage of patients (p less than 0.001 for each active treatment grou study endpoint compared with the placebo group (venlafaxine XR 75 mg, 54.4%; venlafaxine XR 150 mg full-symptom panic attacks was also significantly greater in the three active treatment groups compared t venlafaxine XR 150 mg, (-6.5) p less than or equal to 0.001, paroxetine, (-6) p less than or equal to 0.01) in Panic Disorder Severity Scale total score compared with placebo at week 12 (p less than 0.001 for ea patients who responded to active treatments were 76.6% (venlafaxine XR 75 mg), 79.2% (venlafaxine X less than 0.001 for all three active treatment groups relative to placebo). The percentage of patients who mg), 43.4%% (venlafaxine XR 150 mg), and 44.4% (paroxetine) compared with 23.7% of patients receiv Adverse events were mild or moderate and similar between treatment groups. The most common advers tremor (Pollack et al, 2007).

2) In 2 double-blind, multicenter, placebo-controlled studies, venlafaxine hydrochloride extended-release patients with panic disorder. The 12-week studies included adult outpatients who met DSM-IV criteria for venlafaxine (75 or 150 milligrams (mg)/day in one study and 75 or 225 mg/day in the other study) or plac free of full-symptom panic attacks on the Panic and Anticipatory Anxiety Scale (PAAS); the mean change the percentage of patients who were much or very much improved (rated as responders) on the Clinical venlafaxine than with placebo. A dose-response relationship was not established in these fixed-dose stu phase study with venlafaxine extended-release capsules (75 to 225 mg/day) were randomly assigned to defined as having 2 or more full-symptom panic attacks per week for 2 consecutive weeks or discontinua average for 34 days. Results from the randomized phase indicated that patients who continued to receiv extended-release oral capsules, 2008).

4.5.A.16 Posttraumatic stress 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:

Venlafaxine extended-release was somewhat effective and well tolerated for the treatment of posttra controlled trial (n=538) (Davidson et al, 2006) and a 6-month, double-blind, randomized controlled tr

c) Adult:

The efficacy and safety of venlafaxine extended-release (XR) were demonstrated in a 6-month, double-b diagnosis of posttraumatic stress disorder (PTSD). Patients were included in the study if they had a scor symptoms of PTSD for at least the previous 6 months. Following a washout period of at least 1 week, pa (n=161; mean age, 42.2 years) or placebo (n=168; mean age, 40.5 years) for 24 weeks. The primary out Secondary measures included the frequency of remission (defined as 20 or less on the CAPS-SX-17), ti 224 (68%) completed the study. The mean maximum daily dose of venlafaxine XR was 221.5 mg/day. Ir 29.2 at week 24 in the venlafaxine-XR group compared with a decrease from 82.9 to 38.1 in the placebo week 24 in completers were -59.2 and -54, for venlafaxine XR and placebo, respectively, and were not s improvement from week 4 onward (last observation carried forward (LOCF). Mean LOCF change scores 0.001). Efficacy measures related to symptom cluster scores are outlined in the table:

Outcome Measure	Venlafaxine XR Baseline	Venlafaxine XR Week 24
CAPS-SX-17 cluster B (reexperiencing) score	24.6	8
CAPS-SX-17 cluster C (avoidance/numbing) score	31.8	11.5
CAPS-SX-17 cluster D (hyperarousal) score	24.6	9.8

LOCF remission rates for venlafaxine XR and placebo were 50.9% and 37.5% (p=0.01), respectively, at were 44.7% and 33.3%, respectively (p=0.04). The most commonly reported adverse effects associated weight change of at least 7% occurred more frequently in venlafaxine-treated patients (12%) than placeb

The efficacy and safety of venlafaxine extended-release (XR) were demonstrated in a 12-week, double-b diagnosis of posttraumatic stress disorder (PTSD). Patients were included in the study if they had a scor symptoms of PTSD for at least the previous 6 months. Following a washout period of at least 1 week, pa (n=179), flexible-dose sertraline (50 to 200 mg/day) (n=173), or placebo (n=179) for 12 weeks. The prim baseline in the CAPS-SX-17 score week 12. Secondary efficacy measures included changes in CAPS-S (defined as a CAPS-SX-17 score of 20 or less). Of the 538 patients randomized, 531 received treatment venlafaxine XR was 224.6 mg compared with 151.4 mg for sertraline. Change scores for the primary out (LOCF) for venlafaxine and placebo are summarized in the table below. The magnitude of the difference to both primary and secondary efficacy values was minimal and clinically insignificant.

	Mean Change From Baseline (95% Confidence Interval)	
CAPS-SX-17 Outcome Measure	Venlafaxine XR	Pla
Total Score	-41.51	-3
Reexperiencing Cluster Score	-12.54	-1
Avoidance Cluster Score	-16.99	-1
Hyperarousal Cluster Score	-11.57	-9

Remission rates at week 12 were 30.2% for venlafaxine XR and 19.6% for placebo (p less than 0.05). Ve adverse effects being headache (29%), nausea (24%), and dry mouth (18%) (Davidson et al, 2006).

4.5.A.17 Premenstrual dysphoric 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:

Venlafaxine was superior to placebo for alleviation of premenstrual dysphoric disorder symptoms du

c) Adult:

1) Venlafaxine was superior to placebo for alleviation of symptoms associated with premenstrual dysph dysphoric disorder (renamed PMDD in DSM-IV) after 3 levels of screening were randomly assigned to re cycles. The initial dose of venlafaxine was 25 milligrams (mg) twice daily. In the absence of response, th 200 mg daily. Data from 143 women were used in the efficacy analysis. The mean doses of venlafaxine cycle, venlafaxine was associated with a 42% decrease in symptoms, as assessed by the Daily Symptor the second cycle and thereafter, decrease from baseline was 57% for venlafaxine and 31% for placebo. symptoms. There was no difference between venlafaxine and placebo in effect on appetite. The rate of r venlafaxine group and 35% in the placebo group (p=0.003). There were no serious adverse effects. The from 36% in the first cycle to 15% in the second cycle; insomnia; dizziness; and decreased libido (Freem

4.5.A.18 Recurrent major depressive episodes; Prophylaxis

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Results from the Prevention of Recurrent Episodes of Depression with Venlafaxine for Two Years (P (ER) was effective in preventing recurrence of depression in patients who had been successfully tre maintenance (1 or 2 years) therapy (Keller et al, 2007a; Kocsis et al, 2007; Keller et al, 2007).

c) Adult:

1) Results of the double-blind, randomized PREVENT (Prevention of Recurrent Episodes of Depression (ER) was effective for the prevention of recurrent depressive episodes when given as long-term mainten depressive symptoms for at least 1 month prior to the start of the study and a score of at least 18 on the randomized to venlafaxine ER 75 to 300 milligrams (mg) per day (n=821) or fluoxetine 20 to 60 mg per d 37.5 mg per day or fluoxetine 10 mg per day and titrated based on response and tolerability. Patients wh 50% or more) or remission (defined as HDRS score of 7 or less), remained on double-blind venlafaxine E responders after the continuation phase were then enrolled into 2 consecutive 12-month maintenance ph acute and continuation phases, while overall the study was powered for the primary endpoint of time to r reduction from acute phase baseline that was not more than 50% at 2 consecutive visits or at last valid v reduction in HDRS score from acute phase baseline) in the maintenance phase for venlafaxine ER comp fluoxetine-treated patients being more severely depressed in the acute phase than venlafaxine-treated p venlafaxine ER and fluoxetine was 79% while remission rates were 49% and 50%, respectively (p=0.719

differences between treatment groups at end point with regard to the proportion of patients who maintain response rates for venlafaxine ER and fluoxetine at the end of the continuation phase were 90% and 92% overall comparison). Venlafaxine ER responders after the 6-month continuation phase were then randon placebo, while fluoxetine responders continued taking fluoxetine during the first one-year maintenance p 129 patients receiving venlafaxine ER and 129 patients receiving placebo. At study endpoint, venlafaxine and secondary definitions of recurrence (p=0.005 and p less than 0.001, respectively). The probability of confidence interval (CI), 31.8 to 52.2%) and 23.1% for venlafaxine ER (95% CI, 15.3 to 30.9%) (p=0.005 enrolled in another 12-month maintenance phase, and venlafaxine responders were randomized to venla responders continued taking fluoxetine. Placebo responders continued to receive placebo in the second longer time to recurrence compared with placebo (p less than 0.001). The probability of recurrence at mo 0 to 16.8%) (p less than 0.001). The rate of response or remission at 12 months was also significantly hi respectively; p=0.002) (Keller et al, 2007a; Kocsis et al, 2007; Keller et al, 2007).

4.5.A.19 Severe major depression with psychotic features

See Drug Consult reference: PSYCHOTIC DEPRESSION - DRUG THERAPY

4.5.A.20 Social phobia

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (extended-release capsule and tablet only); Pediatric, no
Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIa; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Venlafaxine extended-release capsules and tablets are approved for treating adults with social anxie (R) extended-release oral capsules, 2008; Prod Info venlafaxine extended release oral tablets, 2008 Low-dose (75 milligram (mg)/day) and high-dose (150 to 225 mg/day) venlafaxine extended-release month, randomized, placebo-controlled trial (n=395) (Stein et al, 2005).
Results of a randomized, placebo-controlled trial (n=293) demonstrated the efficacy and safety of ve al, 2007).

c) Adult:

1) Venlafaxine extended-release (XR) was safe and effective for the treatment of generalized social anx outpatients (n=395; mean age, approximately 37 years) diagnosed with GSAD as defined by DSM-IV we flexible higher dose of venlafaxine XR 150 to 225 mg per day (n=129), or placebo (n=129) for 28 weeks. (LSAS). Some secondary efficacy measures included the proportion of responders (ie, Clinical Global Im (ie, LSAS score of 30 or less). The proportion of patients who withdrew from the study for any reason wa XR groups, respectively (p less than 0.05 for both). The final intent to treat population was 364, and the m 213.7 mg for the flexible-dose group. The adjusted mean change from baseline in the LSAS total score a 37.8 for the combined venlafaxine XR groups, and -23.5 for the placebo group (p less than 0.001 for all c placebo and venlafaxine XR-treated patients (combined and at low- and high-dose), respectively, were r venlafaxine XR-treated patients (combined and at low- and high-dose), respectively, were remitters (p le groups, the study did not find significant differences in response or remission rates between the low and associated with venlafaxine XR at a higher rate than placebo included abnormal ejaculation (12 to 18% v 12%), dry mouth (19 to 23% vs 6%), nausea (34 to 37% vs 10%), and somnolence (24 to 29% vs 14%). attempts committed suicide on day 86 of the study. There were 3 other reports of suicidal ideation or atte receiving placebo (Stein et al, 2005).

d) Pediatric:

1) Results of a randomized, placebo-controlled trial (n=293) demonstrated the efficacy and safety of ver children and adolescents. Pediatric outpatients (aged 8 to 17 years) diagnosed with SAD were randomiz milligrams (mg) orally daily and was titrated based on patient weight to a maximum dose of 225 mg daily Anxiety Scale (SAS-CA) and the Clinical Global Impression Improvement (CGI-I) score which identified r improved) or 2 (much improved) at week 16. Of the 293 patients randomized, 285 were included in the in receiving venlafaxine XR and in 27% of patients receiving placebo. The most common reason for discon mg/kilogram. The mean SAS-CA scores improved from a baseline of 64.8 +/- 10.1 to 40.6 +/- 1.25 at we group. The ITT random regression analyses indicated a statistically significant improvement associated v adjusted for baseline SAS-CA score were 56% (95% confidence interval (CI), 47% to 64%) for patients r The effect of baseline SAS-CA score was not significant (p=0.172), whereas effect of treatment was (p=0 g=0.46) and number needed to treat (n=5; 95% CI, 3 to 13) indicate a moderately clinically meaningful b were more common than with placebo included asthenia (20% vs 9%; p=0.012), anorexia (22% vs 3%; p mild to moderate and most often resolved with continued therapy. Discontinuation of treatment due to ad respectively. There were 3 cases of suicidal ideation in patients receiving venlafaxine (two during treatm no suicides or suicide attempts reported during the study period (March et al, 2007).

4.5.A.21 Tension-type headache; Prophylaxis

a) Overview

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

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

b) Summary:
Treatment with venlafaxine extended-release resulted in less days with tension-type headache whe
et al, 2007).

c) Adult:
1) Results of a prospective, double-blind, randomized controlled trial demonstrated the efficacy and safe
(TTH) in outpatients (n=60) without a current diagnosis of depression or anxiety disorders or a history of
orally daily for 12 weeks. The dose of venlafaxine XR was 75 milligrams (mg) daily for 1 week and then
variable was the number of days with headache as assessed using patients' diaries. Diary completion ra
57.7% (15/25) for the group receiving placebo. The difference between venlafaxine XR and placebo in te
during period two (days 29 to 56) of the study and remained significant to study endpoint. The median da
and 11, respectively. The median days with headache for patients receiving venlafaxine XR and placebo
(p=0.033) during period three (days 57 to 84). The differences between treatment groups with regard to
significant at during any period. The median percentage change from baseline in headache frequency w
number of responders (defined as a reduction of at least 50% in days with headache, total hours, or HII s
15% for venlafaxine XR and placebo, respectively; p less than 0.05) but not for hours with headache or
(14.7%), nausea (8.8%), stomach ache (8.8%) and dizziness (8.8%) (Zissis et al, 2007).

4.6 Comparative Efficacy / Evaluation With Other Therapies

Bupropion

Buspirone

Clomipramine

Duloxetine

Fluoxetine

Imipramine

Medroxyprogesterone Acetate

Mirtazapine

Paroxetine

Pregabalin

Sertraline

Trazodone

4.6.A Bupropion

4.6.A.1 Bipolar disorder, depressed phase

a) There were no significant differences between bupropion, sertraline, and venlafaxine with regard to respo
switching into hypomania or mania was significantly higher with venlafaxine compared with bupropion and se
outpatients diagnosed with bipolar depression. All patients were receiving at least one mood stabilizer with in
bupropion 75 to 450 milligrams (mg)/day (n=51), sertraline 50 to 200 mg/day (n=58), or venlafaxine 37.5 to 3
Depression Symptomatology (IDS), the Young Mania Rating Scale (YMRS), and the Clinical Global Impressi
antidepressant response (defined as either a 50% or greater improvement in IDS score or a decrease of at le
IDS score less than 12 and/or a CGI-BP depression score of 1 at study endpoint), and antidepressant-relatec
score during any point of the trial or a CGI-BP manic severity score of 3 or more or a YMRS score above 13
were 49%, 53%, and 51%, respectively, while remission rates were 41%, 36%, and 34%, respectively. Differe
reported. Controlling for lithium use did not alter the results. Based on CGI-BP score, switching to mania or h
and sertraline (9%; p less than 0.01 overall). During post hoc analysis, it was demonstrated that the switch ef
venlafaxine and sertraline (p=0.01, adjusted for lithium) and bupropion (p less than 0.01, adjusted for lithium)

Based on YMRS score, switching occurred in 4%, 7%, and 15% of patients receiving bupropion, sertraline, a (31%) and bupropion (14%) and sertraline (16%) treatment groups remained significant when the combinatio for lithium; p=0.02 when controlled for lithium). Post hoc analysis results again showed that the difference wa history of rapid cycling was also higher with venlafaxine (43%) compared to bupropion (14%) and sertraline (for any reason were 31%, 41%, and 45% in the bupropion, sertraline and venlafaxine groups, respectively (P

4.6.B Buspirone

4.6.B.1 Generalized anxiety disorder

a) One small study suggests that venlafaxine could be an alternative to buspirone in patients with generalize of GAD received venlafaxine XR 75 milligrams (mg)/day (n=4), venlafaxine XR 150 mg/day (n=4), buspirone than 50% decline on the Hamilton Anxiety Scale. Improvement was seen in 2 venlafaxine 75 mg patients, 2 v size, no specific conclusions could be made (Rolland et al, 2000).

b) Venlafaxine XR was useful for treating generalized anxiety disorder (GAD); for many efficacy measures, i diagnosed by DSM-IV criteria were randomly assigned to blinded treatment with placebo, buspirone 30 millig treatment was titrated over 1 week. At study conclusion, the Hamilton Rating Scale for Anxiety (HAM-A) scor the HAM-A psychic anxiety, HAM-A anxious mood, and HAM-A tension scores were significantly lower for ve placebo and buspirone for selected weeks on the Clinical Global Impressions-Severity of Illness scale (CGI-S 10%, 22%, 28%, and 15% of patients treated with placebo, venlafaxine XR 75 mg, venlafaxine XR 150 mg, a

4.6.C Clomipramine

4.6.C.1 Depression

a) Venlafaxine 105 milligrams/day (average dose) tended to be more effective than clomipramine 105 milligr patients; however, the difference was not statistically significant (Holliday & Benfield, 1995b). Patients were a Rating Scale, and the Clinical Global Impressions scale. Venlafaxine was associated with fewer anticholinerg

4.6.D Duloxetine

4.6.D.1 Major depressive disorder

a) A meta-analysis of published, peer-reviewed, randomized, placebo-controlled, double-blind trials found th to placebo in remission and response rates for major depressive disorder and although there was a trend in f compared to duloxetine. A systematic literature search of Cochrane, EMBASE, and MEDLINE (1996 to Janua evaluate efficacy (n=1754) and discontinuation/safety (n=1791). Patients had a one week placebo lead-in per to 225 mg per day for a minimum of 8 weeks. The primary outcomes were remission and response rates. Re (HAM-D) score to less than or equal to 7 or to a Montgomery-Asberg Depression Rating Scale (MADRS) sco baseline in either the HAM-D or MADRS scores. The secondary outcomes evaluated were dropout rates and venlafaxine XR and were statistically significant compared to placebo (both p less than 0.001). No significant XR were compared. Patients receiving placebo had a higher dropout rate due to lack of efficacy compared to patients in the active drug treatment groups dropped out due to adverse effects compared to placebo (duloxe XR were compared, no statistically significant differences were found for dropout rates due to lack of efficacy A sensitivity analysis was also performed and included 2 additional studies, one study for venlafaxine XR dea with comorbid pain. Adding the 2 studies demonstrated similar results with both drugs having a statistically si

Outcome	Active Drug	Active Drug vs Placebo		
		Difference(a)	95% CI	p Value(b)
Remission	duloxetine	0.142	0.089 to 0.195	<0.001
	venlafaxine XR	0.178	0.09 to 0.265	<0.001
Response	duloxetine	0.186	0.13 to 0.242	<0.001
	venlafaxine XR	0.244	0.15 to 0.337	<0.001
Dropout rate due to ADRs	duloxetine	0.057	0.015 to 0.1	0.008
	venlafaxine XR	0.061	0.025 to 0.097	<0.001
Dropout rate due to lack of efficacy	duloxetine	-0.111 (c)	-0.159 to -0.63	<0.001
	venlafaxine XR	-0.107	-0.151 to -0.064	<0.001
ADRs = adverse drug reactions; XR = extended release; CI = confidence interval				
(a) The rate when meta-analytic rate of placebo is subtracted from the active drug rate.				
(b) Corresponding p value of the difference rate calculated with a Z-test.				
(c) Negative difference rates indicate a larger effect for placebo.				

4.6.E Fluoxetine

Depression

Mixed anxiety and depressive disorder

4.6.E.1 Depression

a) Analysis of pooled data from 8 randomized, double-blind studies (n=2045) showed a remission rate of dep (SSRIs), and 25% with placebo. Remission was defined as a total score of 7 or less on the 17-item Hamilton effective than SSRIs from 2 weeks onward and from placebo from 3 weeks onward. The end-of-therapy remi ratio for remission was 1.5, in favor of venlafaxine over SSRIs (Thase et al, 2001).

b) Venlafaxine and fluoxetine had similar efficacy in the treatment of major depression in an 8 week, double- 37.5 milligrams (mg) twice daily, and 186 patients were randomized to receive fluoxetine 20 mg daily. If patie 75 mg twice daily and fluoxetine to 20 mg twice daily. Primary outcome measures were scores on the Hamilt Scale (MADRS), the Clinical Global Impressions Severity of Illness Score (CGI-S), and the Clinical Global Im scores improved significantly after 8 weeks of therapy. CGI-I scores were also improved, 80.6% of patients s fluoxetine. Remission rates were equivalent in both groups, 60.2%, as determined by scores of 8 or less on t number of patients that required a dosage increase, fluoxetine (n=54) and venlafaxine (n=43). After treatmen greater in the venlafaxine group than the fluoxetine group. The frequency of adverse events associated with and tolerability between venlafaxine and fluoxetine (Cost e Silva, 1998).

c) Venlafaxine was effective in the treatment of major depression in an 8-week, open-label, comparative trial milligrams (mg) twice daily; 55 received fluoxetine 20 mg daily. If after 15 days of treatment response was ina daily. Both medications were significantly effective in treating major depression, as determined by improveme Asberg Depression Rating Scale (MADRS), and the Clinical Global Impressions Scale (CGI). There were no existed in patients requiring higher doses of venlafaxine than fluoxetine. Patients treated with venlafaxine we (Diaz-Martinez et al, 1998).

d) Venlafaxine 200 mg/day for 4 weeks tended to be more effective than fluoxetine 40 mg/day in the treatme significant by the end of the 6-week study period (Holliday & Benfield, 1995c). Patients were assessed using and the Clinical Global Impressions scale. The incidence of adverse effects was similar for both groups.

4.6.E.2 Mixed anxiety and depressive disorder

a) Extended release (XR) venlafaxine was more effective than placebo for improving the symptoms of depre anxiety disorder (GAD). However, time to response was greater in patients with comorbidity than in patients v better than placebo in patients with comorbidity. From the data of all the patients meeting DSM-IV criteria for subset of patients who had comorbid GAD (n=92) were analyzed separately and compared to results of the r (mg), fluoxetine 20 mg, or placebo for 12 weeks. Doses could be increased to a maximum of 225 mg for venl (from baseline) in the Hamilton-Depression (HAM-D) and Hamilton- Anxiety (HAM-A) scores, improvement w of treatment. There was a similar trend with fluoxetine, but at no time was fluoxetine statistically superior to pl however, overall, there was no evident trend for a placebo- drug difference until after the eighth week of treat as early as week 2. By week 12, response rate was 66% on HAM-D and 59% on HAM-A for those taking ven placebo (Silverstone & Salinas, 2001).

4.6.E.3 Adverse Effects

a) During a randomized, double-blind trial of elderly patients with major depression, the rate of study disconti venlafaxine (27%) compared with patients receiving placebo (9%; p=0.0017) but there were no significant diff (p=0.0666) or when fluoxetine was compared to venlafaxine (p=0.1838). Elderly patients (mean age, 71 year fluoxetine (n=100), or placebo (n=96) for 8 weeks. The dose of venlafaxine was titrated from 37.5 to 225 milli 29-day period. The most frequently reported adverse events in the venlafaxine and fluoxetine groups were na adverse events most frequently reported in the placebo group were headache (22%) and dry mouth (15%) (S

4.6.F Imipramine

4.6.F.1 Depression

a) Venlafaxine and imipramine resulted in similar improvement in depression with melancholia in hospitalize on 1 test (Benkert et al, 1996). Over 5 days, the dose of venlafaxine was rapidly increased from 75 to 375 mi mg/day. The dose of imipramine was increased from 50 to 200 mg/day over 5 days and was continued at this Montgomery-Asberg Depression Rating Scale (MADRS), but for the 21-item Hamilton Rating Scale for Depre (p=0.036). Adverse effects were reported in 69% and 76% of patients treated with venlafaxine and imipramin for imipramine (p less than 0.05) and nausea for venlafaxine (p=0.011). While this study enrolled 167 patients Additional studies are needed to provide conclusive evidence for a more rapid onset of effect with venlafaxine

b) Venlafaxine was found to have antidepressant efficacy comparable to imipramine in outpatients with mod double-blind placebo controlled study in 224 outpatients with depression of moderate to marked severity. Bas Rating Scale for Depression (HAM-D), the Montgomery-Asberg Depression Rating Scale (MADRS), the Clini daily dose of venlafaxine was 182 mg +/- 48 milligrams and the mean maximal total daily dose of imipramine times a day schedule after meals. Venlafaxine showed a significant clinical advantage over imipramine at the to the higher attrition rate for imipramine as compared to venlafaxine. Attrition rates due to adverse effects we mouth, and dizziness were the most prominently reported adverse effects for venlafazine (Schweizer et al, 19

4.6.G Medroxyprogesterone Acetate

4.6.G.1 Hot sweats

a) Single dose medroxyprogesterone acetate (MPA) significantly reduces hot flashes compared to venlafaxi old versus those older than 50), current tamoxifen and raloxifene use, duration of hot flash symptoms (less th flashes per day (two to three versus four to nine or more). Patients were then randomized to receive either ve

MPA 400 mg intramuscularly (IM) for one dose or MPA 500 mg IM at 2 week intervals for three total doses. T
this arm due to unexpectedly slow accrual rate. The completed study analysis refers mainly to the two major
and severity at 1 week of baseline and throughout the 6 week treatment period. After 6 weeks, if patients wer
randomized to MPA). Nurses contacted patients monthly for the next 5 months and then every other month fo
about the average number of mild, moderate, or severe hot flashes they were experiencing per day. At the er
baseline with MPA compared with 53% (n=94) in the venlafaxine group (p<0.0001). No hot flashes were repo
treatment week (p=<0.0001). During the first treatment week, venlafaxine group had significantly more nause
dryness (p=.01) and sleepiness (p=.02) in comparison to the MPA group. As measured by patient diaries and
symptom differences between the two study groups include constipation, hot flash distress and abnormal swe

4.6.H Mirtazapine

4.6.H.1 Major depression, melancholic type

a) Mirtazapine and venlafaxine both were effective in alleviating symptoms of depression in hospitalized pati
be superior with respect to both efficacy and dropout rate due to adverse reactions. In a randomized, double-
(mg)/day and increasing rapidly to as high as 60 mg/day, or venlafaxine, starting at 75 mg/day and increasing
Depression Rating Scale (MADRS) and the Hamilton Rating Scale for Depression (HAM-D-17) improved for b
mirtazapine, although differences were not statistically significant. Sleep disturbances improved more with mi
treated patients (74.4%) than venlafaxine-treated patients (65.8%) reported at least one adverse reaction. Ho
because of adverse events (15.3% vs 5.1%, p=0.037). The most common adverse events in the mirtazapine
sleepiness (7.7%), and nausea (6.4%). In the venlafaxine group, most common were increased sweating (19
(6.3%), and decreased salivation (6.3%) (Guelfi et al, 2001).

4.6.I Paroxetine

Bipolar disorder, depressed phase

Obsessive-compulsive disorder

4.6.I.1 Bipolar disorder, depressed phase

a) Paroxetine and venlafaxine had similar efficacy in the treatment of depression in bipolar patients taking co
week study demonstrated that paroxetine and venlafaxine produced responses in 43% and 48% of the patien
improvement in the Hamilton Rating Scale for Depression (HAM-D) and the Clinical Global Impressions (CGI
and -9.0 for the venlafaxine group. These responses were significantly different compared to baseline, but no
the HAM-D, the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth
All patients were being treated with 1 or more mood stabilizers for at least 6 months prior to onset of the curre
medication for at least 3 months prior to the start of the study. During the study, doses were adjusted for effic
which could be increased in increments of 75 mg per day (mg/d) every week. The starting dose of paroxetine
doses of venlafaxine and paroxetine were 179 mg/d and 32 mg/d, respectively. There were no significant diff
common adverse events were nausea (20% of all patients), and dizziness (8.3% of all patients). One patient
(13%) in the venlafaxine group switched to either hypomania (2 patients) or full mania (2 patients). Limitations
placebo group, a single-blind study design, and a short follow up period (Vieta et al, 2002).

4.6.I.2 Obsessive-compulsive disorder

a) Venlafaxine extended-release (XR) was as effective as paroxetine in the treatment of patients with obsess
patients (n=150) with OCD and a score of at least 18 (or at least 12, if only obsessions or only compulsions w
venlafaxine XR (initial, 75 milligrams (mg)/day, titrated to 300 mg/day by week 7) or paroxetine (initial, 15 mill
venlafaxine XR treatments were effective, producing mean reductions of 7.8 and 7.2 points, respectively, in th
score from baseline was seen at week 3 for venlafaxine XR- treated patients (p=0.008) and at week 5 for pat
rates between treatment groups. In the venlafaxine XR group, 37% and 25% of patients were partial respond
patients were partial responders and full responders, respectively. Additionally, no significant differences wer
symptoms (as measured by the Hamilton Anxiety Scale and the Hamilton Rating Scale for Depression, respe
included somnolence, sweating, insomnia, and nausea (Denys et al, 2003).

4.6.J Pregabalin

4.6.J.1 Generalized anxiety disorder

a) In a multicenter, randomized, double-blind, placebo-controlled, parallel-group study (n=374), treatment wit
compared with placebo in patients with generalized anxiety disorder (GAD). Patients who were 18 to 65 years
A) score of 20 or greater (with a HAM-A psychic and somatic anxiety factors score of 10 or greater) were elig
randomized to receive 8 weeks of oral pregabalin (150 milligrams (mg) twice daily for the first week then titrat
mg/day for the first week than titrated to a dose range of 75 to 225 mg/day administered in the morning with n
pregabalin arm but not the venlafaxine-XR arm had a significant improvement in least squares (LS) mean cha
treatment with pregabalin significantly improved some secondary investigator-rated efficacy measures includi
scale, and the Hamilton Depression Rating Scale (HAM-D) compared to placebo while treatment with venlafa

significantly improved LS mean change HAM-A total scores compared with venlafaxine-XR (p=0.008) or plac
patients (9.1%) compared with venlafaxine-XR-treated patients (20%) (Kasper et al, 2009).

Table 1			
	Pregabalin (n=121)		Venlafaxine
	LS mean +/- SE	p-value	LS mean +/- SE
HAM-A total score (primary endpoint)			
Baseline	27.6 +/- 0.4	0.028	27.4 +/- 0.4
Endpoint change	-14.5 +/- 0.9		-12 +/- 0.9
HAM-A psychic anxiety factor score			
Baseline	14.4 +/- 0.3	0.017	14 +/- 0.3
Endpoint change	-7.3 +/- 05		-5.9 +/- 0.5
HAM-A somatic anxiety factor score			
Baseline	13.3 +/- 0.3	0.11	13.4 +/- 0.3
Endpoint change	-7.3 +/- 0.4		-6.1 +/- 0.5
CGI severity score			
Baseline	4.7 +/- 0.1	0.14	4.6 +/- 0.1
Endpoint change	-2 +/- 0.2		-1.7 +/- 0.2
CGI improvement score			
Endpoint change	2.3 +/- 0.1	0.05	2.5 +/- 0.1
HAM-D score			
Baseline	11.5 +/- 0.2	0.018	11.5 +/- 0.2
Endpoint change	-4.4 +/- 0.5		-3.6 +/- 0.5
LS mean, least squares mean change; SE, standard error; HAM-A, Hamilton Anxiety Rating Scale; CGI Hamilton Depression Rating Scale			

b) Treatment with oral pregabalin at daily doses of 400 or 600 milligrams (mg) per day was comparable to ve
anxiety symptoms in adults with moderate to severe generalized anxiety disorder (GAD) in a randomized, do
years) meeting the DSM-IV criteria for primary GAD and who had total scores of 20 or greater on the Hamilto
Anxiety Scale, and 7 or lower on the Raskin Depression Scale were included. Patients were randomized to re
75 mg/day (n=113), or placebo (n=101) orally (given in divided doses twice daily) for 6 weeks, followed by a
600 mg/day groups, respectively) and titrated up to target doses over 1 week. Based on the modified intentio
the change in mean HAM-A total scores at endpoint from baseline (primary endpoint) was -14.7 +/- 0.8, -14.1
(n=104), and venlafaxine (n=110) arms, respectively, compared with -11.6 +/- 0.8 in the placebo (n=100) arm
A total scores occurred in both pregabalin arms compared with placebo during week 1 of treatment but not in
patients in the pregabalin 400 mg/day (61%; p=0.02) and venlafaxine 75 mg/day (62%; p=0.01) arms respon
difference in response in the pregabalin 600 mg/day (58%; p=0.06) was not significant. Among other seconda
placebo in HAM-A subscale scores of anxiety, tension, and insomnia, except a statistical insignificance on th
much improved or very much improved on the Clinical Global Impression-Improvement (CGI-I) scale was hig
venlafaxine (60.9%) arms compared with placebo (42%; all p less than or equal to 0.04). Treatment was well
commonly reported adverse events in the pregabalin arms and nausea, dizziness, and asthenia being the mo
were lower in the pregabalin 400 mg/day group (6.2%) compared with venlafaxine (20.4%; p less than 0.01) a

4.6.K Sertraline

Bipolar disorder, depressed phase

Depression

Depression, Elderly

4.6.K.1 Bipolar disorder, depressed phase

a) There were no significant differences between bupropion, sertraline, and venlafaxine with regard to respo switching into hypomania or mania was significantly higher with venlafaxine compared with bupropion and se outpatients diagnosed with bipolar depression. All patients were receiving at least one mood stabilizer with in bupropion 75 to 450 milligrams (mg)/day (n=51), sertraline 50 to 200 mg/day (n=58), or venlafaxine 37.5 to 3 Depression Symptomatology (IDS), the Young Mania Rating Scale (YMRS), and the Clinical Global Impressi antidepressant response (defined as either a 50% or greater improvement in IDS score or a decrease of at le IDS score less than 12 and/or a CGI-BP depression score of 1 at study endpoint), and antidepressant-relatec score during any point of the trial or a CGI-BP manic severity score of 3 or more or a YMRS score above 13 were 49%, 53%, and 51%, respectively, while remission rates were 41%, 36%, and 34%, respectively. Differe reported. Controlling for lithium use did not alter the results. Based on CGI-BP score, switching to mania or h and sertraline (9%; p less than 0.01 overall). During post hoc analysis, it was demonstrated that the switch ef venlafaxine and sertraline (p=0.01, adjusted for lithium) and bupropion (p less than 0.01, adjusted for lithium) Based on YMRS score, switching occurred in 4%, 7%, and 15% of patients receiving bupropion, sertraline, a (31%) and bupropion (14%) and sertraline (16%) treatment groups remained significant when the combinatio for lithium; p=0.02 when controlled for lithium). Post hoc analysis results again showed that the difference wa history of rapid cycling was also higher with venlafaxine (43%) compared to bupropion (14%) and sertraline (for any reason were 31%, 41%, and 45% in the bupropion, sertraline and venlafaxine groups, respectively (P

4.6.K.2 Depression

a) An 8-week, randomized, double-blind, active-control study of outpatient adults with major depressive diso not significantly different than that of venlafaxine XR (n=76). Patients were randomized to receive capsules c to 3 capsules/day. Primary outcome measure was the change in Quality of Life Enjoyment and Satisfaction C endpoint (8-weeks). Secondary outcome measures were the changes from baseline to endpoint in the scores Impressions - Severity of Illness scale (CGI-S), the Clinical Global Impressions - Improvement scale (CGI-I), 1 (very much improved) or 2 (much improved) on the CGI-I scale, or a reduction of HAM-D-17 score by at lea less. There were no significant differences between study groups with any outcome measures, including rem most common reported adverse effects during active treatment (10% or greater occurrence) were diarrhea, h scores, response rates, and remission rates for the outcome measures (Shelton et al, 2006):

	Endpoint Scores, Response Rates and Remiss
Measure/Sample	Sertraline (n=82)
Q-LES-Q score, mean (SD)	0.69 (0.12)
HAM-D-17 score, mean (SD)	10.8 (6.4)
HAM-D-17 response rate, (N/N)	55%(45/82)
HAM-D-17 remission rate, (N/N)	38% (31/82)
CGI-S score, mean (SD)	2.6 (1.1)
CGI-I score, mean (SD)	2.3 (1.1)
HAM-A score, mean (SD)	9.1 (5.4)
CGI-I = Clinical Global Impressions-Improvement scale; CGI-S = Clinical Global Impressions-Severity of Rating Scale for Depression; Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire; XR =	

b) In patients with major depressive disorder, almost twice as many experienced a remission with venlafaxin depressive disorder randomly received venlafaxine 37.5 mg twice daily (n=75) or sertraline 50 mg daily (n=72 or the sertraline increased to 50 mg twice daily on day 15. After 8 weeks, patients in both groups showed sig Montgomery- Asberg Depression Rating Scale (p less than 0.05). In the venlafaxine group 83% were respon the venlafaxine group and in 45% of the sertraline group (p=0.008). The most common adverse events were with sertraline (Mehtonen et al, 2000).

4.6.K.3 Depression, Elderly

a) Treatment with venlafaxine had a lower tolerability, but was equally effective to sertraline therapy in elderl study, fifty-two elderly patients (mean age, 82.5 years) with depression received either sertraline (initial, 25 m mg/day, titrated to 150 mg/day) for 10 weeks. No significant differences were found in Hamilton Rating Scale groups. However, early termination and withdrawal rates due to serious adverse events were higher in venlaf tract infection, cerebrovascular accident, hypertension, decreased renal function, rapid atrial fibrillation, anem were observed in both treatment groups. From baseline to endpoint, heart rate increased in the venlafaxine g bpm to 70.9 bpm, respectively). The authors suggest that the lowered tolerability of venlafaxine may be relate

4.6.L Trazodone

4.6.L.1 Depression

a) Venlafaxine produced antidepressant efficacy comparable to trazodone in a double-blind, placebo controll milligrams (mg) per day, trazodone (mean = 300 mg/day) or placebo. Response rates were 72%, 60% and 5 cognitive disturbance and retardation factor as evidenced on the Hamilton Rating Scale for Depression (HAM Nausea was more common in the venlafaxine group compared to dizziness and somnolence in the trazodone

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Last Modified: June 08, 2009