DRUGDEX® Evaluations

ESCITALOPRAM

0.0 Overview

1) Class

a) This drug is a member of the following class(es):
Antianxiety
Antidepressant
Serotonin Reuptake Inhibitor

2) Dosing Information

a) Escitalopram Oxalate

1) Adult

a) Generalized anxiety disorder

1) initial, 10 mg/day ORALLY as a single dose in the morning or ev
Info LEXAPRO(R) Oral solution, Oral tablets, 2009)

2) maintenance, 10 mg/day ORALLY, may increase to 20 mg/day (
after a minimum of one week (Prod Info LEXAPRO(R) Oral solution
2009)

b) Major depressive disorder

1) initial, 10 mg/day ORALLY as a single dose in the morning or ev
Info LEXAPRO(R) Oral solution, Oral tablets, 2009)

2) maintenance, 10 mg/day ORALLY, may increase to 20 mg/day (
after a minimum of one week (Prod Info LEXAPRO(R) Oral solution
2009)

2) Pediatric

a) safety and effectiveness in children for the acute treatment of genera
disorder have not been established (Prod Info LEXAPRO(R) Oral solutic
tablets, 2009)

b) safety and effectiveness in children under the age of 12 years for the
maintenance treatment of major depressive disorder have not been esta
Info LEXAPRO(R) Oral solution, Oral tablets, 2009)

1) Major depressive disorder

a) age 12 years and older: initial, 10 mg/day ORALLY as a sin
morning or evening (Prod Info LEXAPRO(R) Oral solution, Oral
2009)

b) age 12 years and older: maintenance, 10 mg/day ORALLY,
to 20 mg/day ORALLY only after a minimum of 3 weeks (Prod I
LEXAPRO(R) Oral solution, Oral tablets, 2009)

3) Contraindications

a) Escitalopram Oxalate

1) concomitant use of pimozide or monoamine oxidase inhibitors (MAOIs) (F
Lexapro(R) oral tablets, solution, 2009)

2) hypersensitivity to citalopram, escitalopram, or any other component of th
(Prod Info Lexapro(R) oral tablets, solution, 2009)

4) Serious Adverse Effects

a) Escitalopram Oxalate

1) Depression, worsening
2) Diabetes mellitus
3) Grand mal seizure
4) Heart failure
5) Myocardial infarction
6) Neuroleptic malignant syndrome
7) Pancreatitis

8) Prolonged QT interval
9) Rectal hemorrhage
10) Serotonin syndrome
11) Suicidal thoughts
12) Suicide
13) Syndrome of inappropriate antidiuretic hormone secretion
14) Torsades de pointes

5) Clinical Applications
a) Escitalopram Oxalate
1) FDA Approved Indications
a) Generalized anxiety disorder
b) Major depressive disorder

1.0 Dosing Information

Drug Properties

Storage and Stability

Adult Dosage

Pediatric Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referri
Tradename List (Product Index)
B) Synonyms
Escitalopram
Escitalopram Oxalate
C) Physicochemical Properties
1) Molecular Weight
a) 414.40 (Prod Info Lexapro™, 2002a)
2) Solubility
a) Systemic: Escitalopram is freely soluble in methanol and dimethylsulf
(DMSO), sparingly soluble in water and in ethanol, slightly soluble in eth
and insoluble in heptane.(Prod Info Lexapro™, 2002a)

1.2 Storage and Stability

A) Escitalopram Oxalate
1) Preparation
a) Oral route
1) Allow at least 14 days between the discontinuation of an MAOI a
escitalopram or the discontinuation of escitalopram and initiation of
MAO inhibitors (Prod Info LEXAPRO(R) Oral solution, Oral tablets,
2) Administer without regard to meals (Prod Info LEXAPRO(R) Ora
tablets, 2009).
B) Oral route
1) Tablets should be stored at 77 degrees Fahrenheit (25 degrees Celsius);
permitted to 59 to 86 degrees Fahrenheit (15 to 30 degrees Celsius)(Prod In
(TM), 2002g).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Geriatric Patients

Dosage in Other Disease States

1.3.1 Normal Dosage

1.3.1.A Escitalopram Oxalate

1.3.1.A.1 Oral route

Generalized anxiety disorder

Major depressive disorder

1.3.1.A.1.a Generalized anxiety disorder

1) The initial recommended dose in the acute treatment of gen
anxiety disorder in adults is escitalopram 10 milligrams (mg) or
(morning or evening). After one week, the dose may be increas
orally once daily. The efficacy of escitalopram in the treatment
anxiety disorder for longer than 8 weeks has not been establish
on long-term treatment should be reevaluated periodically to de
long term usefulness of escitalopram (Prod Info LEXAPRO(R)
Oral tablets, 2009).

1.3.1.A.1.b Major depressive disorder

1) The initial recommended dose in the acute and maintenanc
major depressive disorder in adults is escitalopram 10 milligram
once daily (morning or evening). After one week the dose may
to 20 mg once daily; however, there were no statistically signific
improvements in efficacy at the higher dose, and higher rates o
effects were reported (Prod Info LEXAPRO(R) Oral solution, O
2009; Wade et al, 2002; Gorman, 2001a).

1.3.1.A.2 Switching To Or From a Monoamine Oxidase Inhibitor

a) Because of a potential interaction, at least 14 days should elaps
discontinuation of a monoamine oxidase inhibitor (MAOI) and the in
escitalopram therapy or between the cessation of escitalopram and
of MAOI therapy (Prod Info LEXAPRO(R) Oral solution, Oral tablets

1.3.2 Dosage in Renal Failure

A) Escitalopram Oxalate

1) In patients with mild to moderate renal impairment, there is no dose a
recommended. Caution should be used in patients with severe renal imp
Info LEXAPRO(R) Oral solution, Oral tablets, 2009).

1.3.3 Dosage in Hepatic Insufficiency

A) Escitalopram Oxalate

1) Escitalopram is extensively metabolized in the liver. The recommend
patients with hepatic impairment is 10 milligrams (mg) orally once daily (
LEXAPRO(R) Oral solution, Oral tablets, 2009).

1.3.4 Dosage in Geriatric Patients

A) Escitalopram Oxalate

1) In pharmacokinetic studies, escitalopram half-life was increased by a
50% in elderly patients as compared with young patients. The recomme
elderly patients is 10 milligrams (mg) of escitalopram once daily (Prod In
(R) Oral solution, Oral tablets, 2009).

1.3.6 Dosage in Other Disease States

A) Escitalopram Oxalate

1) Discontinuation of Treatment

a) Patients should be monitored for withdrawal symptoms when dis
escitalopram treatment and a gradual tapering of the dose, rather th
discontinuation, is recommended whenever possible. If intolerable s
occur after a dose reduction or upon cessation of treatment, the pre
prescribed dose may be reinstated and then the dose may be reduc
gradual rate (Prod Info LEXAPRO(R) Oral solution, Oral tablets, 20

2) Pregnancy

a) Neonates exposed to escitalopram and other selective serotonin

inhibitors (SSRI) or selective noradrenaline reuptake inhibitors (SNR
third trimester have developed complications requiring prolonged ho
tube feeding, and respiratory support. The potential risks and benef
carefully considered when treating pregnant women with escitalopra
third trimester. Tapering escitalopram in the third trimester may be c
(Prod Info LEXAPRO(R) Oral solution, Oral tablets, 2009).

1.4 Pediatric Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Other Disease States

1.4.1 Normal Dosage

1.4.1.A Escitalopram Oxalate

1.4.1.A.1 Oral route

1.4.1.A.1.a Major depressive disorder

1) The initial recommended dose in the acute and maintenanc
major depressive disorder in adolescents age 12 years and old
escitalopram 10 milligrams (mg) orally once daily (morning or e
3 weeks the dose may be increased to 20 mg once daily; howe
were no statistically significant improvements in efficacy at the
and higher rates of adverse effects were reported (Prod Info LE
Oral solution, Oral tablets, 2009).

2) The safety and effectiveness in children for the acute treatment of ge
anxiety disorder have not been established (Prod Info LEXAPRO(R) Ora
Oral tablets, 2009).

3) The safety and effectiveness in children under the age of 12 years fo
and maintenance treatment of major depressive disorder have not been
(Prod Info LEXAPRO(R) Oral solution, Oral tablets, 2009).

1.4.2 Dosage in Renal Failure

A) Escitalopram Oxalate

1) In patients with mild to moderate renal impairment, there is no dose a
recommended. Caution should be used in patients with severe renal imp
Info LEXAPRO(R) Oral solution, Oral tablets, 2009).

1.4.3 Dosage in Hepatic Insufficiency

A) Escitalopram Oxalate

1) Escitalopram is extensively metabolized in the liver. The recommend
patients with hepatic impairment is 10 milligrams (mg) orally once daily (
LEXAPRO(R) Oral solution, Oral tablets, 2009).

1.4.5 Dosage in Other Disease States

A) Escitalopram Oxalate

1) Discontinuation of Treatment

a) Patients should be monitored for withdrawal symptoms when dis
escitalopram treatment and a gradual tapering of the dose, rather th
discontinuation, is recommended whenever possible. If intolerable s
occur after a dose reduction or upon cessation of treatment, the pre
prescribed dose may be reinstated and then the dose may be reduc
gradual rate (Prod Info LEXAPRO(R) Oral solution, Oral tablets, 20

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset

1) Initial Response

a) DEPRESSION, ORAL: 1 to 2 weeks (Montgomery et al, 2001; Wade Burke, 2001a).

1) Indicates time to a significant antidepressant effect compared to doses of 10 or 20 mg daily.

b) ANXIETY IN DEPRESSION, ORAL: 1 week (Lydiard, 2001b).

2.2 Drug Concentration Levels

A) Therapeutic Drug Concentration

1) Not established.

B) Time to Peak Concentration

1) ORAL, TABLET: 3 to 6 hours (single 20-mg dose) (Prod Info Lexapro(TM Drewes et al, 2001; Gutierrez et al, 2001).

a) In healthy subjects, a mean peak plasma level of 18.8 ng/mL was ob hours after single oral doses of escitalopram 20 mg in healthy subjects. its major metabolite, S(+)-desmethylcitalopram, occurred in 14 hours (m ng/mL) (Drewes et al, 2001). After 40-mg oral doses of racemic citalopra study, nearly identical peak levels and times to peak levels of escitalopra in 3.2 hours) and S(+)-desmethylcitalopram (3.5 ng/mL in 14.2 hours) w other pharmacokinetic parameters were also very similar (eg, AUC, half- excretion). These data collectively suggest that 20 mg escitalopram is bi 40 mg citalopram with respect to escitalopram and S(+)-desmethylcitalo

b) Duration: Following single oral doses of escitalopram 20 mg, plasma fallen from a peak of about 19 ng/mL to approximately 1 ng/mL at 120 h et al, 2001).

C) Area Under the Curve

1) 600 to 635 hr x ng/mL (20-mg single dose) (Drewes et al, 2001); (Gutierre

a) AUC (infinity) values for both escitalopram and S(+)-desmethylcitalop similar after oral doses of escitalopram 20 mg and citalopram 40 mg in c S(+)-desmethylcitalopram specifically, the mean AUC was approximatel ng/mL after 20 mg escitalopram (Drewes et al, 2001).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption

A) Bioavailability

1) ORAL, TABLET: 80% for citalopram; no data available for escitalopra Lexapro(TM), 2002h)

a) Escitalopram 20 mg and citalopram 40 mg appear bioequivalent escitalopram and S(+)-desmethylcitalopram (peak plasma levels ac to peak levels, other pharmacokinetic parameters) (Drewes et al, 20

B) Effects of Food

1) None (Prod Info Lexapro(TM), 2002h)

2.3.2 Distribution

A) Distribution Sites

1) Protein Binding
a) 56% (Prod Info Lexapro(TM), 2002h).
B) Distribution Kinetics
1) Volume of Distribution
a) approximately 1330 L (single 20-mg oral dose) (Drewes et al, 20
1) Similar to the value for escitalopram after 40 mg of oral cital (Drewes et al, 2001).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics
1) LIVER, extensive (Prod Info Lexapro(TM), 2002h; Greenblatt et al, 2(Moltke et al, 2001; Greenblatt et al, 2000); (Gutierrez et al, 2001).
a) Escitalopram (S(+)-citalopram) is metabolized to S(+)-desmethyl which is mediated by cytochrome P450 isozymes 2D6, 2C19, and 3 metabolism of S(+)-desmethylcitalopram to S(+)-didesmethylcitalop via cytochrome P450-2D6 (von Moltke et al, 2001; Greenblatt et al, Greenblatt et al, 2000).
b) Studies with human liver microsomes (Greenblatt et al, 2001) ha that escitalopram and S(+)-desmethylcitalopram are only weak or n inhibitors of cytochrome P450 isozymes 1A2, 2C19, 2C9, 2D6, 2E1 (+)-Didesmethylcitalopram was also only a weak inhibitor of 1A2, 2D 3A, although moderate inhibition of the 2C9 and 2C19 isozymes wa with this metabolite; these latter effects do not appear clinically relev the low plasma levels of S(+)-didesmethylcitalopram observed after escitalopram.
c) There is no apparent in vivo interconversion from S-enantiomers enantiomers following oral doses of escitalopram (Drewes et al, 200
B) Metabolites
1) S(+)-Desmethylcitalopram (active in vitro) (von Moltke et al, 2001).
a) Major metabolite; 7 times less potent than escitalopram. Despite evidence of serotonin reuptake inhibition, the contribution of this me clinical activity of escitalopram is considered minimal (Prod Info Lex 2002h).
2) S(+)-Didesmethylcitalopram (active in vitro) (Greenblatt et al, 2001).
a) Twenty-seven times less potent than escitalopram. Despite evid serotonin reuptake inhibition, the contribution of this metabolite to th activity of escitalopram is doubtful as it is present in very low concer plasma (Prod Info Lexapro(TM), 2002h).

2.3.4 Excretion

A) Kidney
1) Renal Clearance (rate)
a) 2.7 L/hr (single 20-mg oral dose) (Drewes et al, 2001).
1) Similar to the value for escitalopram after oral citalopram 40
2) For S(+)-desmethylcitalopram, a value of 6.9 L/hr was repor mg oral escitalopram (Drewes et al, 2001); this was similar to th (+)-desmethylcitalopram after oral citalopram 40 mg.
2) Renal Excretion (%)
a) 8% unchanged (single 20-mg oral dose) (Drewes et al, 2001).
1) Identical to the escitalopram value observed after oral doses 40 mg.
2) Approximately 10% of an oral dose of escitalopram 20 mg is S(+)-desmethylcitalopram (Drewes et al, 2001). This is similar t S(+)-desmethylcitalopram excretion after oral citalopram 40 mg
B) Total Body Clearance
1) 600 mL/min (Prod Info Lexapro(TM), 2002h).
a) Similar to the value for escitalopram clearance after oral doses c 40 mg (Drewes et al, 2001).

2.3.5 Elimination Half-life

A) Parent Compound
1) ELIMINATION HALF-LIFE
a) 22 to 32 hours (single 20-mg oral dose) (Prod Info Lexapro(TM), (Gutierrez et al, 2001)(Drewes et al, 2001).
1) Escitalopram half-life is increased by approximately 50% in patients as compared with young patients. (Prod Info Lexapro(T
2) Similar to the value for escitalopram after oral citalopram 40

et al, 2001).

B) Metabolites

1) S(+)-Desmethylcitalopram, 59 hours (Drewes et al, 2001).

a) Represents value after 20 mg oral escitalopram.

b) This value is similar to that observed for the metabolite following citalopram 40 mg (Drewes et al, 2001).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING

1) Escitalopram Oxalate

a) Oral (Tablet; Solution)

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal think behavior (suicidality) in children, adolescents, and young adults in short- of major depressive disorder (MDD) and other psychiatric disorders. Any considering the use of escitalopram oxalate or any other antidepressant adolescent, or young adult must balance this risk with the clinical need. studies did not show an increase in the risk of suicidality with antidepres compared to placebo in adults beyond age 24; there was a reduction in antidepressants compared to placebo in adults aged 65 and older. Depr certain other psychiatric disorders are themselves associated with increa of suicide. Patients of all ages who are started on antidepressant therap monitored appropriately and observed closely for clinical worsening, suic unusual changes in behavior. Families and caregivers should be advise for close observation and communication with the prescriber. Escitalopra not approved for use in pediatric patients (Prod Info Lexapro(R) oral tabl 2009).

3.1 Contraindications

A) Escitalopram Oxalate

1) concomitant use of pimozide or monoamine oxidase inhibitors (MAOIs) (P Lexapro(R) oral tablets, solution, 2009)

2) hypersensitivity to citalopram, escitalopram, or any other component of th (Prod Info Lexapro(R) oral tablets, solution, 2009)

3.2 Precautions

A) Escitalopram Oxalate

1) suicidal ideation and behavior or worsening depression; increased risk, pa children, adolescents, and young adults, during the first few months of therap changes in dosage (Prod Info Lexapro(R) oral tablets, solution, 2009)

2) abnormal bleeding has been reported, including life-threatening hemorrha Info Lexapro(R) oral tablets, solution, 2009)

3) abrupt withdrawal; serious discontinuation symptoms have been reported Lexapro(R) oral tablets, solution, 2009)

4) bipolar disorder; increased risk of precipitation of a mixed/manic episode Lexapro(R) oral tablets, solution, 2009)

5) concomitant use of NSAIDs, aspirin, or other drugs that affect coagulation bleeding, particularly the gastrointestinal tract, may occur (Prod Info Lexapro tablets, solution, 2009)

6) concomitant serotonergic drug use (serotonin precursors (tryptophan), SS serotonin-norepinephrine reuptake inhibitors); monitoring recommended duri escitalopram initiation and discontinuation (Prod Info Lexapro(R) oral tablets, 2009)

7) diseases or conditions that produce altered metabolism or hemodynamic

(Prod Info Lexapro(R) oral tablets, solution, 2009)
8) hepatic impairment; reduced drug clearance; lower or less frequent dose required (Prod Info Lexapro(R) oral tablets, solution, 2009)
9) mania history; risk of activation of mania/hypomania (Prod Info Lexapro(F solution, 2009)
10) seizure disorder, history (Prod Info Lexapro(R) oral tablets, solution, 200
11) serotonin syndrome has been reported, including cases that are life-thre that resemble neuroleptic malignant syndrome; monitoring recommended (Pr Lexapro(R) oral tablets, solution, 2009)
12) use of escitalopram within 14 days of MAOI discontinuation (Prod Info L tablets, solution, 2009)
13) use of MAOIs within 14 days after escitalopram discontinuation (Prod Int oral tablets, solution, 2009)
14) volume-depleted, elderly, or concurrent diuretic therapy; hyponatremia, s inappropriate antidiuretic hormone secretion (SIADH) has occurred; discontir symptoms develop (Prod Info Lexapro(R) oral tablets, solution, 2009)

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Immunologic Effects

Musculoskeletal Effects

Neurologic Effects

Ophthalmic Effects

Psychiatric Effects

Renal Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

3.3.1.A Escitalopram Oxalate

Bradyarrhythmia

Heart failure

Hypertension

INR raised

Myocardial infarction

Palpitations

Prolonged QT interval

Sudden cardiac death

Torsades de pointes

3.3.1.A.1 Bradyarrhythmia

a) Incidence: 1% or less (Prod Info LEXAPRO(R), 2008)

b) No significant effects on blood pressure, heart rate, or the ECG v observed with therapeutic doses in studies monitoring these parame Info LEXAPRO(R), 2008; Burke, 2001; Burke, 2000).

c) A 60-year-old post-stroke female experienced severe bradycardi consciousness and respiratory failure within 45 minutes of escitalop Upon admission to the stroke unit 3 days prior, neurological examin a left brachiofacial hemiparesis and ECG was normal. Acute ischem the right temporo-insular cortex was confirmed by MRI, while dopple ultrasonography and cerebral angiography revealed 90% stenosis o internal carotid artery and complete occlusion of the right internal ca Because she had a history of depression (untreated at the time) tha after her stroke, she was treated with escitalopram. The episode of (20-30 beats/min) was successfully treated and the patient survived retrospectively remembered experiencing dizziness and fainting foll of citalopram 20 mg several years prior. The exact cause of the life- bradycardia is unclear, but stroke involving the insular cortex has be to induce ECG abnormalities, increasing the risk for cardiac abnorm death (Beyenburg & Schonegger, 2007).

3.3.1.A.2 Heart failure

a) Cardiac failure has been reported in postmarketing spontaneous trials (Prod Info LEXAPRO(R), 2008).

3.3.1.A.3 Hypertension

a) Incidence: 1% (Prod Info LEXAPRO(R), 2008)

b) Hypertension has been reported in at least 1% of patients follow escitalopram treatment (Prod Info LEXAPRO(R), 2008).

c) No significant effects on blood pressure, heart rate, or the ECG v with therapeutic doses in studies monitoring these parameters (Proc LEXAPRO(R), 2008; Burke, 2001; Burke, 2000).

3.3.1.A.4 INR raised

a) Increased INR has been reported in postmarketing spontaneous trials (Prod Info LEXAPRO(R), 2008).

3.3.1.A.5 Myocardial infarction

a) Myocardial infarction has been reported in postmarketing sponta clinical trials (Prod Info LEXAPRO(R), 2008).

3.3.1.A.6 Palpitations

a) Incidence: 1% (Prod Info LEXAPRO(R), 2008)

b) Palpitations have been reported in at least 1% of patients followi escitalopram treatment (Prod Info LEXAPRO(R), 2008).

c) No significant effects on blood pressure, heart rate, or the ECG v with therapeutic doses in studies monitoring these parameters (Proc LEXAPRO(R), 2008; Burke, 2001; Burke, 2000).

3.3.1.A.7 Prolonged QT interval

a) Electrocardiogram QT prolongation has been reported in postma spontaneous and clinical trials (Prod Info LEXAPRO(R), 2008).

3.3.1.A.8 Sudden cardiac death

a) In a large cohort study including 481,744 persons and 1487 case cardiac death occurring in a community setting, the use of selective reuptake inhibitors was not associated with an increased risk of sud death (rate ratio, 0.95; 95% CI, 0.42 to 2.15). In contrast, users of tr antidepressants in doses of 100 mg or higher (amitriptyline or its eq a 41% increased rate of sudden cardiac death (rate ratio, 1.41; 95% 1.95) (Ray et al, 2004).

3.3.1.A.9 Torsades de pointes

a) Torsades de pointes has been reported in postmarketing sponta clinical trials (Prod Info LEXAPRO(R), 2008).

3.3.2 Dermatologic Effects

3.3.2.A Escitalopram Oxalate

Diaphoresis

Erythroderma

Rash

3.3.2.A.1 Diaphoresis

a) Incidence: 4% to 5% (Prod Info Lexapro(R) oral tablets, solution,
b) Increased sweating was observed in 4% to 5% of patients during treatment compared with 1% to 2% in matched placebo groups (Pro Lexapro(R) oral tablets, solution, 2009; Montgomery et al, 2001a).

3.3.2.A.2 Erythroderma

a) A 49-year-old female reported a case of photo-induced erythrode escitalopram therapy. The patient was initiated on escitalopram 10 r reactive depression. She was exposed to UV rays for 15 minutes in tanning bed about 4 hours following her first dose. Thirty-six hours l developed a skin rash which covered her face and body. Escitalopra discontinued 5 days later. Examination revealed diffuse erythema, c sparing only medallion, and string. Skin biopsy results revealed sing necrosis of keratinocytes with mild infiltrate of lymphocytes in the su dermis. Immunological evaluation was unremarkable. Photo-induce erythroderma was diagnosed and a regimen of betamethasone dipr 0.05% was initiated. The rash resolved within 3 weeks but with cont pigmentation (Ram-Wolf et al, 2008).

3.3.2.A.3 Rash

a) Incidence: at least 1% (Prod Info Lexapro(R) oral tablets, solutio
b) Rash has been reported in at least 1% of patients treated with es (Prod Info Lexapro(R) oral tablets, solution, 2009; Montgomery et al

3.3.3 Endocrine/Metabolic Effects

3.3.3.A Escitalopram Oxalate

Diabetes mellitus

Hyponatremia

Syndrome of inappropriate antidiuretic hormone secretion

Weight increased

3.3.3.A.1 Diabetes mellitus

a) Diabetes mellitus has been reported in postmarketing spontaneo

clinical trials (Prod Info LEXAPRO(R), 2008).

3.3.3.A.2 Hyponatremia

a) Individual case reports have described development of hyponatr initiation of escitalopram therapy (Grover et al, 2007; Nirmalani et al Nahshoni et al, 2004). The incidence of hyponatremia associated w SSRI therapy ranges between 0.5% to 25%. Risk factors for the dev hyponatremia include older age, female gender, low body weight, hi SSRI, and concomitant use of diuretics, antipsychotics, narcotics, a hypoglycemic agents. Routine monitoring of electrolyte levels espec elderly during the first 2 to 4 weeks of therapy may be warranted (G 2007).

b) A case report described development of hyponatremia following therapy in a 67-year-old female. The patient, who had a history of h diabetes mellitus, and late-onset bipolar affective disorder, had pres acute-onset, severe depression without psychotic symptoms of 4 m duration. Escitalopram was initiated at 10 mg/day and after 3 weeks escalated to 15 mg/day. The patient had normal electrolyte levels pr of escitalopram, and concomitant drug therapy included sodium valp hydrochlorothiazide, gliclazide, aspirin, losartan, and metoprolol. Wi of the escalated escitalopram dose, the patient became delirious, ar to have serum sodium levels of 127 mEq/L and increased urine sod concentration 160 mmol/L. Following discontinuation of escitaloprar thiazides, and provision of supportive therapy, the patient level and consciousness gradually improved (Grover et al, 2007).

c) Hyponatremia occurred in a 65-year-old male patient subsequer of escitalopram. The patient, who had a history of generalized anxie and hypertension was initiated on escitalopram 10 mg/day after he p anxiety symptoms. Concurrent medications included amlodipine and Within 10 days of initiating escitalopram, the patient experienced on generalized tonic-clonic seizures and was found to have a serum so 126 mEq/L. Following discontinuation of escitalopram and provision care, the patient gradually improved over the next 2 weeks (Grover

d) A 50-year-old black male experienced the syndrome of inapprop antidiuretic hormone (SIADH) within 4 weeks of initiating escitalopra depression. Upon admission to the hospital, he was on no other me physical exam was normal, and all diagnostic tests for acute illness Serum sodium was within the normal range at 138 mmol/L. Escitalo at bedtime and olanzapine 10 mg at bedtime were begun on hospita the doses increased over the next 3 weeks. The patient was taking escitalopram by day 13. Due to lack of efficacy, olanzapine was disc day 23, and risperidone 2 mg/day was initiated. Over the next week patient's depression improved, but by day 28, he complained of wea dizziness, and appeared diaphoretic. The results of a complete mec were unremarkable except for serum sodium of 121 mmol/L, serum mmol/L, and serum osmolality of 254 mOsm/kg (normal 275-300 m Urine osmolality was 617 mOsm/kg (normal 50-1,200 mOsm/kg) an sodium was 115 mmol/L. Following a diagnosis of SIADH, the patie on fluid restriction. Escitalopram 20 mg/day and risperidone 2 mg/da continued. By day 32 the patient's sodium rose to 130 mmol/L, but b had again decreased to 124 mmol/L. The escitalopram was then dis and the patient improved by day 39. Sodium returned to normal at 1 day 41. Depression was successfully treated with mirtazapine 30 m risperidone 2 mg/day and the patient was discharged on day 46 (Ni 2006).

e) The syndrome of inappropriate antidiuretic hormone (SIADH) an hyponatremia was reported in a 62-year-old female patient 3 weeks initiation of escitalopram 10 mg/day for depression. She was admitt hospital following a syncopal fall resulting in head trauma. Upon adr serum sodium level was 110 mmol/L, serum osmolality was 261 mn sodium was 53 mmol/L, and urine osmolality was 286 mmol/kg. The identified for possible causes of SIADH was the use of escitalopram was discontinued. The patient was treated with intravenous normal her sodium levels slowly normalized. At discharge her serum sodiur mmol/L; one week later it was stabilized at 135 mmol/L and serum a osmolality returned to normal levels. The patient's depression was s treated with mirtazapine 30 mg/day without recurrence of hyponatre

(Nahshoni et al, 2004).

3.3.3.A.3 Syndrome of inappropriate antidiuretic hormone secretic

a) A 50-year-old black male experienced the syndrome of inapprop antidiuretic hormone (SIADH) within 4 weeks of initiating escitalopra depression. Upon admission to the hospital, he was on no other me physical exam was normal, and all diagnostic tests for acute illness Serum sodium was within the normal range at 138 mmol/L. Escitalo at bedtime and olanzapine 10 mg at bedtime were begun on hospita the doses increased over the next 3 weeks. The patient was taking escitalopram by day 13. Due to lack of efficacy, olanzapine was disc day 23, and risperidone 2 mg/day was initiated. Over the next week patient's depression improved, but by day 28, he complained of wea dizziness, and appeared diaphoretic. The results of a complete mec were unremarkable except for serum sodium of 121 mmol/L, serum mmol/L, and serum osmolality of 254 mOsm/kg (normal 275-300 m Urine osmolality was 617 mOsm/kg (normal 50-1,200 mOsm/kg) an sodium was 115 mmol/L. Following a diagnosis of SIADH, the patie on fluid restriction. Escitalopram 20 mg/day and risperidone 2 mg/da continued. By day 32 the patient's sodium rose to 130 mmol/L, but b had again decreased to 124 mmol/L. The escitalopram was then dis and the patient improved by day 39. Sodium returned to normal at 1 day 41. Depression was successfully treated with mirtazapine 30 m risperidone 2 mg/day and the patient was discharged on day 46 (Ni 2006).

b) The syndrome of inappropriate antidiuretic hormone (SIADH) an hyponatremia was reported in a 62-year-old female patient 3 weeks initiation of escitalopram 10 mg/day for depression. She was admitt hospital following a syncopal fall resulting in head trauma. Upon adr serum sodium level was 110 mmol/L, serum osmolality was 261 mn sodium was 53 mmol/L, and urine osmolality was 286 mmol/kg. The identified for possible causes of SIADH was the use of escitalopram was discontinued. The patient was treated with intravenous normal her sodium levels slowly normalized. At discharge her serum sodiur mmol/L; one week later it was stabilized at 135 mmol/L and serum a osmolality returned to normal levels. The patient's depression was s treated with mirtazapine 30 mg/day without recurrence of hyponatre (Nahshoni et al, 2004).

3.3.3.A.4 Weight increased

a) Incidence: 1% (Prod Info LEXAPRO(R), 2008)

b) Increased weight has been reported in at least 1% of patients re escitalopram therapy (Prod Info LEXAPRO(R), 2008).

3.3.4 Gastrointestinal Effects

3.3.4.A Escitalopram Oxalate

Abdominal pain

Constipation

Diarrhea

Gastroenteritis

Gastrointestinal hemorrhage

Heartburn

Indigestion

Nausea

Pancreatitis

Rectal hemorrhage

Vomiting

Xerostomia

3.3.4.A.1 Abdominal pain

a) Incidence: 1% to 2% (Prod Info LEXAPRO(R), 2008)

b) Abdominal pain has been reported in 1% to 2% of patients recei escitalopram therapy (Prod Info LEXAPRO(R), 2008; Wade et al, 2(2000; Montgomery et al, 2001a; Gorman, 2001; Burke, 2001) (Lepo 2001).

3.3.4.A.2 Constipation

a) Incidence: 3% to 6% (Prod Info LEXAPRO(R), 2008)

b) Constipation has been reported in 3% to 6% of patients receivin (10 to 20 mg) therapy, at a greater incidence than placebo (Prod Inf (R), 2008; Wade et al, 2001; Burke, 2000; Montgomery et al, 2001a 2001; Burke, 2001) (Lepola et al, 2001).

3.3.4.A.3 Diarrhea

a) Incidence: 6% to 14% (Prod Info LEXAPRO(R), 2008)

b) Diarrhea has been reported in 6% to 14% of patients receiving e (10 to 20 mg) therapy, at a greater incidence than placebo (Prod Inf (R), 2008; Wade et al, 2001; Burke, 2000; Montgomery et al, 2001a 2001; Burke, 2001) (Lepola et al, 2001).

3.3.4.A.4 Gastroenteritis

a) Incidence: 1% (Prod Info LEXAPRO(R), 2008)

b) Gastroenteritis has been reported in at least 1% patients receivi escitalopram therapy (Prod Info LEXAPRO(R), 2008; Wade et al, 2(2000; Montgomery et al, 2001a; Gorman, 2001; Burke, 2001) (Lepo 2001).

3.3.4.A.5 Gastrointestinal hemorrhage

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

3.3.4.A.6 Heartburn

a) Incidence: 1% (Prod Info LEXAPRO(R), 2008)

b) Heartburn has been reported in at least 1% patients receiving es therapy (Prod Info LEXAPRO(R), 2008; Wade et al, 2001; Burke, 2(Montgomery et al, 2001a; Gorman, 2001; Burke, 2001) (Lepola et a

3.3.4.A.7 Indigestion

a) Incidence: 2% to 6% (Prod Info LEXAPRO(R), 2008)

b) Indigestion has been reported in 2% to 6% of patients receiving (10 to 20 mg) therapy, at a greater incidence than placebo (Prod Inf (R), 2008; Wade et al, 2001; Burke, 2000; Montgomery et al, 2001a 2001; Burke, 2001) (Lepola et al, 2001).

3.3.4.A.8 Nausea

a) Incidence: 15% to 18% (Prod Info LEXAPRO(R), 2008)

b) Nausea has been reported in 15% to 18% of patients receiving e (10 to 20 mg) therapy, at a greater incidence than placebo (Prod Inf (R), 2008; Wade et al, 2001; Burke, 2000; Montgomery et al, 2001a 2001; Burke, 2001) (Lepola et al, 2001).

3.3.4.A.9 Pancreatitis

a) Pancreatitis has been reported in postmarketing spontaneous ar trials (Prod Info LEXAPRO(R), 2008).

3.3.4.A.10 Rectal hemorrhage

a) Rectal hemorrhage has been reported in postmarketing spontan clinical trials (Prod Info LEXAPRO(R), 2008).

3.3.4.A.11 Vomiting

a) Incidence: 3% (Prod Info LEXAPRO(R), 2008)

b) Vomiting has been reported in 3% of patients receiving escitalop mg) therapy, at a greater incidence than placebo (Prod Info LEXAP Wade et al, 2001; Burke, 2000; Montgomery et al, 2001a; Gorman, 2001) (Lepola et al, 2001).

3.3.4.A.12 Xerostomia

a) Incidence: 6% to 9% (Prod Info LEXAPRO(R), 2008)

b) Dry mouth has been reported in 6% to 9% of patients receiving e (10 to 20 mg) therapy, at a greater incidence than placebo (Prod Inf (R), 2008; Wade et al, 2001; Burke, 2000; Montgomery et al, 2001a 2001; Burke, 2001) (Lepola et al, 2001).

3.3.5 Hematologic Effects

3.3.5.A Escitalopram Oxalate

Anemia

Contusion

Epistaxis

Hematoma

3.3.5.A.1 Anemia

a) Incidence: 1% or less (Prod Info LEXAPRO(R), 2008)

b) Anemia has been reported in less than 1% of patients receiving therapy (Prod Info LEXAPRO(R), 2008).

3.3.5.A.2 Contusion

a) Incidence: 1% or less (Prod Info LEXAPRO(R), 2008)

b) Bruising has been reported in less than 1% of patients receiving therapy (Prod Info LEXAPRO(R), 2008).

3.3.5.A.3 Epistaxis

a) Incidence: 1% or less (Prod Info LEXAPRO(R), 2008)

b) Nosebleed has been reported in 1% or less of patients receiving therapy, and has been associated with SSRI and serotonin norepine reuptake inhibitor (SNRI) therapy in general (Prod Info LEXAPRO(F

3.3.5.A.4 Hematoma

a) Incidence: 1% or less(Prod Info LEXAPRO(R), 2008)

b) Hematoma has been reported in 1% or less of patients receiving therapy (Prod Info LEXAPRO(R), 2008).

3.3.6 Hepatic Effects

3.3.6.A Escitalopram Oxalate

Fulminant hepatitis

Hepatic necrosis

Liver failure

3.3.6.A.1 Fulminant hepatitis

a) Fulminant hepatitis has been reported in postmarketing spontan clinical trials (Prod Info LEXAPRO(R), 2008).

3.3.6.A.2 Hepatic necrosis

a) Hepatic necrosis has been reported in postmarketing spontaneo trials (Prod Info LEXAPRO(R), 2008).

3.3.6.A.3 Liver failure

a) Hepatic failure has been reported in postmarketing spontaneous trials (Prod Info LEXAPRO(R), 2008).

3.3.7 Immunologic Effects

3.3.7.A Escitalopram Oxalate

3.3.7.A.1 Anaphylaxis

a) Oculogyric crisis with mixed anaphylactic features developed in female after ingestion of 20 milligrams (mg) of escitalopram in addit mg daily dose. The patient experienced a dystonic upward deviatior eye along with diaphoresis, dyspnea, palpitations, and swelling of th tongue. She self-administered a 0.3-mg dose of intramuscular epine autoinjector and symptoms temporarily resolved, but recurred after Resolution of all symptoms was achieved with administration of lora hydroxyzine. The patient had previously reported an episode of ana being treated with sertraline 50 mg daily. It is unclear if the dystonic symptoms of anaphylaxis are related (Patel & Simon, 2006).

3.3.8 Musculoskeletal Effects

3.3.8.A Escitalopram Oxalate

Arthralgia

Fracture of bone

Fracture of bone, Nonvertebral

Myalgia

Rhabdomyolysis

3.3.8.A.1 Arthralgia

a) Incidence: 1% (Prod Info LEXAPRO(R), 2008)

b) Arthralgia has been reported in at least 1% of patients following treatment (Prod Info LEXAPRO(R), 2008).

3.3.8.A.2 Fracture of bone

a) In a population-based, randomly selected, prospective cohort stu for potential covariates, an increased risk of fragility fracture was re 5-year follow-up in patients 50 years of age and older who used dai (n=137; mean age of 65.1 years), including citalopram (escitalopran in this study), compared with those who did not use an SSRI (n=487 of 65.7 years). Daily SSRI use was associated with a significant 2.1 increased risk of fragility fracture (95% confidence interval (CI), 1.3 dose of SSRI use was associated with a 1.5-fold increased risk of fr (95% CI, 1.1 to 2.1). Daily SSRI users who were recurrent (ie, treate at baseline and at 5-year follow-up) had a significant 2.1-fold increa fragility fracture (95% CI, 1.1 to 4). Fractures were reported at the fo forearm (40%), ankle and foot (21%), hip (13%), rib (13%), femur (9 (4%). None were reported at the skull, toes, or fingers (Richards et increased risk of fragility fracture has been reported in a prospective of SSRIs, including citalopram (Richards et al, 2007). Escitalopram included in this study

3.3.8.A.3 Fracture of bone, Nonvertebral

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

3.3.8.A.4 Myalgia

a) Incidence: 1% (Prod Info LEXAPRO(R), 2008)

b) Myalgia has been reported in at least 1% of patients following es treatment (Prod Info LEXAPRO(R), 2008).

3.3.8.A.5 Rhabdomyolysis

a) Rhabdomyolysis has been reported in postmarketing spontaneo trials (Prod Info LEXAPRO(R), 2008).

3.3.9 Neurologic Effects

3.3.9.A Escitalopram Oxalate

Agitation

Dizziness

Feeling nervous

Grand mal seizure

Headache

Insomnia

Lightheadedness

Neuroleptic malignant syndrome

Restless legs syndrome

Serotonin syndrome

Somnolence

Tremor

3.3.9.A.1 Agitation

a) Incidence: 1% or less (Lydiard, 2001a)

b) Agitation has occurred in less than 1% of patients treated with es placebo (Lydiard, 2001a).

3.3.9.A.2 Dizziness

a) Incidence: 4% to 7%(Prod Info LEXAPRO(R), 2008)

b) Dizziness has been reported in 4% to 7% of patients receiving e

(10 to 20 mg) therapy, at a greater incidence than placebo (Prod Inf (R), 2008; Wade et al, 2001; Montgomery et al, 2001b; Montgomery Burke, 2001; Gorman, 2001).

3.3.9.A.3 Feeling nervous

a) Incidence: 1% or less (Lydiard, 2001a)

b) Nervousness has occurred in less than 1% of patients treated w escitalopram or placebo (Lydiard, 2001a).

3.3.9.A.4 Grand mal seizure

a) Grand mal seizures have been reported in postmarketing sponta clinical trials (Prod Info LEXAPRO(R), 2008).

3.3.9.A.5 Headache

a) Incidence: 24% (Prod Info LEXAPRO(R), 2008)

b) Headache has been reported in 24% of patients receiving escita 20 mg) therapy, at a greater incidence than placebo (Prod Info LEX 2008; Wade et al, 2001; Montgomery et al, 2001b; Montgomery et a Burke, 2001; Gorman, 2001).

3.3.9.A.6 Insomnia

a) Incidence: 7% to 14% (Prod Info LEXAPRO(R), 2008)

b) Insomnia has been reported in 7% to 14% of patients receiving e (10 to 20 mg) therapy, at a greater incidence than placebo (Prod Inf (R), 2008; Wade et al, 2001; Montgomery et al, 2001b; Montgomery Burke, 2001; Gorman, 2001).

3.3.9.A.7 Lightheadedness

a) Incidence: 1% (Prod Info LEXAPRO(R), 2008)

b) Lightheadedness has been reported in at least 1% of patients re escitalopram therapy (Prod Info LEXAPRO(R), 2008).

3.3.9.A.8 Neuroleptic malignant syndrome

a) Neuroleptic malignant syndrome has been reported in postmarke spontaneous and clinical trials (Prod Info LEXAPRO(R), 2008).

3.3.9.A.9 Restless legs syndrome

a) In a prospective, naturalistic study of patients (median age, 46 y 18 to 87 years) treated with antidepressants, 24 of 271 (9%) subjec experienced new-onset restless leg syndrome (RLS) or worsening o RLS as a side effect related to treatment. Antidepressants included paroxetine, citalopram, sertraline, escitalopram, venlafaxine, duloxe reboxetine, and mirtazapine. Mirtazapine led to a marked decline of of subjects compared with reboxetine which had none. The other ar showed RLS symptoms (newly occurred or deteriorated) at the rate 10%. Subjects stated symptoms occurred early in treatment (media range 1 to 23 days) (Rottach et al, 2008).

3.3.9.A.10 Serotonin syndrome

a) Serotonin syndrome has been reported in postmarketing sponta clinical trials (Prod Info LEXAPRO(R), 2008).

3.3.9.A.11 Somnolence

a) Incidence: 4% to 13% (Prod Info LEXAPRO(R), 2008)

b) Somnolence has been reported in 4% to 13% of patients receivi escitalopram (10 to 20 mg) therapy, at a greater incidence than plac Info LEXAPRO(R), 2008; Wade et al, 2001; Montgomery et al, 2001 Montgomery et al, 2001a; Burke, 2001; Gorman, 2001).

3.3.9.A.12 Tremor

a) Incidence: 1% or less (Lydiard, 2001a)

b) Tremors have occurred in less than 1% of patients treated with e or placebo (Lydiard, 2001a).

3.3.10 Ophthalmic Effects

3.3.10.A Escitalopram Oxalate

Angle-closure glaucoma

Oculogyric crisis

3.3.10.A.1 Angle-closure glaucoma

a) A case of acute bilateral angle closure glaucoma with choroidal e occurred in a 41-year-old woman following escitalopram use. The w had a history of depression and seasonal allergies, was placed on e 20 mg/day. Four weeks later, she presented with blurry vision in bot had lasted several hours. Ophthalmic examinations revealed elevat pressures of 47 and 45 millimeters of mercury in both eyes and a be visual acuity of 20/40 in both eyes, with a myopic shift of approxima from her current spectacle prescription. In addition, bilaterally shallo chambers and closed angles for 360 degrees in both eyes were not treatments, which consisted of topical timolol, dorzolamide, brimonic acetazolamide, and glycerin, followed by a laser peripheral iridotom eye, were not successful. The patient's corneas became edematous acuity declining from 20/40 to 20/400 in both eyes, over the next 3 h Additional testing confirmed the presence of choroidal effusions with detachments and diffuse choroidal thickening in each eye. Subsequ treatment was initiated oral prednisone (1 mg/kg), topical prednisolc and cycloplegic drops, and escitalopram was discontinued. Over the the patient's clinical symptoms resolved as evidenced by 20/20 visic eyes, normal intraocular pressures, and deepening of anterior cham postulated that escitalopram induced bilateral uveal effusions which angle closure in the patient (Zelefsky et al, 2006).

3.3.10.A.2 Oculogyric crisis

a) Oculogyric crisis with mixed anaphylactic features developed in a female after ingestion of 20 milligrams (mg) of escitalopram in addit mg daily dose. The patient experienced a dystonic upward deviation eye along with diaphoresis, dyspnea, palpitations, and swelling of th tongue. She self-administered a 0.3-mg dose of intramuscular epine autoinjector and symptoms temporarily resolved, but recurred after Resolution of all symptoms was achieved with administration of lora hydroxyzine. The patient had previously reported an episode of ana being treated with sertraline 50 mg daily. It is unclear if the dystonic symptoms of anaphylaxis are related (Patel & Simon, 2006).

3.3.12 Psychiatric Effects

3.3.12.A Escitalopram Oxalate

Depression, exacerbation

Depression, worsening

Psychotic disorder, acute

Suicidal thoughts

Suicide

3.3.12.A.1 Depression, exacerbation

a) Adult and pediatric patients who experience symptoms of anxiety panic attacks, insomnia, irritability, hostility (aggressiveness), impuls akathisia (psychomotor restlessness), hypomania, or mania may be worsening of their depression. This same concern applies to treating other psychiatric and nonpsychiatric disorders. If these symptoms a therapy should be reevaluated and it may be necessary to discontin medications when symptoms are severe, sudden in onset, or were n patient's initial symptoms (Prod Info LEXAPRO(R) Oral solution, Or

2009; Anon, 2004; Prod Info LEXAPRO(R), 2008).

3.3.12.A.2 Depression, worsening

a) Incidence: rare

b) Clinical worsening of depression has been reported in patients r escitalopram therapy, particularly during the initial few months of tre during dose adjustments. It may persist until significant remission oc patients treated with antidepressants for any indication should be m signs of clinical worsening (Prod Info LEXAPRO(R) Oral solution, O 2009).

3.3.12.A.3 Psychotic disorder, acute

a) Acute psychosis has been reported during postmarketing use of (Prod Info LEXAPRO(R) Oral solution, Oral tablets, 2009).

3.3.12.A.4 Suicidal thoughts

a) Incidence: rare

b) Adult and pediatric patients being treated with antidepressants f depressive disorder who experience symptoms of anxiety, agitation attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, (psychomotor restlessness), hypomania, or mania may be at risk of ideation and behavior (suicidality). This same concern applies to tre with other psychiatric and nonpsychiatric disorders. If these sympto observed, therapy should be reevaluated and it may be necessary t medications when symptoms are severe, sudden in onset, or were patient's initial symptoms. Patients and their caregivers should be p the Medication Guide that is available for this drug. Closely monitor especially during the initial few months of therapy or at times of dos (Prod Info LEXAPRO(R) Oral solution, Oral tablets, 2009; Anon, 20 2004).

c) A causal role for antidepressants in inducing suicidality has beer in pediatric patients. Anyone considering the use of antidepressants adolescent must balance this risk with the clinical need. In pooled a short-term, placebo-controlled trials of nine antidepressants (citalop fluoxetine, fluvoxamine, paroxetine, sertraline, bupropion, mirtazapi nefazodone, and venlafaxine extended-release) including over 440 patients with major depressive disorder (MDD), obsessive compulsi (OCD), or other psychiatric disorders, a greater risk of suicidal beha ideation during the first few months of therapy was demonstrated in receiving antidepressants as compared with placebo (4% vs 2%). T suicidality was most consistently observed in the trials that included MDD, but there were signs of risk emerging from trials in other psyc indications, such as obsessive compulsive disorder and social anxie (Anon, 2004).

1) In a pooled analyses of placebo-controlled trials in adults wi other psychiatric disorders including 295 short-term trials (medi 2 months) of 11 antidepressant drugs in greater than 77,000 pa of suicidality varied among the drugs studied. However, for alm studied, there was a tendency toward increasing suicidality in y patients. The risk difference (drug versus placebo in the numbe suicidality per 1000 patients treated) was 14 additional cases ir than 18 years of age, 5 additional cases in patients 18 to 24 ye case in patients 25 to 64 years, and 6 fewer cases in patients 6 older. No suicides occurred in the pediatric trials. Suicides did adult trials; however, the number of suicides was insufficient to causality. The risk of suicidality during longer-term use (ie, bey months) in pediatric patients is not known. However, evidence placebo-controlled, maintenance trials in adults with depressior substantiate a delay in the recurrence of depression with antide (Prod Info LEXAPRO(R) Oral solution, Oral tablets, 2009; Anor

3.3.12.A.5 Suicide

a) Incidence: rare

b) Suicide has been reported in adult patients receiving escitalopra clinical trials; however, the number of suicides was insufficient to de causality (Prod Info LEXAPRO(R) Oral solution, Oral tablets, 2009).

3.3.13 Renal Effects

3.3.13.A Escitalopram Oxalate

3.3.13.A.1 Urogenital finding

a) EJACULATION DISTURBANCES (primary ejaculatory delay) ha
reported in 9% to 14% of patients during escitalopram treatment in
studies compared with 2% to less than 1% in matched placebo grou
DECREASED LIBIDO (7%) and ANORGASMIA (6%) have also bee
following treatment with escitalopram (Prod Info Lexapro(TM), 2004
Gorman, 2001; Wade et al, 2001; Montgomery et al, 2001a).

3.3.15 Respiratory Effects

3.3.15.A Escitalopram Oxalate

3.3.15.A.1 Respiratory finding

a) BRONCHITIS, SINUS CONGESTION, COUGH, NASAL CONGI
SINUS HEADACHE have occurred in at least 1% of patients treatec
escitalopram (Prod Info Lexapro(TM), 2004).

3.3.16 Other

3.3.16.A Escitalopram Oxalate

Drug withdrawal

Fatigue

Serotonin syndrome

3.3.16.A.1 Drug withdrawal

See Drug Consult reference: WITHDRAWAL SYNDROME OF SEL
SEROTONIN REUPTAKE INHIBITORS

3.3.16.A.2 Fatigue

a) Incidence: 2% to 8% (Prod Info LEXAPRO(R), 2008)

b) Fatigue has been reported in 2% to 8% of patients receiving esc
to 20 mg) therapy, at a greater incidence than placebo (Prod Info LE
2008; Wade et al, 2001; Montgomery et al, 2001b; Montgomery et a
Burke, 2001; Gorman, 2001).

3.3.16.A.3 Serotonin syndrome

a) Serotonin syndrome, including life-threatening cases, or neurole
syndrome (NMS)-like reactions have been reported with the use of
alone. Signs and symptoms of serotonin syndrome include mental s
(eg, agitation, hallucination, coma), autonomic instability (eg, tachyc
blood pressure, hyperthermia), neuromuscular aberrations (eg, hyp
incoordination) and/or gastrointestinal symptoms (eg, nausea, vomi
Severe serotonin syndrome can resemble NMS with symptoms incl
hyperthermia, muscle rigidity, autonomic instability with possible rap
of vital signs, and mental status changes. Serotonin syndrome occu
commonly with the concomitant use of serotonergic drugs, including
drugs that impair metabolism of serotonin, including MAOIs, or with
or other dopamine antagonists (Prod Info Lexapro(R) oral tablets, s

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (P
LEXAPRO(R) oral tablets, solution, 2007) (All Trimesters)

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

2) Australian Drug Evaluation Committee's (ADEC) Category: C (Australian Department of Health and Ageing Therapeutic Goods Administration, 2006)

a) Drugs which, owing to their pharmacological effects, have caused or suspected of causing harmful effects on the human fetus or neonate witl malformations. These effects may be reversible. Accompanying texts sh consulted for further details.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Yes

4) Clinical Management

a) There are no data on the use of escitalopram, the S(+)-enantiomer o during human pregnancy at this time. However, complications have bee neonates exposed to other SSRIs or serotonin and norepinephrine reupt (SNRIs) in the third trimester. Nonteratogenic effects (pulmonary hyperte newborn (PPHN) and clinical findings consistent with serotonin syndrom increased special or intensive unit care of the infant were demonstrated maternal use of SSRIs during the third trimester of pregnancy (Chamber One study revealed that women who discontinued antidepressant medic pregnancy had a greater likelihood of relapse compared with those who antidepressant therapy throughout the pregnancy (Prod Info LEXAPRO(tablets, solution, 2007). Animal studies of escitalopram and citalopram u gestation have shown adverse effects only with doses much higher than to humans. When deciding whether to treat a pregnant woman with esci during the third trimester, evaluate the potential risk to the fetus and the benefit to the mother. Consider tapering the escitalopram dose during th trimester of pregnancy (Prod Info LEXAPRO(R) oral tablets, solution, 20

5) Literature Reports

a) Neonates exposed to escitalopram and other SSRIs or serotonin-nor reuptake inhibitors (SNRIs) late in the third trimester have developed co some arising immediately upon delivery, including respiratory distress, s vomiting, tremor, and irritability, that were consistent with either direct S selective SNRI toxicity or a possible drug discontinuation syndrome. In s clinical findings were consistent with serotonin syndrome (Prod Info LEX tablets, solution, 2007).

b) In a case control study of women who delivered infants with pulmona hypertension of the newborn (PPHN; n=377) and women who delivered infants (n=836), the risk for developing PPHN was approximately six-fol infants exposed to SSRIs after week 20 of gestation compared with infa exposed to SSRIs during gestation. This study demonstrates a potential of PPHN, associated with considerable neonatal morbidity and mortality exposed to SSRIs later in the pregnancy. Because this is the first study PPHN with SSRI use during pregnancy and there are not enough cases to individual SSRIs, it can not be determined if all SSRIs posed similar le risk. In the general population, PPHN occurs in 1 to 2 per 1000 live birth LEXAPRO(R) oral tablets, solution, 2007; Chambers et al, 2006).

c) In a prospective longitudinal study of 201 women with a history of ma depression and no signs of depression at the beginning of pregnancy, th greater likelihood of relapse of major depression in those who discontinu antidepressant drugs during pregnancy compared with those who contin antidepressant drugs throughout the pregnancy (Prod Info LEXAPRO(R solution, 2007).

d) Fetal structural abnormalities, reduced fetal body weight, growth reta death were reported in the offspring of rats and rabbits treated with eithe escitalopram or racemic citalopram during pregnancy at doses considera than the maximum recommended human dose. Mild maternal toxicity wa reported in rat studies of escitalopram use during pregnancy (Prod Info L oral tablets, solution, 2007).

B) Breastfeeding

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

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

2) Clinical Management

a) Escitalopram is the S(+)-enantiomer of citalopram. Citalopram is sec human breast milk and has been associated with some adverse effects infants. Although there is no specific data on escitalopram, effects can b be similar to that seen with citalopram. Bottle feeding is suggested durin escitalopram therapy, and for at least 5 days after therapy discontinuatic

1998). The American Academy of Pediatrics considers antidepressants
that warrant concern in the nursing infant, particularly if used for long pe
2001). A decision should be made whether to discontinue nursing or dis
drug, taking into consideration the potential risks of citalopram exposure
and the benefits of treatment for the mother (Prod Info LEXAPRO(R) ora
solution, 2007). If the use of escitalopram in a nursing mother is necessa
monitoring the infant for unusual sleepiness, changes in appetite, and w
The long-term effects of exposure to SSRIs via breast milk on the cognit
development of the infant have not been determined.

3) Literature Reports

a) In a study describing 8 lactating women treated with an escitalopram
daily dose of 10 mg (range, 10 to 20 mg) that began 55 days before the
the infant plasma concentrations of escitalopram and its active metabolit
demethylescitalopram, were undetectable (n=4), low (n=1), or not measu
The total relative infant dose for escitalopram and its metabolite was a m
(95% confidence interval (CI), 4.2% to 6.2%) of the maternal weight-adju
and the absolute doses were 7.6 mcg/kg/day (95% CI, 5.2 to 10) and 3 m
(95% CI, 2.4 to 3.6) for escitalopram and demethylescitalopram, respect
mean milk/plasma ratio was 2.2 for both escitalopram (95% confidence i
to 2.4) and demethylescitalopram (95% CI, 1.9 to 2.5). The authors sugg
escitalopram is safe for use in nursing mothers; however, individual case
decided based on a risk/benefit analysis (Rampono et al, 2006).

b) Although specific data are not available for escitalopram, racemic cita
appears in breast milk. There have been two case reports of excessive s
weight loss, and decreased feeding in nursing infants whose mothers we
citalopram. One infant reportedly recovered completely upon maternal c
discontinuation; follow-up information was not available for the other infa
LEXAPRO(R) oral tablets, solution, 2007; Anon, 1998).

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Food Combinations

3.5.1 Drug-Drug Combinations

Abciximab

Aceclofenac

Acemetacin

Acenocoumarol

Alclofenac

Almotriptan

Anagrelide

Ancrod

Anisindione

Antithrombin III Human

Ardeparin

Aspirin

Benoxaprofen

Bivalirudin

Bromfenac

Bufexamac

Cannabis

Carprofen

Celecoxib

Certoparin

Cilostazol

Cimetidine

Clonixin

Clopidogrel

Clorgyline

Cyclobenzaprine

Dalteparin

Danaparoid

Defibrotide

Dehydroepiandrosterone

Dermatan Sulfate

Desipramine

Desirudin

Desvenlafaxine

Dexketoprofen

Diclofenac

Dicumarol

Diflunisal

Dipyridamole

Dipyrone

Droxicam

Duloxetine

Eletriptan

Enoxaparin

Epoprostenol

Eptifibatide

Etodolac

Etofenamate

Etoricoxib

Felbinac

Fenbufen

Fenoprofen

Fentiazac

Floctafenine

Flufenamic Acid

Flurbiprofen

Fondaparinux

Frovatriptan

Furazolidone

Ginkgo

Heparin

Hydrocodone

Hydroxytryptophan

Ibuprofen

Iloprost

Indomethacin

Indoprofen

Isocarboxazid

Isoxicam

Ketoconazole

Ketoprofen

Ketorolac

Lamifiban

Lamotrigine

Lazabemide

Lexipafant

Linezolid

Lithium

Lornoxicam

Meclofenamate

Mefenamic Acid

Meloxicam

Methylphenidate

Metoprolol

Milnacipran

Moclobemide

Morniflumate

Nabumetone

Nadroparin

Naproxen

Naratriptan

Niflumic Acid

Nimesulide

Oxaprozin

Oxycodone

Parecoxib

Parnaparin

Pentosan Polysulfate Sodium

Phenelzine

Phenindione

Phenprocoumon

Phenylbutazone

Pirazolac

Piroxicam

Pirprofen

Propyphenazone

Proquazone

Rasagiline

Reviparin

Rizatriptan

Rofecoxib

Selegiline

Sibrafiban

Sibutramine

St John's Wort

Sulfinpyrazone

Sulindac

Sulodexide

Sumatriptan

Suprofen

Tapentadol

Tapentadol

Tenidap

Tenoxicam

Tiaprofenic Acid

Ticlopidine

Tinzaparin

Tirofiban

Tolmetin

Tramadol

Tranylcypromine

Valdecoxib

Warfarin

Xemilofiban

Zolmitriptan

Zomepirac

3.5.1.A Abciximab

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maint
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and antiplatelet agents has been associated with an increased ris
Bleeding events reported have included epistaxis, ecchymosis, hematon
and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, susp
Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

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

7) Probable Mechanism: unknown

3.5.1.B Aceclofenac

1) Interaction Effect: an increased risk of bleeding

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

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

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

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp

those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).

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

3.5.1.C Acemetacin

1) Interaction Effect: an increased risk of bleeding

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

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

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

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).

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

3.5.1.D Acenocoumarol

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main hemostasis. Case-control and cohort studies have shown that the combi SSRIs and anticoagulants has been associated with an increased risk of (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R solution, 2008). Bleeding events reported have included epistaxis, ecchy hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa (including increased bleeding) have been reported with the coadministra with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When escitalopram and an anticoagulant are g concurrently, monitor patients for signs of increased bleeding. Patients v warfarin should be monitored closely for altered anticoagulant effects, in increased bleeding, when escitalopram therapy is initiated or discontinue LEXAPRO(R) oral tablets, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an of clinically relevant bleeding (hospital admission due to bleeding) ir

receiving warfarin for atrial fibrillation during concomitant SSRI thera
weeks following SSRI therapy termination. Patients with a mean ag
years receiving warfarin plus SSRI (n=117) were matched with ranc
patients who received warfarin only (n=117). SSRI included fluoxeti
citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin
experienced 11 bleeding episodes during 213.9 treatment years in t
plus SSRI group, and 10 patients experienced 14 bleedings during
treatment years in the warfarin-only group. The corresponding total
bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel
ratio for first bleedings during treatment with warfarin plus SSRI was
CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir
patients experiencing bleeding at the time of concomitant administra
sertraline or citalopram. The addition of an SSRI was not associatec
change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T
the study may be limited by earlier bleeding events, unknown patier
and exclusion of clopidogrel, dipyridamol, corticosteroids and antico
other than warfarin in the model (Wallerstedt et al, 2009).

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

3.5.1.E Alclofenac

1) Interaction Effect: an increased risk of bleeding

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

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

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

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).

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

3.5.1.F Almotriptan

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: Concomitant use of almotriptan and selective serotonin re
inhibitors (SSRI's) has been reported to cause weakness, hyperreflexia,
incoordination (Prod Info Axert(TM), 2001). Concurrent use of a triptan a

may result in serotonin syndrome which may be life-threatening. Sympto
serotonin syndrome may include restlessness, hallucinations, loss of co
heart beat, rapid changes in blood pressure, increased body temperatur
overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should
triptans may be commonly used intermittently and that either the triptan
may be prescribed by a different physician. Discuss the risks of serotoni
with patients who are prescribed this combination and monitor them clos
symptoms of serotonin syndrome (US Food and Drug Administration, 20
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of a triptan, such as almotript
SSRI may result in a life-threatening condition called serotonin syndrom
that triptans may be commonly used intermittently and that either the trip
SSRI may be prescribed by a different physician. If these agents are use
discuss the risks of serotonin syndrome with the patient and monitor clos
symptoms of serotonin syndrome (restlessness, hyperthermia, hyperrefl
incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in exc
serotonergic stimulation
8) Literature Reports
a) Concomitant administration of fluoxetine and almotriptan is well
fluoxetine has only a modest effect on almotriptan maximum plasma
concentration (Cmax). Other almotriptan pharmacokinetics are not s
affected. A randomized, open-label, two-way crossover study involv
volunteers has been conducted. Subjects received each of the follo
treatments with a minimum 3-week washout between periods: (1) th
fluoxetine capsules on day 1 to 8 and one dose almotriptan 12.5 mg
one dose of almotriptan 12.5 mg on day 8 with no treatment on days
Peak almotriptan concentrations were 18% higher following concom
administration of fluoxetine than after almotriptan administration alo
difference was statistically significant (p equal 0.023). Mean almotrip
under the concentration-time curve (AUC) and oral clearance were
statistically different between treatment groups. Mean half-life was n
different between the treatment groups. During fluoxetine coadminis
was shorter, suggesting that the absorption rate of almotriptan may
increased by fluoxetine. The author concludes that based on the res
study and the lack of effect of fluoxetine on almotriptan pharmacokin
almotriptan and fluoxetine can be safely used concomitantly in migr
management (Fleishaker et al, 2001).

3.5.1.G Anagrelide

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

3.5.1.H Ancrod

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and anticoagulants has been associated with an increased risk of
(Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(P
solution, 2008). Bleeding events reported have included epistaxis, ecchy
hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa
(including increased bleeding) have been reported with the coadministra

with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When escitalopram and an anticoagulant are g concurrently, monitor patients for signs of increased bleeding. Patients v warfarin should be monitored closely for altered anticoagulant effects, in increased bleeding, when escitalopram therapy is initiated or discontinue LEXAPRO(R) oral tablets, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an of clinically relevant bleeding (hospital admission due to bleeding) ir receiving warfarin for atrial fibrillation during concomitant SSRI thera weeks following SSRI therapy termination. Patients with a mean ag years receiving warfarin plus SSRI (n=117) were matched with rand patients who received warfarin only (n=117). SSRI included fluoxeti citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin experienced 11 bleeding episodes during 213.9 treatment years in t plus SSRI group, and 10 patients experienced 14 bleedings during treatment years in the warfarin-only group. The corresponding total bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel ratio for first bleedings during treatment with warfarin plus SSRI was CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir patients experiencing bleeding at the time of concomitant administra sertraline or citalopram. The addition of an SSRI was not associated change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T the study may be limited by earlier bleeding events, unknown patier and exclusion of clopidogrel, dipyridamol, corticosteroids and antico other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin user (acenocoumarol and phenprocoumon) with concomitant selective se reuptake inhibitors (SSRIs) resulted in an increased risk of hospitali nongastrointestinal bleeding. Using national pharmacy and hospitali records, Netherlands researchers identified 1848 cases that were a abnormal bleeding and compared them with 5818 control subjects a coumarins. Median duration of treatment in patients was 220 days (4690 days). Patients on SSRIs showed greater risk for hospitalizatio nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% cor interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleedir OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schaleka 2008).

3.5.1.l Anisindione

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maint hemostasis. Case-control and cohort studies have shown that the combi SSRIs and anticoagulants has been associated with an increased risk of (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R solution, 2008). Bleeding events reported have included epistaxis, ecchy hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa (including increased bleeding) have been reported with the coadministra with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When escitalopram and an anticoagulant are g concurrently, monitor patients for signs of increased bleeding. Patients v warfarin should be monitored closely for altered anticoagulant effects, in increased bleeding, when escitalopram therapy is initiated or discontinue LEXAPRO(R) oral tablets, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an of clinically relevant bleeding (hospital admission due to bleeding) ir

receiving warfarin for atrial fibrillation during concomitant SSRI thera
weeks following SSRI therapy termination. Patients with a mean ag
years receiving warfarin plus SSRI (n=117) were matched with ranc
patients who received warfarin only (n=117). SSRI included fluoxeti
citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin
experienced 11 bleeding episodes during 213.9 treatment years in t
plus SSRI group, and 10 patients experienced 14 bleedings during
treatment years in the warfarin-only group. The corresponding total
bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel
ratio for first bleedings during treatment with warfarin plus SSRI was
CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir
patients experiencing bleeding at the time of concomitant administra
sertraline or citalopram. The addition of an SSRI was not associated
change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T
the study may be limited by earlier bleeding events, unknown patier
and exclusion of clopidogrel, dipyridamol, corticosteroids and antico
other than warfarin in the model (Wallerstedt et al, 2009).

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

3.5.1.J Antithrombin III Human

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and anticoagulants has been associated with an increased risk o
(Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R
solution, 2008). Bleeding events reported have included epistaxis, ecchy
hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa
(including increased bleeding) have been reported with the coadministra
with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table
2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When escitalopram and an anticoagulant are g
concurrently, monitor patients for signs of increased bleeding. Patients v
warfarin should be monitored closely for altered anticoagulant effects, in
increased bleeding, when escitalopram therapy is initiated or discontinue
LEXAPRO(R) oral tablets, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an
of clinically relevant bleeding (hospital admission due to bleeding) ir
receiving warfarin for atrial fibrillation during concomitant SSRI thera
weeks following SSRI therapy termination. Patients with a mean ag
years receiving warfarin plus SSRI (n=117) were matched with ranc
patients who received warfarin only (n=117). SSRI included fluoxeti
citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin
experienced 11 bleeding episodes during 213.9 treatment years in t
plus SSRI group, and 10 patients experienced 14 bleedings during
treatment years in the warfarin-only group. The corresponding total
bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel
ratio for first bleedings during treatment with warfarin plus SSRI was
CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir
patients experiencing bleeding at the time of concomitant administra
sertraline or citalopram. The addition of an SSRI was not associated
change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T

the study may be limited by earlier bleeding events, unknown patier and exclusion of clopidogrel, dipyridamol, corticosteroids and antico other than warfarin in the model (Wallerstedt et al, 2009).

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

3.5.1.K Ardeparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maint hemostasis. Case-control and cohort studies have shown that the combi SSRIs and anticoagulants has been associated with an increased risk of (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R solution, 2008). Bleeding events reported have included epistaxis, ecchy hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa (including increased bleeding) have been reported with the coadministra with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When escitalopram and an anticoagulant are g concurrently, monitor patients for signs of increased bleeding. Patients v warfarin should be monitored closely for altered anticoagulant effects, in increased bleeding, when escitalopram therapy is initiated or discontinue LEXAPRO(R) oral tablets, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an of clinically relevant bleeding (hospital admission due to bleeding) ir receiving warfarin for atrial fibrillation during concomitant SSRI thera weeks following SSRI therapy termination. Patients with a mean age years receiving warfarin plus SSRI (n=117) were matched with rand patients who received warfarin only (n=117). SSRI included fluoxeti citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin experienced 11 bleeding episodes during 213.9 treatment years in t plus SSRI group, and 10 patients experienced 14 bleedings during treatment years in the warfarin-only group. The corresponding total bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel ratio for first bleedings during treatment with warfarin plus SSRI was CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir patients experiencing bleeding at the time of concomitant administra sertraline or citalopram. The addition of an SSRI was not associated change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T the study may be limited by earlier bleeding events, unknown patier and exclusion of clopidogrel, dipyridamol, corticosteroids and antico other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin user (acenocoumarol and phenprocoumon) with concomitant selective se reuptake inhibitors (SSRIs) resulted in an increased risk of hospitali nongastrointestinal bleeding. Using national pharmacy and hospitali records, Netherlands researchers identified 1848 cases that were a abnormal bleeding and compared them with 5818 control subjects a coumarins. Median duration of treatment in patients was 220 days (4690 days). Patients on SSRIs showed greater risk for hospitalizatio nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% cor interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleedir OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schaleka

2008).

3.5.1.L Aspirin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maint hemostasis. Case-control and cohort studies have shown that the combi SSRIs and antiplatelet agents has been associated with an increased ris Bleeding events reported have included epistaxis, ecchymosis, hematon and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, susp Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

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

7) Probable Mechanism: unknown

3.5.1.M Benoxaprofen

1) Interaction Effect: an increased risk of bleeding

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

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

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

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).

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

3.5.1.N Bivalirudin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maint hemostasis. Case-control and cohort studies have shown that the combi SSRIs and anticoagulants has been associated with an increased risk of (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R solution, 2008). Bleeding events reported have included epistaxis, ecchy hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa (including increased bleeding) have been reported with the coadministra with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When escitalopram and an anticoagulant are g concurrently, monitor patients for signs of increased bleeding. Patients v

warfarin should be monitored closely for altered anticoagulant effects, in increased bleeding, when escitalopram therapy is initiated or discontinue LEXAPRO(R) oral tablets, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an of clinically relevant bleeding (hospital admission due to bleeding) ir receiving warfarin for atrial fibrillation during concomitant SSRI thera weeks following SSRI therapy termination. Patients with a mean ag years receiving warfarin plus SSRI (n=117) were matched with ranc patients who received warfarin only (n=117). SSRI included fluoxeti citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin experienced 11 bleeding episodes during 213.9 treatment years in t plus SSRI group, and 10 patients experienced 14 bleedings during treatment years in the warfarin-only group. The corresponding total bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel ratio for first bleedings during treatment with warfarin plus SSRI was CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir patients experiencing bleeding at the time of concomitant administra sertraline or citalopram. The addition of an SSRI was not associated change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T the study may be limited by earlier bleeding events, unknown patier and exclusion of clopidogrel, dipyridamol, corticosteroids and antico other than warfarin in the model (Wallerstedt et al, 2009).

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

3.5.1.O Bromfenac

1) Interaction Effect: an increased risk of bleeding

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

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

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

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as been associated with hallucinations in some patients (Prod Info TOF

oral tablets, 2007).

3.5.1.P Bufexamac

1) Interaction Effect: an increased risk of bleeding

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

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

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

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).

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

3.5.1.Q Cannabis

1) Interaction Effect: manic symptoms

2) Summary: One case of mania following use of marijuana with fluoxet has been reported (Stoll et al, 1991a). Although an interaction is propose authors also state the manic symptoms could have resulted from the fluo marijuana alone. Caution is advised for patients using marijuana and tak or other serotonin reuptake inhibitors.

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Caution patients taking selective serotonin reu inhibitors to avoid concomitant use of marijuana.

7) Probable Mechanism: additive serotonergic stimulation

8) Literature Reports

a) A 21-year-old female presented with mania, agitation, and grand delusions following use of marijuana with fluoxetine therapy. She ha fluoxetine 20 mg daily for 4 weeks and reported smoking 2 "joints" o hour period. Over the next 24 hours, she developed increased ener hypersexuality, pressured speech, and grandiose delusions. Loraze perphenazine were given for agitation and excitement which gradua over 4 days. She remained hospitalized for 36 days. Fluoxetine 20 m other day was reintroduced one week prior to discharge. One week discharge, she discontinued fluoxetine due to insomnia and feeling These symptoms resolved rapidly upon discontinuation of fluoxetine rapid switch to mania after smoking marijuana with fluoxetine, the m symptoms were associated with the concomitant use of fluoxetine a though mania could have developed from either fluoxetine or mariju (Stoll et al, 1991).

3.5.1.R Carprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main hemostasis. Case-control and cohort studies have shown that the combi

SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOR
oral tablets, 2007).

3.5.1.S Celecoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOR
oral tablets, 2007).

3.5.1.T Certoparin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and anticoagulants has been associated with an increased risk o
(Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R
solution, 2008). Bleeding events reported have included epistaxis, ecchy

hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa
(including increased bleeding) have been reported with the coadministra
with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table
2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When escitalopram and an anticoagulant are g
concurrently, monitor patients for signs of increased bleeding. Patients v
warfarin should be monitored closely for altered anticoagulant effects, in
increased bleeding, when escitalopram therapy is initiated or discontinue
LEXAPRO(R) oral tablets, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an
of clinically relevant bleeding (hospital admission due to bleeding) ir
receiving warfarin for atrial fibrillation during concomitant SSRI thera
weeks following SSRI therapy termination. Patients with a mean ag
years receiving warfarin plus SSRI (n=117) were matched with rand
patients who received warfarin only (n=117). SSRI included fluoxeti
citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin
experienced 11 bleeding episodes during 213.9 treatment years in t
plus SSRI group, and 10 patients experienced 14 bleedings during
treatment years in the warfarin-only group. The corresponding total
bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel
ratio for first bleedings during treatment with warfarin plus SSRI was
CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir
patients experiencing bleeding at the time of concomitant administra
sertraline or citalopram. The addition of an SSRI was not associated
change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T
the study may be limited by earlier bleeding events, unknown patier
and exclusion of clopidogrel, dipyridamol, corticosteroids and antico
other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin user
(acenocoumarol and phenprocoumon) with concomitant selective se
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitali
nongastrointestinal bleeding. Using national pharmacy and hospitali
records, Netherlands researchers identified 1848 cases that were a
abnormal bleeding and compared them with 5818 control subjects a
coumarins. Median duration of treatment in patients was 220 days (
4690 days). Patients on SSRIs showed greater risk for hospitalizatio
nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% cor
interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleedir
OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schaleka
2008).

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

3.5.1.V Cimetidine
1) Interaction Effect: increased bioavailability of escitalopram
2) Summary: In a clinical study, citalopram maximum plasma concentra
under the concentration-time curve increased by 39% and 43%, respect

subjects treated for 21 days with racemic citalopram 40 mg/day concurre
8-day regimen of cimetidine 400 mg/day (Prod Info LEXAPRO(R) Oral T
Solution, 2005).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients for signs of escitalopram toxic
serotonin syndrome. Doses of escitalopram may need to be reduced.
7) Probable Mechanism: unknown

3.5.1.W Clonixin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOR
oral tablets, 2007).

3.5.1.X Clopidogrel

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

3.5.1.Y Clorgyline

1) Interaction Effect: CNS toxicity and/or serotonin syndrome (hypertens
hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with esc
a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or sero
syndrome, a hyperserotonergic state characterized by symptoms such a
restlessness, myoclonus, changes in mental status, hyperreflexia, diaph
shivering, and tremor. Serious, even fatal, reactions have been reported

Lexapro(TM), 2002b). Concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of escitalopram and clorgyline contraindicated. Wait at least two weeks after discontinuing a MAO inhib initiating escitalopram therapy. In addition, wait at least five weeks after escitalopram before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoam

3.5.1.Z Cyclobenzaprine
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Clinical symptoms of serotonin syndrome have been repo concurrent use of cyclobenzaprine with escitalopram. (Day & Jeanmono Caution is advised if cyclobenzaprine and escitalopram are coadminister patients for signs and symptoms of serotonin syndrome.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: A case of serotonin syndrome was reported wi concomitant use of cyclobenzaprine and escitalopram, and therefore, co is discouraged (Day & Jeanmonod, 2008).
7) Probable Mechanism: additive serotonergic effects
8) Literature Reports
a) A 27-year-old female admitted to the hospital for possible overdo experienced serotonin syndrome following coadministration of cyclo and escitalopram. The patient stated she had taken "5 or 6" 10 mg cyclobenzaprine tablets and 2 rum beverages the previous evening currently being treated with escitalopram 10 mg daily for mild depre Lortab(R) and cyclobenzaprine as needed for lower back pain. The initially responsive, but quickly became stuporous, marked by eye o pain, nonsensical speech, and localization to painful stimuli. Her ten 101.7, pulse of 140, blood pressure of 159/76, respirations of 24, ar oximetry of 94% on 6 L. Physical exam showed skin flushing, diaph tremors, rigidity in lower extremities, horizontal nystagmus and hype the patella. Laboratory results showed a respiratory acidosis (7.29/5 creatinine kinase fraction of 3862 units/L, serum ethanol of 44 mg/d positive tricyclic and opiate screens. An ECG showed tachycardia w morphology or interval changes. A diagnosis of serotonin syndrome and the patient was treated accordingly. Over the next 12 hours, the temperature, tachycardia, tremors, and creatinine kinase fraction de mental status improved and she was oriented. After a psychiatric ev was discharged with direction to discontinue cyclobenzaprine while escitalopram (Day & Jeanmonod, 2008).

3.5.1.AA Dalteparin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main hemostasis. Case-control and cohort studies have shown that the combi SSRIs and anticoagulants has been associated with an increased risk of (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R solution, 2008). Bleeding events reported have included epistaxis, ecchy hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa (including increased bleeding) have been reported with the coadministra with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When escitalopram and an anticoagulant are g concurrently, monitor patients for signs of increased bleeding. Patients v warfarin should be monitored closely for altered anticoagulant effects, in increased bleeding, when escitalopram therapy is initiated or discontinue LEXAPRO(R) oral tablets, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an

of clinically relevant bleeding (hospital admission due to bleeding) ir
receiving warfarin for atrial fibrillation during concomitant SSRI thera
weeks following SSRI therapy termination. Patients with a mean ag
years receiving warfarin plus SSRI (n=117) were matched with ranc
patients who received warfarin only (n=117). SSRI included fluoxeti
citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin
experienced 11 bleeding episodes during 213.9 treatment years in t
plus SSRI group, and 10 patients experienced 14 bleedings during
treatment years in the warfarin-only group. The corresponding total
bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel
ratio for first bleedings during treatment with warfarin plus SSRI was
CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir
patients experiencing bleeding at the time of concomitant administra
sertraline or citalopram. The addition of an SSRI was not associatec
change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T
the study may be limited by earlier bleeding events, unknown patier
and exclusion of clopidogrel, dipyridamol, corticosteroids and antico
other than warfarin in the model (Wallerstedt et al, 2009).

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

3.5.1.AB Danaparoid

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and anticoagulants has been associated with an increased risk o
(Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R
solution, 2008). Bleeding events reported have included epistaxis, ecchy
hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa
(including increased bleeding) have been reported with the coadministra
with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table
2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When escitalopram and an anticoagulant are g
concurrently, monitor patients for signs of increased bleeding. Patients v
warfarin should be monitored closely for altered anticoagulant effects, in
increased bleeding, when escitalopram therapy is initiated or discontinue
LEXAPRO(R) oral tablets, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an
of clinically relevant bleeding (hospital admission due to bleeding) ir
receiving warfarin for atrial fibrillation during concomitant SSRI thera
weeks following SSRI therapy termination. Patients with a mean ag
years receiving warfarin plus SSRI (n=117) were matched with ranc
patients who received warfarin only (n=117). SSRI included fluoxeti
citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin
experienced 11 bleeding episodes during 213.9 treatment years in t
plus SSRI group, and 10 patients experienced 14 bleedings during
treatment years in the warfarin-only group. The corresponding total
bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel
ratio for first bleedings during treatment with warfarin plus SSRI was
CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir
patients experiencing bleeding at the time of concomitant administra
sertraline or citalopram. The addition of an SSRI was not associatec

change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T
the study may be limited by earlier bleeding events, unknown patier
and exclusion of clopidogrel, dipyridamol, corticosteroids and antico
other than warfarin in the model (Wallerstedt et al, 2009).

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

3.5.1.AC Defibrotide

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and anticoagulants has been associated with an increased risk of
(Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R
solution, 2008). Bleeding events reported have included epistaxis, ecchy
hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa
(including increased bleeding) have been reported with the coadministra
with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table
2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When escitalopram and an anticoagulant are g
concurrently, monitor patients for signs of increased bleeding. Patients v
warfarin should be monitored closely for altered anticoagulant effects, in
increased bleeding, when escitalopram therapy is initiated or discontinue
LEXAPRO(R) oral tablets, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an
of clinically relevant bleeding (hospital admission due to bleeding) ir
receiving warfarin for atrial fibrillation during concomitant SSRI thera
weeks following SSRI therapy termination. Patients with a mean age
years receiving warfarin plus SSRI (n=117) were matched with rand
patients who received warfarin only (n=117). SSRI included fluoxeti
citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin
experienced 11 bleeding episodes during 213.9 treatment years in t
plus SSRI group, and 10 patients experienced 14 bleedings during 5
treatment years in the warfarin-only group. The corresponding total
bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel
ratio for first bleedings during treatment with warfarin plus SSRI was
CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir
patients experiencing bleeding at the time of concomitant administra
sertraline or citalopram. The addition of an SSRI was not associated
change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T
the study may be limited by earlier bleeding events, unknown patier
and exclusion of clopidogrel, dipyridamol, corticosteroids and antico
other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin user
(acenocoumarol and phenprocoumon) with concomitant selective se
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitali
nongastrointestinal bleeding. Using national pharmacy and hospitali
records, Netherlands researchers identified 1848 cases that were a
abnormal bleeding and compared them with 5818 control subjects a
coumarins. Median duration of treatment in patients was 220 days (
4690 days). Patients on SSRIs showed greater risk for hospitalizatio
nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% cor
interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleedir

OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schaleka 2008).

3.5.1.AD Dehydroepiandrosterone

1) Interaction Effect: development of manic symptoms

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

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use of dehydroepiandroster and selective serotonin reuptake inhibitors. If patients present with mani (i.e. agitation, anger, irritability, aggressive behavior), determine if the pa DHEA and discontinue DHEA.

7) Probable Mechanism: serotonergic activity of dehydroepiandrosteron increased androgen levels

8) Literature Reports

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

3.5.1.AE Dermatan Sulfate

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maint hemostasis. Case-control and cohort studies have shown that the combi SSRIs and anticoagulants has been associated with an increased risk of (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R solution, 2008). Bleeding events reported have included epistaxis, ecchy hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa (including increased bleeding) have been reported with the coadministra with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When escitalopram and an anticoagulant are g concurrently, monitor patients for signs of increased bleeding. Patients v warfarin should be monitored closely for altered anticoagulant effects, in increased bleeding, when escitalopram therapy is initiated or discontinue LEXAPRO(R) oral tablets, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an of clinically relevant bleeding (hospital admission due to bleeding) in receiving warfarin for atrial fibrillation during concomitant SSRI thera

weeks following SSRI therapy termination. Patients with a mean ag
years receiving warfarin plus SSRI (n=117) were matched with ranc
patients who received warfarin only (n=117). SSRI included fluoxeti
citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin
experienced 11 bleeding episodes during 213.9 treatment years in t
plus SSRI group, and 10 patients experienced 14 bleedings during
treatment years in the warfarin-only group. The corresponding total
bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel
ratio for first bleedings during treatment with warfarin plus SSRI was
CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir
patients experiencing bleeding at the time of concomitant administra
sertraline or citalopram. The addition of an SSRI was not associatec
change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T
the study may be limited by earlier bleeding events, unknown patier
and exclusion of clopidogrel, dipyridamol, corticosteroids and antico
other than warfarin in the model (Wallerstedt et al, 2009).

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

3.5.1.AF Desipramine

1) Interaction Effect: increase in the bioavailability and plasma concentr
desipramine

2) Summary: Desipramine plasma concentration and area under the co
time curve increased by 40% and 100%, respectively, when a single dos
desipramine 50 milligrams (mg) was administered concurrently with a 21
of escitalopram 20 mg/day (Prod Info LEXAPRO(R) Oral Tablet, Oral Sc

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Caution is indicated in the coadministration of
and escitalopram due to the risk for increased desipramine plasma conc

7) Probable Mechanism: escitalopram inhibition of cytochrome P450-2D
desipramine metabolism

3.5.1.AG Desirudin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and anticoagulants has been associated with an increased risk of
(Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R
solution, 2008). Bleeding events reported have included epistaxis, ecchy
hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa
(including increased bleeding) have been reported with the coadministra
with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table
2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When escitalopram and an anticoagulant are g
concurrently, monitor patients for signs of increased bleeding. Patients v
warfarin should be monitored closely for altered anticoagulant effects, in
increased bleeding, when escitalopram therapy is initiated or discontinue
LEXAPRO(R) oral tablets, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an
of clinically relevant bleeding (hospital admission due to bleeding) ir

receiving warfarin for atrial fibrillation during concomitant SSRI thera
weeks following SSRI therapy termination. Patients with a mean ag
years receiving warfarin plus SSRI (n=117) were matched with ranc
patients who received warfarin only (n=117). SSRI included fluoxeti
citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin
experienced 11 bleeding episodes during 213.9 treatment years in t
plus SSRI group, and 10 patients experienced 14 bleedings during
treatment years in the warfarin-only group. The corresponding total
bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel
ratio for first bleedings during treatment with warfarin plus SSRI was
CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir
patients experiencing bleeding at the time of concomitant administra
sertraline or citalopram. The addition of an SSRI was not associatec
change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T
the study may be limited by earlier bleeding events, unknown patier
and exclusion of clopidogrel, dipyridamol, corticosteroids and antico
other than warfarin in the model (Wallerstedt et al, 2009).

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

3.5.1.AH Desvenlafaxine

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

2) Summary: Concurrent use of desvenlafaxine and a selective seroton
inhibitor (SSRI) may result in serotonin syndrome, which may be life-thre
Symptoms of serotonin syndrome may include restlessness, hallucinatio
coordination, fast heart beat, rapid changes in blood pressure, increasec
temperature, overreactive reflexes, nausea, vomiting, and diarrhea (Proc
PRISTIQ(TM) oral extended-release tablets, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of desvenlafaxine and an SS
in a life-threatening condition called serotonin syndrome. If these agents
together, discuss the risks of serotonin syndrome with the patient and m
for symptoms of serotonin syndrome (restlessness, hyperthermia, hyper
incoordination), especially during treatment initiation and dose increases
PRISTIQ(TM) oral extended-release tablets, 2008).

7) Probable Mechanism: additive serotonergic effect

3.5.1.AI Dexketoprofen

1) Interaction Effect: an increased risk of bleeding

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

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

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

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th

potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).

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

3.5.1.AJ Diclofenac

1) Interaction Effect: an increased risk of bleeding

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

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

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

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).

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

3.5.1.AK Dicumarol

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and anticoagulants has been associated with an increased risk of
(Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(F
solution, 2008). Bleeding events reported have included epistaxis, ecchy
hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa
(including increased bleeding) have been reported with the coadministra
with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table
2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When escitalopram and an anticoagulant are g
concurrently, monitor patients for signs of increased bleeding. Patients v
warfarin should be monitored closely for altered anticoagulant effects, in
increased bleeding, when escitalopram therapy is initiated or discontinue
LEXAPRO(R) oral tablets, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an of clinically relevant bleeding (hospital admission due to bleeding) ir receiving warfarin for atrial fibrillation during concomitant SSRI thera weeks following SSRI therapy termination. Patients with a mean ag years receiving warfarin plus SSRI (n=117) were matched with ranc patients who received warfarin only (n=117). SSRI included fluoxeti citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin experienced 11 bleeding episodes during 213.9 treatment years in t plus SSRI group, and 10 patients experienced 14 bleedings during treatment years in the warfarin-only group. The corresponding total bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel ratio for first bleedings during treatment with warfarin plus SSRI was CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir patients experiencing bleeding at the time of concomitant administra sertraline or citalopram. The addition of an SSRI was not associatec change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T the study may be limited by earlier bleeding events, unknown patier and exclusion of clopidogrel, dipyridamol, corticosteroids and antico other than warfarin in the model (Wallerstedt et al, 2009).

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

3.5.1.AL Diflunisal

1) Interaction Effect: an increased risk of bleeding

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

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

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

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).

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

3.5.1.AM Dipyridamole

1) Interaction Effect: an increased risk of bleeding

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

3.5.1.AN Dipyrone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maint
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOR
oral tablets, 2007).

3.5.1.AO Droxicam

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

those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).

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

3.5.1.AP Duloxetine

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: Duloxetine is a selective serotonin and norepinephrine reu inhibitor. The concomitant use of duloxetine with escitalopram, a selectiv reuptake inhibitor, is not recommended due to the potential for serotonin (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of duloxetine and escitalo recommended due to the potential for development of serotonin syndron CYMBALTA(R) delayed-release oral capsules, 2008).

7) Probable Mechanism: additive serotonergic effects

3.5.1.AQ Eletriptan

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: There have been case reports of weakness, hyperreflexia incoordination following concomitant use of sumatriptan, a 5-hydroxytryp (5HT-1) agonist, and a serotonin specific reuptake inhibitor (SSRI) (Proc (R) Nasal Spray, 2003). Because eletriptan is a 5HT 1B/1D agonist, a si interaction between SSRIs and eletriptan may occur (Prod Info Relpax(R Concurrent use of a triptan and an SSRI may result in serotonin syndron be life-threatening. Symptoms of serotonin syndrome may include restle hallucinations, loss of coordination, fast heart beat, rapid changes in blo increased body temperature, overreactive reflexes, nausea, vomiting, ar Clinicians should be aware that triptans may be commonly used intermit either the triptan or the SSRI may be prescribed by a different physician risks of serotonin syndrome with patients who are prescribed this combi monitor them closely for symptoms of serotonin syndrome (US Food and Administration, 2006).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Coadministration of a triptan, such as eletriptan SSRI may result in a life-threatening condition called serotonin syndrom that triptans may be commonly used intermittently and that either the trip SSRI may be prescribed by a different physician. If these agents are use discuss the risks of serotonin syndrome with the patient and monitor clos symptoms of serotonin syndrome (restlessness, hyperthermia, hyperrefl incoordination).

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

3.5.1.AR Enoxaparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main hemostasis. Case-control and cohort studies have shown that the combi SSRIs and anticoagulants has been associated with an increased risk of (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R solution, 2008). Bleeding events reported have included epistaxis, ecchy hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa (including increased bleeding) have been reported with the coadministra with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table 2008).

3) Severity: major

4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When escitalopram and an anticoagulant are g concurrently, monitor patients for signs of increased bleeding. Patients v warfarin should be monitored closely for altered anticoagulant effects, in increased bleeding, when escitalopram therapy is initiated or discontinue LEXAPRO(R) oral tablets, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an of clinically relevant bleeding (hospital admission due to bleeding) ir receiving warfarin for atrial fibrillation during concomitant SSRI thera weeks following SSRI therapy termination. Patients with a mean ag years receiving warfarin plus SSRI (n=117) were matched with ranc patients who received warfarin only (n=117). SSRI included fluoxeti citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin experienced 11 bleeding episodes during 213.9 treatment years in t plus SSRI group, and 10 patients experienced 14 bleedings during treatment years in the warfarin-only group. The corresponding total bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel ratio for first bleedings during treatment with warfarin plus SSRI was CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir patients experiencing bleeding at the time of concomitant administra sertraline or citalopram. The addition of an SSRI was not associatec change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T the study may be limited by earlier bleeding events, unknown patier and exclusion of clopidogrel, dipyridamol, corticosteroids and antico other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin user (acenocoumarol and phenprocoumon) with concomitant selective se reuptake inhibitors (SSRIs) resulted in an increased risk of hospitali nongastrointestinal bleeding. Using national pharmacy and hospitali records, Netherlands researchers identified 1848 cases that were a abnormal bleeding and compared them with 5818 control subjects a coumarins. Median duration of treatment in patients was 220 days (4690 days). Patients on SSRIs showed greater risk for hospitalizatic nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% cor interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleedir OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schaleka 2008).

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

3.5.1.AT Eptifibatide
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main hemostasis. Case-control and cohort studies have shown that the combi SSRIs and antiplatelet agents has been associated with an increased ris Bleeding events reported have included epistaxis, ecchymosis, hematon and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, susp Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution
3) Severity: major

4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are g
concurrently, monitor patient for signs of increased bleeding (Prod Info F
tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayec
capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.AU Etodolac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOF
oral tablets, 2007).

3.5.1.AV Etofenamate

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased

further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as t
been associated with hallucinations in some patients (Prod Info TOF
oral tablets, 2007).

3.5.1.AW Etoricoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as t
been associated with hallucinations in some patients (Prod Info TOF
oral tablets, 2007).

3.5.1.AX Felbinac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as t
been associated with hallucinations in some patients (Prod Info TOF

oral tablets, 2007).

3.5.1.AY Fenbufen

1) Interaction Effect: an increased risk of bleeding

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

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

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

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).

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

3.5.1.AZ Fenoprofen

1) Interaction Effect: an increased risk of bleeding

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

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

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

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).

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

3.5.1.BA Fentiazac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOR
oral tablets, 2007).

3.5.1.BB Floctafenine

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOR
oral tablets, 2007).

3.5.1.BC Flufenamic Acid

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi

SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOR
oral tablets, 2007).

3.5.1.BD Flurbiprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOR
oral tablets, 2007).

3.5.1.BE Fondaparinux

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and anticoagulants has been associated with an increased risk o
(Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R
solution, 2008). Bleeding events reported have included epistaxis, ecchy

hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa
(including increased bleeding) have been reported with the coadministra
with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table
2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When escitalopram and an anticoagulant are g
concurrently, monitor patients for signs of increased bleeding. Patients v
warfarin should be monitored closely for altered anticoagulant effects, in
increased bleeding, when escitalopram therapy is initiated or discontinue
LEXAPRO(R) oral tablets, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an
of clinically relevant bleeding (hospital admission due to bleeding) ir
receiving warfarin for atrial fibrillation during concomitant SSRI thera
weeks following SSRI therapy termination. Patients with a mean ag
years receiving warfarin plus SSRI (n=117) were matched with rand
patients who received warfarin only (n=117). SSRI included fluoxeti
citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin
experienced 11 bleeding episodes during 213.9 treatment years in t
plus SSRI group, and 10 patients experienced 14 bleedings during
treatment years in the warfarin-only group. The corresponding total
bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel
ratio for first bleedings during treatment with warfarin plus SSRI was
CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir
patients experiencing bleeding at the time of concomitant administra
sertraline or citalopram. The addition of an SSRI was not associated
change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T
the study may be limited by earlier bleeding events, unknown patier
and exclusion of clopidogrel, dipyridamol, corticosteroids and antico
other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin user
(acenocoumarol and phenprocoumon) with concomitant selective se
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitali
nongastrointestinal bleeding. Using national pharmacy and hospitali
records, Netherlands researchers identified 1848 cases that were a
abnormal bleeding and compared them with 5818 control subjects a
coumarins. Median duration of treatment in patients was 220 days (
4690 days). Patients on SSRIs showed greater risk for hospitalizatio
nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% cor
interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleedir
OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schaleka
2008).

3.5.1.BF Frovatriptan
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: There have been case reports of weakness, hyperreflexia
incoordination following concomitant use of sumatriptan, a 5-hydroxytryp
(5HT-1) agonist, and a serotonin specific reuptake inhibitor (SSRI) (Proc
(R) Nasal Spray, 2003). Because frovatriptan is a 5HT 1B/1D agonist, a
interaction between SSRIs and frovatriptan may occur (Prod Info Frova(
Concurrent use of frovatriptan and an SSRI may result in serotonin synd
may be life-threatening. Symptoms of serotonin syndrome may include r
hallucinations, loss of coordination, fast heart beat, rapid changes in blo
increased body temperature, overreactive reflexes, nausea, vomiting, ar
Clinicians should be aware that triptans may be commonly used intermit
either the triptan or the SSRI may be prescribed by a different physician.
risks of serotonin syndrome with patients who are prescribed this combi
monitor them closely for symptoms of serotonin syndrome (US Food and
Administration, 2006).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as frovatrip
SSRI may result in a life-threatening condition called serotonin syndrom

that triptans may be commonly used intermittently and that either the trip
SSRI may be prescribed by a different physician. If these agents are use
discuss the risks of serotonin syndrome with the patient and monitor clos
symptoms of serotonin syndrome (restlessness, hyperthermia, hyperrefl
incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in exc
serotonergic stimulation

3.5.1.BG Furazolidone

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

3.5.1.BH Ginkgo

1) Interaction Effect: increased risk of serotonin syndrome (hypertensio
hyperthermia, myoclonus, mental status changes)
2) Summary: The addition of Ginkgo biloba and/or St. John's Wort to th
buspirone and fluoxetine may have precipitated a hypomanic episode in
(Spinella & Eaton, 2002a). It is unclear if Ginkgo or St. John's Wort, the
both, or other patient factors, contributed to the effect. Theoretically, Gin
increase the risk of serotonin syndrome when taken with selective seroto
inhibitors (SSRIs). Caution is advised, especially when ginkgo is taken to
sexual dysfunction associated with SSRIs. Ginkgo may inhibit monoamin
(Sloley et al, 2000; White et al, 1996), and has demonstrated serotonerg
animals (Ramassamy et al, 1992) which might increase the risk of seroto
when ginkgo is combined with SSRIs. The potential MAO inhibitory activ
is questionable. A human study did not show MAO inhibition in the brain
consumption (Fowler et al, 2000). Ginkgo biloba extract inhibited MAO-A
the rat brain in vitro (Sloley et al, 2000; White et al, 1996) and MAO-B in
platelets in vitro (White et al, 1996). No significant MAO inhibition was fo
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 seroto
if ginkgo is combined with selective serotonin reuptake inhibitors (SSRIs
7) Probable Mechanism: additive pharmacologic effects resulting in exc
serotonergic stimulation
8) Literature Reports
a) A 42-year-old female experienced symptoms consistent with a m
hypomanic episode following concomitant use of fluoxetine, buspiro
biloba, and St. John's Wort. The symptoms resolved following disco
Ginkgo and St. John's Wort. The patient was being treated for depre
following a mild traumatic brain injury with fluoxetine 20 milligrams (
daily and buspirone 15 mg twice daily. Several weeks prior to prese
buspirone was increased to 20 mg twice daily for persistent anxiety
patient began taking Ginkgo biloba, melatonin, and St. John's Wort
doses. Melatonin was considered unlikely to have contributed to her
Ginkgo and St. John's Wort were considered possible contributors s
potentiate antidepressants, and considering the temporal relationsh
the use of the herbs and onset of symptoms and discontinuation of

resolution of symptoms. However, the brain injury was considered a contributor (Spinella & Eaton, 2002).

3.5.1.BI Heparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maint hemostasis. Case-control and cohort studies have shown that the combi SSRIs and anticoagulants has been associated with an increased risk of (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R solution, 2008). Bleeding events reported have included epistaxis, ecchy hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa (including increased bleeding) have been reported with the coadministra with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When escitalopram and an anticoagulant are g concurrently, monitor patients for signs of increased bleeding. Patients v warfarin should be monitored closely for altered anticoagulant effects, in increased bleeding, when escitalopram therapy is initiated or discontinue LEXAPRO(R) oral tablets, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an of clinically relevant bleeding (hospital admission due to bleeding) ir receiving warfarin for atrial fibrillation during concomitant SSRI thera weeks following SSRI therapy termination. Patients with a mean age years receiving warfarin plus SSRI (n=117) were matched with rand patients who received warfarin only (n=117). SSRI included fluoxeti citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin experienced 11 bleeding episodes during 213.9 treatment years in t plus SSRI group, and 10 patients experienced 14 bleedings during 5 treatment years in the warfarin-only group. The corresponding total bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel ratio for first bleedings during treatment with warfarin plus SSRI was CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir patients experiencing bleeding at the time of concomitant administra sertraline or citalopram. The addition of an SSRI was not associated change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T the study may be limited by earlier bleeding events, unknown patier and exclusion of clopidogrel, dipyridamol, corticosteroids and antico other than warfarin in the model (Wallerstedt et al, 2009).

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

3.5.1.BJ Hydrocodone

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

2) Summary: Coadministration of escitalopram and hydrocodone has re development of visual hallucinations in a 90-year-old woman. While no c symptoms suggestive of serotonin syndrome were reported for this patie symptoms such as visual hallucinations are usually reported less commo serotonin syndrome (approximately 10% of cases). Clinical symptoms of syndrome have been reported with concurrent use of escitalopram with c (Gnanadesigan et al, 2005). Caution is advised if escitalopram and hydr coadministered. Monitor patients for signs and symptoms of serotonin sy

(tachycardia, hyperthermia, myoclonus, mental status changes).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant administration of escitalopram an hydrocodone may increase the risk of developing serotonin syndrome. If are coadministered, monitor patients for symptoms of serotonin syndrom (tachycardia, hyperthermia, myoclonus, mental status changes).
7) Probable Mechanism: additive pharmacologic effects resulting in exc serotonergic stimulation
8) Literature Reports
a) Visual hallucinations developed in an 90-year-old woman followi administration of hydrocodone and escitalopram. The woman was b with hydrocodone and citalopram 10 mg/day. Citalopram was chang escitalopram 10 mg once daily and a few weeks later, the patient be experiencing visual hallucinations. Improvement in pain symptoms c hydrocodone to be subsequently discontinued. One month later, the hallucinations had resolved. Prior to escitalopram therapy, the patie treated with paroxetine and later, citalopram along with the same hy dose. However, this had not resulted in any hallucinations or any se syndrome-related symptoms (Gnanadesigan et al, 2005).

3.5.1.BK Hydroxytryptophan

1) Interaction Effect: an increased risk of serotonin syndrome (hyperten hyperthermia, myoclonus, mental status changes)
2) Summary: Hydroxytryptophan (5-HTP) may potentiate the serotonerg selective serotonin reuptake inhibitors (SSRIs) (Meltzer et al, 1997a). Si increases serotonin levels, when combined with an SSRI, the serotonin increased sufficiently to produce serotonin syndrome. Caution is advised concomitant use of 5-HTP and SSRIs.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: No cases have been reported of serotonin syn resulting from this combination. Caution is advised if hydroxytryptophan selective serotonin reuptake inhibitor (SSRI) are used concomitantly. Mo patient for early signs of serotonin syndrome such as anxiety, confusion, disorientation.
7) Probable Mechanism: additive serotonergic effect
8) Literature Reports
a) Hydroxytryptophan (5-HTP) (200 milligrams (mg) orally) as a sin increased plasma cortisol and prolactin levels in both medicated and unmedicated patients with major depression or obsessive compulsiv (OCD). These responses were greater if the patient was also taking = 16) (p less than 0.0001). Mean fluoxetine dose for depressed pati mg/day,and for OCD patients it was 60 mg/day. Cortisol or prolactin in patients taking 5-HTP with tricyclic antidepressants (n = 14) or the no medication (n = 83) were not significantly different from each oth measurement of serotonergic effects of antidepressants can be eva measuring hypothalamic-pituitary-adrenal (HPA) axis or PRL respon clinical manifestations of serotonin syndrome were reported in patie HTP concomitantly with fluoxetine (Meltzer et al, 1997).

3.5.1.BL Ibuprofen

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

7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as been associated with hallucinations in some patients (Prod Info TOR oral tablets, 2007).

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

3.5.1.BN Indomethacin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main hemostasis. Case-control and cohort studies have shown that the combi SSRIs and NSAIDs has been associated with an increased risk of bleed events have included epistaxis, ecchymosis, hematoma, petechiae, and threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as been associated with hallucinations in some patients (Prod Info TOR oral tablets, 2007).

3.5.1.BO Indoprofen

1) Interaction Effect: an increased risk of bleeding

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

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

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

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).

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

3.5.1.BP Isocarboxazid

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

2) Summary: Concurrent administration or overlapping therapy with esc a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or sero syndrome, a hyperserotonergic state characterized by symptoms such a restlessness, myoclonus, changes in mental status, hyperreflexia, diaph shivering, and tremor. Serious, even fatal, reactions have been reported Lexapro(TM), 2002a). Concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of escitalopram and isocarbox contraindicated. Wait at least two weeks after discontinuing a MAO inhib initiating escitalopram therapy. In addition, wait at least five weeks after escitalopram before initiating therapy with a MAO inhibitor.

7) Probable Mechanism: inhibition of serotonin metabolism by monoam

3.5.1.BQ Isoxicam

1) Interaction Effect: an increased risk of bleeding

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

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

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

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th

potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).

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

3.5.1.BR Ketoconazole

1) Interaction Effect: decreased ketoconazole bioavailability

2) Summary: Concomitant administration of escitalopram 40 milligrams
ketoconazole 200 mg induced reductions in ketoconazole maximum plas
concentrations and area under the concentration-time curve by 21% and
respectively; escitalopram pharmacokinetics were unaffected by coadmi
(Prod Info LEXAPRO(R) Oral Tablet, Oral Solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: If concurrent therapy is required, a dosage adj
be required for ketoconazole in order to achieve and maintain a consiste
effect.

7) Probable Mechanism: unknown

3.5.1.BS Ketoprofen

1) Interaction Effect: an increased risk of bleeding

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

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

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

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).

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

3.5.1.BT Ketorolac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed

events have included epistaxis, ecchymosis, hematoma, petechiae, and threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as been associated with hallucinations in some patients (Prod Info TOR oral tablets, 2007).

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

3.5.1.BV Lamotrigine
1) Interaction Effect: an increased risk of myoclonus
2) Summary: Myoclonus occurred in 2 patients receiving escitalopram a lamotrigine concomitantly, where symptoms resolved following withdraw escitalopram in 1 patient. There was no evidence of a metabolic enzyme with lamotrigine, and the interaction was believed to be due to an additiv effect of lamotrigine and escitalopram on the 5-HT1A receptors, or by ar inhibition of voltage-gated calcium channels by both agents (Rosenhage Exercise caution when using both drugs concurrently and monitor for sig symptoms of myoclonus including involuntary twitching and jerking.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Use caution if escitalopram and lamotrigine are concurrently as this resulted in myoclonus in 2 patients. In one patient, n resolved after escitalopram was withdrawn (Rosenhagen et al, 2006). M signs and symptoms of myoclonus including involuntary twitching and je
7) Probable Mechanism: additive inhibition of voltage-gated calcium cha additive or synergistic effects on the 5-HT1A receptor
8) Literature Reports
a) Myoclonus occurred in 2 patients following concomitant treatmer escitalopram and lamotrigine. The first patient, a 22-year-old woma escitalopram 30 mg/day for depression, developed daytime and nig

myoclonus after 8 weeks of receiving lamotrigine (titrated to 100 mg treatment of bipolar type II disorder. Serum levels of both drugs, me the onset of myoclonus, were within the expected drug reference ra escitalopram levels remained stable compared to a baseline level d starting lamotrigine therapy. Neither drug was discontinued and the continued to have myoclonus while on escitalopram and lamotrigine Further analysis revealed that the patient was a normal metabolizer CYP2C19, and CYP2D6 enzymes. The second patient, a 28-year-o taking lamotrigine 300 mg/day for a seizure disorder, developed day nighttime myoclonus after 2 weeks of receiving escitalopram (titrate mg/day) for generalized anxiety disorder. For 6 months, the patient the same frequency of myoclonus while on both therapies; however myoclonus resolved 2 weeks after escitalopram was withdrawn. Lar serum levels, measured at the onset and after the myoclonus resolv change. Although escitalopram is metabolized by hepatic enzymes CYP2C19, and CYP2D6, there was no evidence of a metabolic enz interaction with lamotrigine. It was postulated that the myoclonus ma caused by an additive or synergistic effect of lamotrigine and escital 5-HT1A receptors, or by an additive inhibition of voltage-gated calci by both agents (Rosenhagen et al, 2006).

3.5.1.BW Lazabemide

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

2) Summary: Concurrent administration or overlapping therapy with esc a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or sero syndrome, a hyperserotonergic state characterized by symptoms such a restlessness, myoclonus, changes in mental status, hyperreflexia, diaph shivering, and tremor. Serious, even fatal, reactions have been reported Lexapro(TM), 2002d). Concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of escitalopram and lazabemic contraindicated. Wait at least two weeks after discontinuing a MAO inhib initiating escitalopram therapy. In addition, wait at least five weeks after escitalopram before initiating therapy with a MAO inhibitor.

7) Probable Mechanism: inhibition of serotonin metabolism by monoam

3.5.1.BX Lexipafant

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maint hemostasis. Case-control and cohort studies have shown that the combi SSRIs and antiplatelet agents has been associated with an increased ris Bleeding events reported have included epistaxis, ecchymosis, hematon and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, susp Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

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

7) Probable Mechanism: unknown

3.5.1.BY Linezolid

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

2) Summary: Linezolid is a reversible, nonselective inhibitor of monoam Concurrent administration or overlapping therapy with escitalopram and oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrom hyperserotonergic state characterized by symptoms such as restlessnes changes in mental status, hyperreflexia, diaphoresis, shivering, and trem even fatal, reactions have been reported. There have been spontaneous serotonin syndrome associated with concomitant use of linezolid and se agents (Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension, 2

Info Lexapro(R), 2002). If escitalopram and linezolid are used concomita
closely for symptoms of serotonin syndrome. Serotonin syndrome can b
threatening. If serotonin syndrome develops, discontinue the offending a
provide supportive care and other therapy as necessary (Boyer & Shanr
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Unless carefully monitored for serotonin syndr
should not be administered to patients taking escitalopram (Prod Info ZY
injection, oral tablets, oral suspension, 2008) If escitalopram and linezoli
concomitantly, monitor closely for symptoms of serotonin syndrome such
neuromuscular abnormalities (including hyper-reflexia, tremor, muscle ri
peripheral hypertonicity, and shivering), autonomic hyperactivity (includi
tachycardia, mydriasis, diaphoresis, and diarrhea), and mental status ch
(including agitation and delirium). Serotonin syndrome can be life-threate
serotonin syndrome develops, discontinue the offending agents and pro
supportive care and other therapy as necessary (Boyer & Shannon, 200
7) Probable Mechanism: inhibition of serotonin metabolism by monoam

3.5.1.BZ Lithium

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

lithium toxicity in this patient was obscured by the fact that the lithiu
reduced at the time of fluoxetine withdrawal.
b) A 53-year old woman who had been taking fluoxetine 20 mg dail
lorazepam 0.5 mg four times daily for a major depressive disorder h
mg per day added to her regimen in order to augment her response
Within 48 hours, the patient became confused, ataxic, and develope
tremor in her right arm. Vital signs showed a rectal temperature of 1
and laboratory values were normal except for an elevated leukocyte
slightly elevated bilirubin level. After discontinuation of lithium and fl
patient's symptoms resolved over the next four days. At no point dic
levels reach a toxic level, suggesting that the patient's symptoms w
toxic reaction between fluoxetine and lithium (Noveske et al, 1989).
c) Serotonin syndrome was precipitated when lithium 300 mg twice
added to a three-month regimen of fluoxetine 40 mg per day. Five d
patient's lithium level was measured at 0.65 mEq/L and the dose wa
to 300 mg three times daily. Two days after this dosage change, the
experienced akathisia, myoclonus, hyperreflexia, shivering, tremor,
incoordination. After discontinuation of lithium and initiation of cypro
therapy, the patient's symptoms began to improve. The patient was
on a regimen of fluoxetine 40 mg per day without further symptoms
syndrome (Muly et al, 1993).
d) Eight healthy male volunteers completed three phases of an inte
to determine the effects of coadministered lithium and citalopram. A
were extensive metabolizers of sparteine, indicating normal cytochr
2D6 enzyme activity. Although lithium is not influenced by drug oxid
citalopram metabolites are excreted by the kidney, as is lithium. Eac
received citalopram 40 mg alone as a single daily dose for 10 days,
mmol (1980 mg) alone daily for five days, and lithium coadministere
citalopram on days 3-7. At least two weeks separated each treatme
Results showed that the concurrent administration of citalopram and
not significantly alter the pharmacokinetics of lithium (Gram et al, 19
e) Twenty-four patients experiencing depression (DSM III criteria) v
randomized under double-blind conditions to receive citalopram (40
daily) and lithium carbonate (800 mg daily) or placebo. All of the sub
failed to respond to four weeks of citalopram monotherapy. Lithium
coadministered on days 29 to 42. No evidence of a pharmacokinetic
between lithium and citalopram was noted, and cotherapy was well
(Baumann et al, 1996).
f) Serotonin syndrome was described in a 53-year-old patient who
on lithium 1400 mg daily (serum level 0.71 mmol/L) and was given f
50 mg daily. Over a 10-day period the fluvoxamine dose was increa
daily; tremor and difficulty with fine hand movements developed. Aft
tremor, impaired motor function coordination, marked bilateral hype
biceps and knee jerks, and clonus in both ankles were seen. After 1
continued therapy, during which time no further deterioration occurr
nortriptyline 100 mg daily replaced fluvoxamine, and the neuromusc
symptoms abated over a 2-week period. After four weeks the patier
neurological exam was normal (Ohman & Spigset, 1993).
g) Three cases of mania were reported in patients who were treate
and fluvoxamine. The mania appeared 10 days, four weeks, and fiv
respectively, after cotherapy was begun. Fluvoxamine was discontir
two of the three patients, the mania resolved, and successful treatm
depression occurred with lithium alone. The third patient improved,
depression reappeared within a month of fluvoxamine discontinuatic
al, 1991).
h) In an open-labeled, placebo-controlled study, lithium 600 mg wa
administered to 16 subjects orally twice daily on days one through e
in the morning on day nine. In addition, oral sertraline 100 mg or pla
given twice, ten hours and two hours prior to lithium dosing on day r
steady-state lithium level was only decreased by 1.4% (0.01 mEq/L)
lithium renal clearance increased by 6.9% (0.11 L/hour) when sertra
coadministered. Seven subjects experienced side effects, mainly tre
receiving lithium and sertraline, whereas no subjects who ingested p
lithium experienced side effects (Wilner et al, 1991).

3.5.1.CA Lornoxicam

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maint
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOF
oral tablets, 2007).

3.5.1.CB Meclofenamate

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maint
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOF
oral tablets, 2007).

3.5.1.CC Mefenamic Acid

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

events have included epistaxis, ecchymosis, hematoma, petechiae, and threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as been associated with hallucinations in some patients (Prod Info TOF oral tablets, 2007).

3.5.1.CD Meloxicam

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main hemostasis. Case-control and cohort studies have shown that the combi SSRIs and NSAIDs has been associated with an increased risk of bleed events have included epistaxis, ecchymosis, hematoma, petechiae, and threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as been associated with hallucinations in some patients (Prod Info TOF oral tablets, 2007).

3.5.1.CE Methylphenidate

1) Interaction Effect: increased selective serotonin reuptake inhibitor pla concentrations
2) Summary: Human pharmacologic studies have demonstrated that me may inhibit the metabolism of selective serotonin reuptake inhibitors (SS Downward dose adjustments of the SSRI may be necessary when it is u concurrently with methylphenidate. Additionally, when initiating or discor methylphenidate, the SSRI dose may need to be adjusted as needed (P

METADATE CD(R) extended-release oral capsules, 2007).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing methylphenidate who take an selective serotonin reuptake inhibitor (SSRI). Concomitant u methylphenidate and an SSRI may cause elevated SSRI plasma concer Consider a decrease in the dose of SSRI when these agents are coadm Additionally, consider adjusting the SSRI dose if necessary when initiatir discontinuing methylphenidate therapy (Prod Info METADATE CD(R) ex release oral capsules, 2007).
7) Probable Mechanism: inhibition of selective serotonin reuptake inhibi metabolism by methylphenidate

3.5.1.CF Metoprolol
1) Interaction Effect: increased metoprolol plasma concentrations and p metoprolol cardioselectivity
2) Summary: Administration of a single dose of metoprolol 100 milligran following administration of escitalopram 20 mg daily for 21 days produce 50% and 82% in metoprolol maximum plasma concentrations and area u concentration-time curve, respectively. No clinically significant changes i pressure or heart rate were observed; however, increased metoprolol pl have been associated with decreased cardioselectivity (Prod Info LEXAI Tablet, Oral Solution, 2005).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Patients stabilized on metoprolol who are adm escitalopram should be observed for signs of increased beta blockade s bradycardia, hypotension or heart failure. At higher metoprolol concentra cardioselectivity may be diminished; monitor appropriate measures of di when escitalopram and metoprolol are used concomitantly.
7) Probable Mechanism: unknown

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

3.5.1.CH Moclobemide
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with esc a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or sero syndrome, a hyperserotonergic state characterized by symptoms such a restlessness, myoclonus, changes in mental status, hyperreflexia, diaph shivering, and tremor. Serious, even fatal, reactions have been reported Lexapro(TM), 2002e). Concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid

5) Substantiation: theoretical
6) Clinical Management: Concurrent use of escitalopram and moclobem contraindicated. Wait at least two weeks after discontinuing a MAO inhib initiating escitalopram therapy. In addition, wait at least five weeks after escitalopram before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoam

3.5.1.CI Morniflumate

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main hemostasis. Case-control and cohort studies have shown that the combi SSRIs and NSAIDs has been associated with an increased risk of bleed events have included epistaxis, ecchymosis, hematoma, petechiae, and threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as been associated with hallucinations in some patients (Prod Info TOF oral tablets, 2007).

3.5.1.CJ Nabumetone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main hemostasis. Case-control and cohort studies have shown that the combi SSRIs and NSAIDs has been associated with an increased risk of bleed events have included epistaxis, ecchymosis, hematoma, petechiae, and threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).

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

3.5.1.CK Nadroparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maint
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and anticoagulants has been associated with an increased risk of
(Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R
solution, 2008). Bleeding events reported have included epistaxis, ecchy
hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa
(including increased bleeding) have been reported with the coadministra
with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table
2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When escitalopram and an anticoagulant are g
concurrently, monitor patients for signs of increased bleeding. Patients v
warfarin should be monitored closely for altered anticoagulant effects, in
increased bleeding, when escitalopram therapy is initiated or discontinue
LEXAPRO(R) oral tablets, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an
of clinically relevant bleeding (hospital admission due to bleeding) in
receiving warfarin for atrial fibrillation during concomitant SSRI thera
weeks following SSRI therapy termination. Patients with a mean age
years receiving warfarin plus SSRI (n=117) were matched with rand
patients who received warfarin only (n=117). SSRI included fluoxeti
citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin
experienced 11 bleeding episodes during 213.9 treatment years in t
plus SSRI group, and 10 patients experienced 14 bleedings during 5
treatment years in the warfarin-only group. The corresponding total
bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel
ratio for first bleedings during treatment with warfarin plus SSRI was
CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI in
patients experiencing bleeding at the time of concomitant administra
sertraline or citalopram. The addition of an SSRI was not associated
change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T
the study may be limited by earlier bleeding events, unknown patien
and exclusion of clopidogrel, dipyridamol, corticosteroids and antico
other than warfarin in the model (Wallerstedt et al, 2009).

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

3.5.1.CL Naproxen

1) Interaction Effect: an increased risk of bleeding

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

3) Severity: moderate

4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOF
oral tablets, 2007).

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

3.5.1.CN Niflumic Acid
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi

upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).

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

3.5.1.CO Nimesulide

1) Interaction Effect: an increased risk of bleeding

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

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

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

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).

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

3.5.1.CP Oxaprozin

1) Interaction Effect: an increased risk of bleeding

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

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

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

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants

of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).

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

3.5.1.CQ Oxycodone

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

2) Summary: Coadministration of oxycodone and escitalopram resulted
development of serotonin syndrome in an 88-year-old woman (Gnanade
2005). Caution is advised if escitalopram and oxycodone are coadminist
patients for signs and symptoms of serotonin syndrome (tachycardia, hy
myoclonus, mental status changes).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concomitant administration of escitalopram an
may increase the risk of developing serotonin syndrome. If these agents
coadministered, monitor patients for symptoms of serotonin syndrome (t
hyperthermia, myoclonus, mental status changes).

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

8) Literature Reports

a) Symptoms of serotonin syndrome developed in an 88-year-old w
following concurrent administration of oxycodone and escitalopram.
was taking escitalopram 10 mg/day and extended-release oxycodon
twice daily. Approximately 5 weeks prior to the current presentation,
extended-release oxycodone had been doubled. She presented to t
room with acutely elevated blood pressure (200/90 millimeters of m
frequent myoclonic jerks in the lower extremities. Both escitalopram
oxycodone were stopped and the patient was treated with intraveno
which led to resolution of the myoclonic jerks and a return to baselir
pressure in less than a day. Subsequent re-initiation of extended-re
oxycodone (20 mg twice daily), but not escitalopram, did not result i
or blood pressure elevation (Gnanadesigan et al, 2005).

3.5.1.CR Parecoxib

1) Interaction Effect: an increased risk of bleeding

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

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

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

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of

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

3.5.1.CS Parnaparin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and anticoagulants has been associated with an increased risk o
(Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R
solution, 2008). Bleeding events reported have included epistaxis, ecchy
hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa
(including increased bleeding) have been reported with the coadministra
with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table
2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When escitalopram and an anticoagulant are g
concurrently, monitor patients for signs of increased bleeding. Patients v
warfarin should be monitored closely for altered anticoagulant effects, in
increased bleeding, when escitalopram therapy is initiated or discontinue
LEXAPRO(R) oral tablets, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an
of clinically relevant bleeding (hospital admission due to bleeding) ir
receiving warfarin for atrial fibrillation during concomitant SSRI thera
weeks following SSRI therapy termination. Patients with a mean ag
years receiving warfarin plus SSRI (n=117) were matched with ranc
patients who received warfarin only (n=117). SSRI included fluoxeti
citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin
experienced 11 bleeding episodes during 213.9 treatment years in t
plus SSRI group, and 10 patients experienced 14 bleedings during
treatment years in the warfarin-only group. The corresponding total
bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel
ratio for first bleedings during treatment with warfarin plus SSRI was
CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir
patients experiencing bleeding at the time of concomitant administra
sertraline or citalopram. The addition of an SSRI was not associated
change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T
the study may be limited by earlier bleeding events, unknown patier
and exclusion of clopidogrel, dipyridamol, corticosteroids and antico
other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin user
(acenocoumarol and phenprocoumon) with concomitant selective se
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitali
nongastrointestinal bleeding. Using national pharmacy and hospitali
records, Netherlands researchers identified 1848 cases that were a
abnormal bleeding and compared them with 5818 control subjects a
coumarins. Median duration of treatment in patients was 220 days (
4690 days). Patients on SSRIs showed greater risk for hospitalizatio
nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% cor
interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleedi
OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schaleka
2008).

3.5.1.CT Pentosan Polysulfate Sodium

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and anticoagulants has been associated with an increased risk o
(Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R
solution, 2008). Bleeding events reported have included epistaxis, ecchy

hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa
(including increased bleeding) have been reported with the coadministra
with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table
2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When escitalopram and an anticoagulant are g
concurrently, monitor patients for signs of increased bleeding. Patients v
warfarin should be monitored closely for altered anticoagulant effects, in
increased bleeding, when escitalopram therapy is initiated or discontinue
LEXAPRO(R) oral tablets, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an
of clinically relevant bleeding (hospital admission due to bleeding) ir
receiving warfarin for atrial fibrillation during concomitant SSRI thera
weeks following SSRI therapy termination. Patients with a mean ag
years receiving warfarin plus SSRI (n=117) were matched with rand
patients who received warfarin only (n=117). SSRI included fluoxeti
citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin
experienced 11 bleeding episodes during 213.9 treatment years in t
plus SSRI group, and 10 patients experienced 14 bleedings during
treatment years in the warfarin-only group. The corresponding total
bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel
ratio for first bleedings during treatment with warfarin plus SSRI was
CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir
patients experiencing bleeding at the time of concomitant administra
sertraline or citalopram. The addition of an SSRI was not associated
change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T
the study may be limited by earlier bleeding events, unknown patier
and exclusion of clopidogrel, dipyridamol, corticosteroids and antico
other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin user
(acenocoumarol and phenprocoumon) with concomitant selective se
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitali
nongastrointestinal bleeding. Using national pharmacy and hospitali
records, Netherlands researchers identified 1848 cases that were a
abnormal bleeding and compared them with 5818 control subjects a
coumarins. Median duration of treatment in patients was 220 days (
4690 days). Patients on SSRIs showed greater risk for hospitalizatio
nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% cor
interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleedir
OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schaleka
2008).

3.5.1.CU Phenelzine
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension,
myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with esc
a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or sero
syndrome, a hyperserotonergic state characterized by symptoms such a
restlessness, myoclonus, changes in mental status, hyperreflexia, diaph
shivering, and tremor. Serious, even fatal, reactions have been reported
Lexapro(TM), 2002f). Concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of escitalopram and phenelzin
contraindicated. Wait at least two weeks after discontinuing a MAO inhib
initiating escitalopram therapy. In addition, wait at least five weeks after
escitalopram before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoam

3.5.1.CV Phenindione
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main

hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and anticoagulants has been associated with an increased risk o
(Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R
solution, 2008). Bleeding events reported have included epistaxis, ecchy
hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa
(including increased bleeding) have been reported with the coadministra
with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table
2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When escitalopram and an anticoagulant are g
concurrently, monitor patients for signs of increased bleeding. Patients v
warfarin should be monitored closely for altered anticoagulant effects, in
increased bleeding, when escitalopram therapy is initiated or discontinue
LEXAPRO(R) oral tablets, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an
of clinically relevant bleeding (hospital admission due to bleeding) ir
receiving warfarin for atrial fibrillation during concomitant SSRI thera
weeks following SSRI therapy termination. Patients with a mean ag
years receiving warfarin plus SSRI (n=117) were matched with ranc
patients who received warfarin only (n=117). SSRI included fluoxeti
citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin
experienced 11 bleeding episodes during 213.9 treatment years in t
plus SSRI group, and 10 patients experienced 14 bleedings during
treatment years in the warfarin-only group. The corresponding total
bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel
ratio for first bleedings during treatment with warfarin plus SSRI was
CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir
patients experiencing bleeding at the time of concomitant administra
sertraline or citalopram. The addition of an SSRI was not associated
change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T
the study may be limited by earlier bleeding events, unknown patier
and exclusion of clopidogrel, dipyridamol, corticosteroids and antico
other than warfarin in the model (Wallerstedt et al, 2009).

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

3.5.1.CW Phenprocoumon

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and anticoagulants has been associated with an increased risk o
(Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R
solution, 2008). Bleeding events reported have included epistaxis, ecchy
hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa
(including increased bleeding) have been reported with the coadministra
with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table
2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When escitalopram and an anticoagulant are g
concurrently, monitor patients for signs of increased bleeding. Patients v
warfarin should be monitored closely for altered anticoagulant effects, in

increased bleeding, when escitalopram therapy is initiated or discontinue
LEXAPRO(R) oral tablets, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an
of clinically relevant bleeding (hospital admission due to bleeding) ir
receiving warfarin for atrial fibrillation during concomitant SSRI thera
weeks following SSRI therapy termination. Patients with a mean ag
years receiving warfarin plus SSRI (n=117) were matched with ranc
patients who received warfarin only (n=117). SSRI included fluoxeti
citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin
experienced 11 bleeding episodes during 213.9 treatment years in t
plus SSRI group, and 10 patients experienced 14 bleedings during
treatment years in the warfarin-only group. The corresponding total
bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel
ratio for first bleedings during treatment with warfarin plus SSRI was
CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir
patients experiencing bleeding at the time of concomitant administra
sertraline or citalopram. The addition of an SSRI was not associated
change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T
the study may be limited by earlier bleeding events, unknown patier
and exclusion of clopidogrel, dipyridamol, corticosteroids and antico
other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin user
(acenocoumarol and phenprocoumon) with concomitant selective se
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitali
nongastrointestinal bleeding. Using national pharmacy and hospitali
records, Netherlands researchers identified 1848 cases that were a
abnormal bleeding and compared them with 5818 control subjects a
coumarins. Median duration of treatment in patients was 220 days (
4690 days). Patients on SSRIs showed greater risk for hospitalizatio
nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% cor
interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleedir
OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schaleka
2008).

3.5.1.CX Phenylbutazone
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOF
oral tablets, 2007).

3.5.1.CY Pirazolac

1) Interaction Effect: an increased risk of bleeding

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

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

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

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).

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

3.5.1.CZ Piroxicam

1) Interaction Effect: an increased risk of bleeding

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

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

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

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).

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

3.5.1.DA Pirprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maint
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOF
oral tablets, 2007).

3.5.1.DB Propyphenazone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maint
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOF
oral tablets, 2007).

3.5.1.DC Proquazone

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

events have included epistaxis, ecchymosis, hematoma, petechiae, and threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as been associated with hallucinations in some patients (Prod Info TOR oral tablets, 2007).

3.5.1.DD Rasagiline

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, myoclonus, mental status changes)
2) Summary: Concomitant use of rasagiline and escitalopram should be Concurrent administration or overlapping therapy with SSRIs and non-se MAOIs has been reported to cause serious, sometimes fatal reactions. S symptoms included hyperthermia, rigidity, myoclonus, autonomic instabi vital sign fluctuations, and mental status changes progressing to extrem delirium, and coma. Data from clinical studies, where rasagiline-treated (n=141) were concomitantly exposed to SSRIs, are insufficient to rule ou interaction. At least 14 days should elapse after discontinuing rasagiline initiating escitalopram therapy (Prod Info AZILECT(R) oral tablets, 2006) least 14 days should also elapse after discontinuing escitalopram before therapy with rasagiline (Prod Info CELEXA(R) oral tablets, solution, 200
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of escitalopram and rasagiline recommended. Wait at least 14 days after discontinuing rasagiline befor therapy with escitalopram (Prod Info AZILECT(R) oral tablets, 2006). Sin least 14 days after discontinuing escitalopram before initiating therapy w (Prod Info CELEXA(R) oral tablets, solution, 2007).
7) Probable Mechanism: inhibition of serotonin metabolism by monoam

3.5.1.DE Reviparin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main hemostasis. Case-control and cohort studies have shown that the combi SSRIs and anticoagulants has been associated with an increased risk of (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R solution, 2008). Bleeding events reported have included epistaxis, ecchy hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa (including increased bleeding) have been reported with the coadministra with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When escitalopram and an anticoagulant are g concurrently, monitor patients for signs of increased bleeding. Patients v

warfarin should be monitored closely for altered anticoagulant effects, in increased bleeding, when escitalopram therapy is initiated or discontinue LEXAPRO(R) oral tablets, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an of clinically relevant bleeding (hospital admission due to bleeding) ir receiving warfarin for atrial fibrillation during concomitant SSRI thera weeks following SSRI therapy termination. Patients with a mean ag years receiving warfarin plus SSRI (n=117) were matched with ranc patients who received warfarin only (n=117). SSRI included fluoxeti citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin experienced 11 bleeding episodes during 213.9 treatment years in t plus SSRI group, and 10 patients experienced 14 bleedings during 5 treatment years in the warfarin-only group. The corresponding total bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel ratio for first bleedings during treatment with warfarin plus SSRI was CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir patients experiencing bleeding at the time of concomitant administra sertraline or citalopram. The addition of an SSRI was not associated change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T the study may be limited by earlier bleeding events, unknown patier and exclusion of clopidogrel, dipyridamol, corticosteroids and antico other than warfarin in the model (Wallerstedt et al, 2009).

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

3.5.1.DF Rizatriptan

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: There have been case reports of weakness, hyperreflexia incoordination following concomitant use of sumatriptan, a 5-hydroxytryp (5HT-1) agonist, and a serotonin specific reuptake inhibitor (SSRI) (Proc (R), 1998). Because rizatriptan is a 5HT 1B/1D receptor agonist, a simila between SSRIs and rizatriptan may occur (Prod Info Maxalt(R), 1998a). use of a triptan and an SSRI may result in serotonin syndrome which ma threatening. Symptoms of serotonin syndrome may include restlessness hallucinations, loss of coordination, fast heart beat, rapid changes in blo increased body temperature, overreactive reflexes, nausea, vomiting, ar Clinicians should be aware that triptans may be commonly used intermit either the triptan or the SSRI may be prescribed by a different physician risks of serotonin syndrome with patients who are prescribed this combi monitor them closely for symptoms of serotonin syndrome (US Food and Administration, 2006).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Coadministration of a triptan, such as rizatripta SSRI may result in a life-threatening condition called serotonin syndrom that triptans may be commonly used intermittently and that either the trip SSRI may be prescribed by a different physician. If these agents are use discuss the risks of serotonin syndrome with the patient and monitor clos symptoms of serotonin syndrome (restlessness, hyperthermia, hyperrefl incoordination).

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

8) Literature Reports

a) Twelve healthy volunteers received paroxetine 20 mg daily for tw

a single dose of rizatriptan 10 mg. Plasma concentrations of rizatrip
altered by the administration of paroxetine (Prod Info Maxalt(R), 19

3.5.1.DG Rofecoxib

1) Interaction Effect: an increased risk of bleeding

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

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

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

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).

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

3.5.1.DH Selegiline

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

2) Summary: Concurrent administration or overlapping therapy with esc
a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or sero
syndrome, a hyperserotonergic state characterized by symptoms such a
restlessness, myoclonus, changes in mental status, hyperreflexia, diaph
shivering, and tremor. Serious, even fatal, reactions have been reported
Lexapro(TM), 2002c). Concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of escitalopram and selegiline
contraindicated. Wait at least two weeks after discontinuing a MAO inhib
initiating escitalopram therapy. In addition, wait at least five weeks after
escitalopram before initiating therapy with a MAO inhibitor.

7) Probable Mechanism: inhibition of serotonin metabolism by monoam

3.5.1.DI Sibrafiban

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and antiplatelet agents has been associated with an increased ris
Bleeding events reported have included epistaxis, ecchymosis, hematon
and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, susp
Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

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

capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.DJ Sibutramine
1) Interaction Effect: an increased risk of serotonin syndrome (hyperten
hyperthermia, myoclonus, mental status changes)
2) Summary: Sibutramine inhibits the reuptake of norepinephrine, dopa
serotonin. In addition, the two major metabolites of sibutramine, M1 and
inhibit the reuptake of these neurotransmitters. A hyperserotonergic stat
serotonin syndrome, may result if sibutramine is given concurrently with
serotonin reuptake inhibitor. Coadministration of sibutramine and selecti
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 s
agents, including selective serotonin reuptake inhibitors, because of the
of serotonin syndrome.
7) Probable Mechanism: additive pharmacologic effects resulting in exc
serotonergic stimulation
8) Literature Reports
a) Serotonin syndrome is a condition of serotonergic hyperstimulati
manifests as restlessness, myoclonus, changes in mental status, hy
diaphoresis, shivering, and tremor. If the syndrome is not recognize
correctly treated, death can result (Sternbach, 1991).

3.5.1.DK St John's Wort
1) Interaction Effect: an increased risk of serotonin syndrome (hyperten
hyperthermia, myoclonus, mental status changes)
2) Summary: Case reports describe the onset of serotonin syndrome-lik
mania, and hypomania following the addition of St. John's Wort to sertra
fluoxetine, and paroxetine therapy (Spinella & Eaton, 2002c; Barbanel e
Waksman et al, 2000a; Lantz et al, 1999a). A patient exhibited a syndro
resembling sedative/hypnotic intoxication after adding St. John's Wort to
therapy (Gordon, 1998a). St. John's Wort is thought to inhibit serotonin r
may have mild monoamine oxidase inhibitory activity (Singer et al, 1999
Walper, 1994), which when added to selective serotonin reuptake inhibit
in serotonin syndrome.
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Patients should be advised to wait two weeks
St. John's Wort before restarting selective serotonin reuptake inhibitor th
patient plans to replace selective serotonin reuptake inhibitor (SSRI) the
John's Wort, the half-life of the specific SSRI should be taken into consid
waiting at least 5 half-lives for the SSRI to be metabolized out of the boc
7) Probable Mechanism: additive serotonergic effect
8) Literature Reports
a) Five cases have been reported of serotonin syndrome in the eld
combining prescription antidepressants and St. John's Wort. Case 1
dizziness, nausea, vomiting and a headache 4 days after starting St
300 milligrams (mg) three times daily combined with sertraline 50 m
symptoms resolved 2 to 3 days after stopping all medications. Case
nausea, epigastric pain and anxiety 3 days after starting St. John's
twice daily combined with sertraline 75 mg daily. His symptoms reso
week after discontinuing both medications, and he resumed sertralin
complications. The third case developed nausea, vomiting, anxiety,
2 days after starting St. John's Wort 300 mg twice daily combined w
50 mg daily. His symptoms improved in 4 to 5 days after stopping b
medications and taking cyproheptadine 4 mg three times daily. Cas
nausea, anxiety, restless, and irritability 2 days after starting St. Joh
mg three times daily combined with sertraline 50 mg daily. Cyprohe
twice daily was administered for seven days, and his symptoms imp
week after stopping the medication. Cases 1 through 4 resumed the
sertraline after symptoms subsided and had no further problems. Ca
developed nausea, vomiting and restlessness 3 days after starting S
Wort 300 mg three times daily combined with nefazodone 100 mg tw

She continued to take St. John's Wort but discontinued the nefazod
1 week her symptoms Improved. She refused to resume therapy wi
nefazodone, but continued therapy with St. John's Wort and mild to
symptoms of depression and anxiety returned (Lantz et al, 1999).
b) A 50-year-old female taking St. John's Wort 600 mg daily experi
symptoms of sedative intoxication when she ingested a single dose
20 mg. She was incoherent, groggy, slow-moving, and complained
weakness. Prior to starting St. John's Wort, she had been receiving
mg daily for eight months without adverse effects. After a night of sl
returned to her baseline mental status (Gordon, 1998).
c) A 61-year-old female experienced restlessness and involuntary
her extremities after beginning paroxetine 20 milligrams (mg) two da
discontinuing St. John's Wort 600 mg daily. The patient reported ag
akathisia 8 hours after taking the first dose of paroxetine. She prese
diaphoresis and involuntary movement of all extremities with hyperr
rigidity. Blood pressure, heart rate, and temperature were normal. A
admission, blood pressure increased to 200/116 mmHg and heart ra
to 145 beats per minute. Creatine kinase increased from 212 units/l
initially to 1024 U/L. The patient was managed with supportive care
lorazepam and discharged after two days (Waksman et al, 2000).
d) A 28-year-old male developed a manic syndrome following com
St. John's Wort and sertraline. The patient was also on testosterone
therapy following bilateral orchidectomy 2 years earlier, but testoste
were subtherapeutic. The patient was prescribed sertraline 50 millig
depression following a 2 week trial of St. John's Wort per patient pre
not specified). Before sertraline was started, the patient was instruc
discontinue St. John'sWort, but continued it despite this advice. The
experienced improved mood so did not see his physician, believing
not need further treatment. Over 2 months, the patient had elated m
irritable, and overspent, buying a car he could not afford, and was u
arrested for stealing fuel for the car. On arrest, he was referred to ps
services due to irritability and disinhibition. He was observed to be d
distractible, have flight of ideas, and grandiose delusions, leading to
of a manic episode. The authors state the possibility of the manic st
from sertraline therapy alone, and that St. John's Wort may have inc
risk as a result of monoamine oxidase inhibition. Since the patient's
level was subnormal, the possibility of its contribution to the manic s
considered low. However, the patient had elevated gonadotropin lev
(luteinizing hormone and follicle-stimulating hormone) which may ha
predisposed the patient to mania (Barbanel et al, 2000).
e) A 42-year-old female experienced symptoms consistent with a m
hypomanic episode following concomitant use of fluoxetine, buspiro
biloba, and St. John's Wort. The symptoms resolved following disco
Ginkgo and St. John's Wort. The patient was being treated for depre
following a mild traumatic brain injury with fluoxetine 20 milligrams (
daily and buspirone 15 mg twice daily. Several weeks prior to prese
buspirone was increased to 20 mg twice daily for persistent anxiety
patient began taking Ginkgo biloba, melatonin, and St. John's Wort
doses. Melatonin was considered unlikely to have contributed to her
Ginkgo and St. John's Wort were considered possible contributors s
potentiate antidepressants, and considering the temporal relationsh
the use of the herbs and onset of symptoms and discontinuation of
resolution of symptoms. However, the brain injury was considered a
contributor (Spinella & Eaton, 2002b).

3.5.1.DL Sulfinpyrazone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and antiplatelet agents has been associated with an increased ris
Bleeding events reported have included epistaxis, ecchymosis, hematon
and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, susp
Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are g

concurrently, monitor patient for signs of increased bleeding (Prod Info F tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayec capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.DM Sulindac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main hemostasis. Case-control and cohort studies have shown that the combi SSRIs and NSAIDs has been associated with an increased risk of bleed events have included epistaxis, ecchymosis, hematoma, petechiae, and threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as been associated with hallucinations in some patients (Prod Info TOF oral tablets, 2007).

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

3.5.1.DO Sumatriptan
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: There have been rare postmarketing reports describing pa weakness, hyperreflexia, and incoordination following the use of a selec reuptake inhibitor and sumatriptan (Prod Info Lexapro(TM), 2003). Conc a triptan and an SSRI may result in serotonin syndrome which may be lif Symptoms of serotonin syndrome may include restlessness, hallucinatio coordination, fast heart beat, rapid changes in blood pressure, increasec temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clin be aware that triptans may be commonly used intermittently and that eitl or the SSRI may be prescribed by a different physician. Discuss the risk syndrome with patients who are prescribed this combination and monito for symptoms of serotonin syndrome (US Food and Drug Administration

3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as sumatrip SSRI, such as escitalopram, may result in a life-threatening condition ca syndrome. Be aware that triptans may be commonly used intermittently the triptan or the SSRI may be prescribed by a different physician. If thes used together, discuss the risks of serotonin syndrome with the patient a closely for symptoms of serotonin syndrome (restlessness, hyperthermia hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in exc serotonergic stimulation

3.5.1.DP Suprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main hemostasis. Case-control and cohort studies have shown that the combi SSRIs and NSAIDs has been associated with an increased risk of bleed events have included epistaxis, ecchymosis, hematoma, petechiae, and threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as been associated with hallucinations in some patients (Prod Info TOR oral tablets, 2007).

3.5.1.DQ Tapentadol

1) Interaction Effect: increased risk of serotonin syndrome (hypertensio hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent use of tapentadol and a selective serotonin re inhibitor (SSRI) may result in serotonin syndrome, which may be life-thre Symptoms of serotonin syndrome may include restlessness, hallucinatio coordination, fast heart beat, rapid changes in blood pressure, increased temperature, overreactive reflexes, nausea, vomiting, and diarrhea (Proc tapentadol immediate release oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of tapentadol and an SSRI m life-threatening condition called serotonin syndrome. If these agents are together, monitor the patient closely for symptoms of serotonin syndrom (restlessness, hyperthermia, hyperreflexia, incoordination), especially du initiation and dose increases (Prod Info tapentadol immediate release or 2008).
7) Probable Mechanism: additive serotonergic effect

3.5.1.DR Tapentadol

1) Interaction Effect: an increase in central nervous system and respirat

depression
2) Summary: The concomitant use of tapentadol with central nervous sy
depressants including sedatives (eg, alprazolam, midazolam, or zolpider
in additive CNS and respiratory depressant effects, including hypotensio
sedation and/or coma. When administering tapentadol and a sedative to
dosage of one or both agents may be reduced (Prod Info NUCYNTA(TM
release oral tablets, 2009).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Consider monitoring the patient for cardiorespi
depression when tapentadol and sedatives are used in combination. A r
dose of one or both drugs may be necessary (Prod Info NUCYNTA(TM)
release oral tablets, 2009).
7) Probable Mechanism: additive effects

3.5.1.DS Tenidap
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOR
oral tablets, 2007).

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

antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).

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

3.5.1.DU Tiaprofenic Acid

1) Interaction Effect: an increased risk of bleeding

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

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

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

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).

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

3.5.1.DV Ticlopidine

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and antiplatelet agents has been associated with an increased ris
Bleeding events reported have included epistaxis, ecchymosis, hematon
and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, susp
Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

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

7) Probable Mechanism: unknown

3.5.1.DW Tinzaparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and anticoagulants has been associated with an increased risk of

(Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R
solution, 2008). Bleeding events reported have included epistaxis, ecchy
hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa
(including increased bleeding) have been reported with the coadministra
with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table
2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When escitalopram and an anticoagulant are g
concurrently, monitor patients for signs of increased bleeding. Patients v
warfarin should be monitored closely for altered anticoagulant effects, in
increased bleeding, when escitalopram therapy is initiated or discontinue
LEXAPRO(R) oral tablets, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an
of clinically relevant bleeding (hospital admission due to bleeding) ir
receiving warfarin for atrial fibrillation during concomitant SSRI thera
weeks following SSRI therapy termination. Patients with a mean ag
years receiving warfarin plus SSRI (n=117) were matched with ranc
patients who received warfarin only (n=117). SSRI included fluoxeti
citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin
experienced 11 bleeding episodes during 213.9 treatment years in t
plus SSRI group, and 10 patients experienced 14 bleedings during
treatment years in the warfarin-only group. The corresponding total
bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel
ratio for first bleedings during treatment with warfarin plus SSRI was
CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir
patients experiencing bleeding at the time of concomitant administra
sertraline or citalopram. The addition of an SSRI was not associated
change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T
the study may be limited by earlier bleeding events, unknown patier
and exclusion of clopidogrel, dipyridamol, corticosteroids and antico
other than warfarin in the model (Wallerstedt et al, 2009).

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

3.5.1.DX Tirofiban

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and antiplatelet agents has been associated with an increased ris
Bleeding events reported have included epistaxis, ecchymosis, hematon
and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, susp
Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

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

7) Probable Mechanism: unknown

3.5.1.DY Tolmetin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maint
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOR
oral tablets, 2007).

3.5.1.DZ Tramadol
1) Interaction Effect: an increased risk of seizures and serotonin syndro
(hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Seizures and serotonin syndrome have been reported in p
tramadol. The risk of seizures and serotonin syndrome may be enhance
escitalopram and tramadol therapy are combined (Prod Info Ultram(R),
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Caution should be used if tramadol is to be adı
patients receiving concomitant escitalopram therapy. If possible, avoid th
combination, especially in patients with underlying conditions that might
them to seizures . Observe the patient closely for signs and symptoms o
syndrome.
7) Probable Mechanism: increased concentration of serotonin in the ner
and periphery

3.5.1.EA Tranylcypromine
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension,
myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with esc
a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or sero
syndrome, a hyperserotonergic state characterized by symptoms such a
restlessness, myoclonus, changes in mental status, hyperreflexia, diaph
shivering, and tremor. Serious, even fatal, reactions have been reported
Lexapro(TM), 2002). Concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of escitalopram and tranylcypr
contraindicated. Wait at least two weeks after discontinuing a MAO inhib
initiating escitalopram therapy. In addition, wait at least five weeks after
escitalopram before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoam

3.5.1.EB Valdecoxib
1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maint
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and NSAIDs has been associated with an increased risk of bleed
events have included epistaxis, ecchymosis, hematoma, petechiae, and
threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension,
Info Lexapro(TM), 2003a; Dalton et al, 2003a; Prod Info CELEXA (R) ora
solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concu
monitor patient for signs of increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and th
potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi
upper gastrointestinal bleeding were searched among 26,005 users
antidepressant medications and compared with the number of hosp
those patients who did not receive prescriptions for antidepressants
of upper GI bleeding episodes was 3.6 times more than expected (9
confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA
dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1
5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
demonstrate an increased risk of upper GI bleeding during the use
Combined use of SSRIs and NSAIDs or low-dose aspirin increased
further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as
been associated with hallucinations in some patients (Prod Info TOR
oral tablets, 2007).

3.5.1.EC Warfarin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maint
hemostasis. Case-control and cohort studies have shown that the combi
SSRIs and anticoagulants has been associated with an increased risk of
(Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info LEXAPRO(R
solution, 2008). Bleeding events reported have included epistaxis, ecchy
hematoma, petechiae, and life-threatening hemorrhages. Altered anticoa
(including increased bleeding) have been reported with the coadministra
with warfarin (Schalekamp et al, 2008; Prod Info LEXAPRO(R) oral table
2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When escitalopram and an anticoagulant are g
concurrently, monitor patients for signs of increased bleeding. Patients v
warfarin should be monitored closely for altered anticoagulant effects, in
increased bleeding, when escitalopram therapy is initiated or discontinue
LEXAPRO(R) oral tablets, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an
of clinically relevant bleeding (hospital admission due to bleeding) ir
receiving warfarin for atrial fibrillation during concomitant SSRI thera
weeks following SSRI therapy termination. Patients with a mean ag
years receiving warfarin plus SSRI (n=117) were matched with ranc
patients who received warfarin only (n=117). SSRI included fluoxeti
citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nin
experienced 11 bleeding episodes during 213.9 treatment years in t
plus SSRI group, and 10 patients experienced 14 bleedings during
treatment years in the warfarin-only group. The corresponding total
bleedings were 51.4 and 23.9 per 1000 treatment years, respectivel
ratio for first bleedings during treatment with warfarin plus SSRI was
CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI ir
patients experiencing bleeding at the time of concomitant administra
sertraline or citalopram. The addition of an SSRI was not associated
change in warfarin dose or INR (p=0.48 and p=0.31 respectively). T

the study may be limited by earlier bleeding events, unknown patier and exclusion of clopidogrel, dipyridamol, corticosteroids and antico other than warfarin in the model (Wallerstedt et al, 2009).

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

3.5.1.ED Xemilofiban

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for main hemostasis. Case-control and cohort studies have shown that the combi SSRIs and antiplatelet agents has been associated with an increased ris Bleeding events reported have included epistaxis, ecchymosis, hematon and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, susp Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

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

7) Probable Mechanism: unknown

3.5.1.EE Zolmitriptan

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: There have been case reports of weakness, hyperreflexia incoordination following concomitant use of sumatriptan, a 5-hydroxytryp (5HT-1) agonist, and a serotonin specific reuptake inhibitor (SSRI) (Proc (R), 1998a; Prod Info Zomig(TM), 1997). Because zolmitriptan is a 5HT agonist, a similar interaction between SSRIs and zolmitriptan may occur Zomig(TM), 1997). Concurrent use of zolmitriptan and an SSRI may resu syndrome which may be life-threatening. Symptoms of serotonin syndro include restlessness, hallucinations, loss of coordination, fast heart beat changes in blood pressure, increased body temperature, overreactive re nausea, vomiting, and diarrhea. Clinicians should be aware that triptans commonly used intermittently and that either the triptan or the SSRI may prescribed by a different physician. Discuss the risks of serotonin syndrc patients who are prescribed this combination and monitor them closely f of serotonin syndrome (US Food and Drug Administration, 2006).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Coadministration of a triptan, such as zolmitrip SSRI may result in a life-threatening condition called serotonin syndrom that triptans may be commonly used intermittently and that either the trip SSRI may be prescribed by a different physician. If these agents are use discuss the risks of serotonin syndrome with the patient and monitor clos symptoms of serotonin syndrome (restlessness, hyperthermia, hyperrefl incoordination).

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

8) Literature Reports

a) The pharmacokinetics of a single 10 mg dose of zolmitriptan wer by four weeks of fluoxetine 20 mg daily pretreatment in healthy volu effects of zolmitriptan on blood pressure were also not changed by t therapy (Prod Info Zomig(R), 2002).

3.5.1.EF Zomepirac

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

a) SSRIs increase the risk of upper gastrointestinal bleeding and th potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospi upper gastrointestinal bleeding were searched among 26,005 users antidepressant medications and compared with the number of hosp those patients who did not receive prescriptions for antidepressants of upper GI bleeding episodes was 3.6 times more than expected (9 confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSA dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of demonstrate an increased risk of upper GI bleeding during the use Combined use of SSRIs and NSAIDs or low-dose aspirin increased further (Dalton et al, 2003).

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

3.5.2 Drug-Food Combinations

3.5.2.A Ethanol

1) Interaction Effect: potentiation of the cognitive and motor effects of al
2) Summary: According to the manufacturer, escitalopram did not poter cognitive and motor effects of alcohol. The concomitant use, however, is recommended (Prod Info Lexapro(TM), 2003b).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The use of alchohol by patients taking escitalo recommended.
7) Probable Mechanism: unknown

4.0 Clinical Applications

4.1 Monitoring Parameters

A) Escitalopram Oxalate
1) Therapeutic

a) Physical Findings
1) Symptoms of depression or anxiety/depression (improvement)
2) Maintenance therapy should be periodically reevaluated during l to determine the clinical need (Prod Info LEXAPRO(R) Oral solutior 2009).

2) Toxic
a) Laboratory Parameters
1) Serum sodium levels should be monitored (levels lower than 11(been reported) as medically warranted. There is an increased risk o hyponatremia (as a result of the syndrome of inappropriate antidiure secretion) in patients receiving concomitant diuretics, patients who a depleted, and the elderly. If hyponatremia is confirmed, escitaloprar discontinued and medical management may be necessary.

b) Physical Findings
1) Abnormal bleeding should be monitored for ecchymoses, hemat epistaxis and petechiae especially in patients receiving concomitant NSAIDs, warfarin or other anticoagulants.
2) Hyponatremia (as a result of SIADH) should be monitored includ of headache, difficulty concentrating, memory impairment, confusion and unsteadiness. More severe symptoms include hallucination, syı seizure, coma, and respiratory arrest including fatalities. There is ar risk of hyponatremia in patients receiving concomitant diuretics, pat volume depleted, and the elderly. If hyponatremia is confirmed, esci should be discontinued and medical management may be necessar
3) If intolerable withdrawal symptoms occur following a decrease in therapy is being discontinued, it may be necessary to resume the pı prescribed dose and taper the dose at a more gradual rate (Prod Int (R) Oral solution, Oral tablets, 2009).
4) Mania/hypomania may be activated in patients with undiagnosec disorder. Monitoring is recommended especially in patients with a h mania. Escitalopram is not indicated for use in bipolar disorder.
5) Monitor patients receiving antidepressants for worsening of depr suicidality, or unusual changes in behavior, especially at the initiatic or when the dose increases or decreases (Prod Info LEXAPRO(R) Oral tablets, 2009). Such monitoring should include at least weekly contact with patients or their family members or caregivers during th weeks of treatment, then visits every other week for the next 4 weel weeks, and then as clinically indicated beyond 12 weeks. Families a should be advised of the need for close observation (i.e., daily obse patients and communication with the prescriber (Anon, 2004)
6) Patients who experience symptoms of anxiety, agitation, panic a insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, or mania may be at an increased risk for worsening depression or s these symptoms are observed, therapy should be reevaluated and i necessary to discontinue medications when symptoms are severe, s onset, or were not part of the patient's initial symptoms (Prod Info LI Oral solution, Oral tablets, 2009; Anon, 2004)
7) Seizures should be monitored, especially in patients with a histo disorder.
8) Serotonin syndrome or neuroleptic malignant syndrome-like reac be monitored including mental status changes, autonomic instability labile blood pressure, hyperthermia), neuromuscular aberrations (m hyperreflexia, incoordination) and/or gastrointestinal symptoms. The increased risk of this reaction with concomitant use of serotonergic (including triptans), drugs which impair metabolism of serotonin, or or dopamine antagonists, all of which are not recommended during therapy. Treatment should be discontinued if serotonin syndrome or malignant syndrome-like reactions occur (Prod Info LEXAPRO(R) C Oral tablets, 2009).

4.2 Patient Instructions

A) Escitalopram (By mouth)
Escitalopram

Treats severe depression and generalized anxiety disorder (GAD). This med selective serotonin reuptake inhibitor (SSRI).

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to escit
citalopram (Celexa®), or if you are using pimozide (Orap®). You should not u
medicine if you have used an MAO inhibitor (such as Eldepryl®, Marplan®, M
Parnate®) within the past 14 days. Do not use an MAO inhibitor for at least 1
you stop using escitalopram.

How to Use This Medicine:
Liquid, Tablet
Your doctor will tell you how much of this medicine to use and how often
more medicine or use it more often than your doctor tells you to.
You may take this medicine with or without food.
Measure the oral liquid medicine with a marked measuring spoon, oral s
medicine cup.
This medicine should come with a Medication Guide. Read and follow th
instructions carefully. Ask your doctor or pharmacist if you have any que
your pharmacist for the Medication Guide if you do not have one. Your d
ask you to sign some forms to show that you understand this information

If a Dose is Missed:
If you miss a dose or forget to use your medicine, use it as soon as you
almost time for your next dose, wait until then to use the medicine and s
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 fror
moisture, and direct light.
Ask your pharmacist, doctor, or health caregiver about the best way to d
leftover medicine after you have finished your treatment. You will also ne
away old medicine after the expiration date has passed.
Keep all medicine away from children and never share your medicine wi

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including ove
medicines, vitamins, and herbal products.
Do not use citalopram (Celexa®) while you are using escitalopram. Thes
medicines are closely related and using both could be dangerous.
Make sure your doctor knows if you are using linezolid (Zyvox®), lithium
St. John's Wort, pain or migraine medicines (such as aspirin, tramadol, s
zolmitriptan, rizatriptan, Ultram®, Imitrex®, Zomig®, or Maxalt®), pain or
medicines called NSAIDs (such as diclofenac, ibuprofen, naproxen, Adv
Feldene®, Daypro®, Motrin®, Orudis®, Relafen®, or Voltaren®), or a bl
such as warfarin (Coumadin®). Tell your doctor if you are also using cim
(Tagamet®), carbamazepine (Tegretol®), ketoconazole (Nizoral®), meto
(Lopressor®), or other medicines for depression (such as amitriptyline, i
Norpramin®, or Tofranil®).
Tell your doctor if you are using any medicines that make you sleepy. Th
sleeping pills, cold and allergy medicine, narcotic pain relievers, and sed
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant or breastfeeding, or if y
bleeding problems, kidney disease, liver disease, heart disease, hypona
sodium in the blood), or a history of seizure disorder (such as epilepsy) o
your doctor if you have a history of neuroleptic malignant syndrome (NM
serotonin syndrome.
For some children, teenagers, and young adults, this medicine can incre
of suicide. Tell your doctor or your child's doctor right away if you or you
feel more depressed and have thoughts about hurting yourselves. Repo
thoughts or behaviors that trouble you or your child, especially if they are
getting worse quickly. Make sure the doctor knows if you or your child ha
sleeping, get upset easily, have a big increase in energy, or start to act r
tell the doctor if you or your child have sudden or strong feelings, such a
nervous, angry, restless, violent, or scared. Let the doctor know if you, y
anyone in your family has bipolar disorder (manic-depressive) or has trie
suicide.
You may need to take this medicine for up to 4 weeks before you feel be

using this medicine for the full treatment time. If you feel that the medicir
working well, do not take more than your prescribed dose. Call your doc
instructions.
This medicine may make you dizzy or drowsy. Avoid driving, using mach
anything else that could be dangerous if you are not alert.
Do not stop using this medicine suddenly without asking your doctor. Yo
slowly decrease your dose before stopping it completely.
Your doctor will need to check your progress at regular visits while you a
medicine. Be sure to keep all appointments.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swellin
your mouth or throat, chest tightness, trouble breathing.
Blistering, peeling, or red skin rash.
Change in how much or how often you urinate, or painful urination.
Chest pain or shortness of breath.
Confusion, weakness, or muscle twitching.
Fast, pounding, or uneven heartbeat.
Fever, chills, cough, sore throat, and body aches.
Painful, prolonged erection of the penis.
Swelling in your hands, ankles, or feet.
Unusual behavior or thoughts of hurting yourself or others.
Unusual bleeding or bruising.

If you notice these less serious side effects, talk with your doctor:
Dry mouth.
Headache, dizziness, or drowsiness.
Nausea, diarrhea, constipation, or upset stomach.
Problems with sex.
Runny or stuffy nose.
Sweating.
Tiredness.
Trouble with sleeping.

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

4.3 Place In Therapy

A) Depression

1) Escitalopram is indicated for the acute and maintenance treatment of maj
disorder in adults and adolescents age 12 years and older (Prod Info LEXAP
solution, Oral tablets, 2009).

2) The selective serotonin (5-HT) reuptake inhibitors (SSRIs) are considered
choice for mild or moderate depression by many specialists. More severe de
depression unresponsive to the SSRIs, is usually treated by tricyclic antidepr
inhibitors, or bupropion or venlafaxine. There is no consistent evidence that c
superior to another.

3) In several studies, escitalopram has been reported effective in major depr
pooled analysis of placebo-controlled trials escitalopram demonstrated a stat
significant improvement in depressive symptoms compared to placebo at one
compared to 4 weeks for citalopram. The actual improvement in depressive s
escitalopram compared to placebo at weeks one and 2 was an approximately
decrease (out of a possible 60) as measured on the Montgomery Asberg De
Rating Scale (Gorman et al, 2002). The clinical significance of this change is
There was no statistically significant difference between escitalopram 10 mg
placebo in regards to discontinuation rates due to adverse effects or in the ra
treatment-emergent adverse events. Both escitalopram 20 mg per day and c
mg per day did show statistically significant higher rates for discontinuation d
effects and in treatment-emergent adverse events (Burke et al, 2002). A com
equivalent doses of escitalopram 10 mg per day and citalopram 20 mg per da
to determine if escitalopram offers clinical advantages over citalopram in the
adverse drug effects.

B) Generalized Anxiety Disorder

1) Escitalopram is indicated in the acute treatment of generalized anxiety dis
adults (Prod Info LEXAPRO(R) Oral solution, Oral tablets, 2009).

2) For the acute treatment of generalized anxiety disorder (GAD), SSRIs suc
paroxetine, sertraline, and escitalopram, as well as venlafaxine, benzodiazep

alprazolam and diazepam, and the tricyclic antidepressant (TCA) imipramine
The SSRIs and venlafaxine are preferred to benzodiazepines and TCAs due
tolerability. Studies have shown that long-term treatment with SSRIs or venla
increases response rates and prevents relapse (Baldwin & Nair, 2005).
3) Escitalopram has been shown to be effective for the acute and chronic tre
GAD, as well as in the prevention of relapse (Goodman et al, 2005; Davidsor
Allgulander et al, 2006). In three 8-week randomized controlled trials, patient
escitalopram 10 milligrams (mg) daily showed statistically significant improve
placebo as early as 1 week, as measured by change from baseline Hamilton
for Anxiety (HAMA) scores (Goodman et al, 2005). Patients completing the 8
were invited to participate in a 24-week, open-label extension in which all pat
escitalopram. Initially, patients who received escitalopram in the lead-in trials
improvements than patients who received placebo, but by week 4 of the exte
patients were at the same level of improvement regardless of previous treatn
76% of patients were considered responders and 49% achieved remission (D
2005). In a relapse prevention study lasting 24 to 76 weeks, patients on place
times more likely to relapse than patients who were treated with escitalopram
(Allgulander et al, 2006). A comparison study found escitalopram to be as eff
paroxetine in the treatment of GAD; however, escitalopram was better tolerat
al, 2005).

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) Antidepressant effects are secondary to inhibition of reuptake of serotonir
serotonergic neurons via binding to the serotonin transporter, resulting in incr
synaptic availability of 5-HT (Owens et al, 2001; Owens & Knight, 2000).

B) PHARMACOLOGY

1) The antidepressant citalopram is a selective serotonin (5-HT) reuptake inl
it is available for clinical use as a racemic mixture (S(+)-citalopram and R(-)-c
1:1 ratio) (Montgomery et al, 2001; Sanchez & Hogg, 2000). Escitalopram is
enantiomer of citalopram, and appears responsible for most or all antidepres
the racemic compound (Sanchez & Hogg, 2000; Sanchez & Brennum, 2000;
al, 2001; Mitchell & Hogg, 2001). In vitro, escitalopram was about twice as po
racemic citalopram and 130 times as potent as R(-)-citalopram as an inhibito
reuptake (Sanchez & Brennum, 2000; Sanchez & Hogg, 2000; Owens et al,
Bergqvist et al, 2001) and exhibited minimal-to-no effect on norepinephrine c
reuptake (Sanchez & Brennum, 2000).
2) Subcutaneous escitalopram was reported effective in an animal model pr
antidepressant activity, and at least twice as potent as subcutaneous citalopr
& Hogg, 2001). The onset of antidepressant activity with escitalopram was fa
of racemic citalopram (Montgomery et al, 2001) or tricyclic antidepressants (I
Sanchez, 2001) in rat models of depression.
3) Escitalopram has demonstrated anxiolytic activity in animal models of ger
panic anxiety, whereas the R(-)-enantiomer was essentially inactive (Sanche
These data suggest that the clinical anxiolytic actions observed with racemic
are due to escitalopram.

4.5 Therapeutic Uses

4.5.A Escitalopram Oxalate

Cerebrovascular accident - Depression; Prophylaxis

Generalized anxiety disorder

Major depressive disorder

Mixed anxiety and depressive disorder

Obsessive-compulsive disorder

Panic disorder

Trichotillomania

4.5.A.1 Cerebrovascular accident - Depression; 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 EVIDENC

b) Summary:

In a 12-month, multicenter, randomized, double-blind study (n= prophylaxis with oral escitalopram 5 or 10 milligrams/day was n than placebo or problem-solving therapy in reducing the freque onset depression in adults with recent ischemic or hemorrhagic (Robinson et al, 2008)

c) Adult:

1) Prophylaxis with oral escitalopram was more effective than place lowering incidence of depression in nondepressed patients with rec 12-month, multicenter, randomized, double-blind study (n=176); hov benefit seen in patients exposed to nonblinded problem-solving ther not statistically significant compared to placebo. Patients older than less than 90 years of age (mean age, 62 years) who had experience ischemic or hemorrhagic stroke within 3 months were included, prov not meet the DSM-IV diagnostic criteria for major or minor depressiv had a Hamilton-17 Depression Rating Scale (HDRS) score of greate (mean score range at baseline, 7 to 7.22). Patients were randomize double-blinded therapy with either escitalopram 5 milligrams (mg)/d patients older than 65 years) or 10 mg/day (for patients 65 years or or placebo (n=58), or nonblinded problem-solving therapy (n=59) fo In the problem-solving therapy arm, patients selected a problem and through 7 steps to form a course of action; therapy involved 6 treatn over the first 12 weeks and 6 reinforcement sessions over the rema months. Assessments were conducted at 3 month intervals using th Clinical Interview for DSM-IV, and patients meeting major or minor d diagnostic criteria and with a HDRS score of greater than 12 were d depression (primary outcome measure). At 12 months, there are 11 minor cases of depression (total, 22.4%) in the placebo arm compar and 2 minor cases (total, 8.5%) in the escitalopram arm. Excluding ((13.5%) of the study patients who dropped out for various reasons p receiving treatment and after adjusting for prior history of mood disc each arm), patients in the placebo group were significantly more like depression compared to patients in the escitalopram group (adjuste (HR), 4.5; 95% confidence interval (CI), 2.4 to 8.2; p less than 0.001 number needed to treat (NNT) of 7.2 acute stroke patients. In the pr therapy group, there were 5 major and 2 minor cases of depression adjusted HR (vs placebo), 2.2; 95% CI, 1.4 to 3.5; p less than 0.001 NNT of 9.1 acute stroke patients. Notably, an intention-to-treat analy included post-randomization dropouts (n=27), with the assumption t developed depression, revealed statistical significance compared to the escitalopram group (34.5% vs 23.1%, respectively; adjusted HR 1.2 to 3.9; p=0.007) but not for the problem-solving therapy group (3 30.5%, respectively; adjusted HR, 1.1; 95% CI, 0.8 to 1.5; p=0.51). secondary efficacy variables, activities of daily living (measured usir Functional Independence Measure) as well as social functioning (m the Social Functioning Exam scores) improved across all 3 groups, significant time to treatment interaction. Additionally, there were no differences in frequency of adverse events, including all-cause hosp and gastrointestinal effects, between the groups (Robinson et al, 20

4.5.A.2 Generalized anxiety disorder

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 EVIDENC

b) Summary:

Indicated in the acute treatment of generalized anxiety disorder (Prod Info LEXAPRO(R) Oral solution, Oral tablets, 2009).
Treatment with escitalopram in older adults (60 years or older) generalized anxiety disorder (GAD) was associated with improv clinical response rates in anxiety symptoms and self-reported r compared to placebo, in a 12 week, randomized, double-blind, controlled, phase 2 study (n=179); however, statistical significa observed only in the modified intent-to-treat analysis (Lenze et

c) Adult:

1) A pooled analysis of three short-term double-blind, placebo-cont flexible-dose studies showed that escitalopram is more effective tha treating generalized anxiety disorder (GAD). Patients (mean age, a 39 years) with a diagnosis of GAD and a Hamilton Rating Scale for (HAMA) total score of at least 18 and at least a score of 2 on the te anxiety items were included. Those with diagnoses of major depres schizophrenia, psychosis, bipolar disorder, developmental or cognit and substance abuse within the past 6 months were excluded. Follo week placebo lead-in period, patients were randomized to receive e escitalopram 10 milligrams (mg) daily (n=429) or placebo (n=427). T escitalopram dose could be increased to 20 mg daily after 4 weeks was judged to be insufficient by the investigator. The primary endpo change in HAMA total score from baseline to week 8. The mean cha baseline for HAMA total score was a 10.1-point decrease (+/-0.3) fo and a 7.6-point decrease (+/-0.3) for placebo (p less than 0.001). At response, defined as a decrease of at least 50% in mean HAMA sc in 47.5% of escitalopram-treated patients and 28.6% of placebo-trea (p less than 0.001). Remission, defined as a HAMA score of 7 or les 26.4% of escitalopram-treated patients and 14.1% of placebo-treate less than 0.001). Clinical Global Impressions of Improvement (CGI- defined as a CGI-I score of 1 or 2, occurred in 52% of escitalopram- patients and 37% of placebo-treated patients (p less than 0.001). In trials, the most commonly reported adverse effects were nausea (es 18.2%; placebo, 7.5%), ejaculation disorder (escitalopram, 14.3%; p 1.5%), insomnia (escitalopram, 11.9%; placebo, 5.6%), fatigue (esc 7.7%; placebo, 2.1%), decreased libido (escitalopram, 6.8%; placeb anorgasmia (escitalopram, 5.7%; placebo, 0.4%) (Goodman et al, 2
Patients who completed 8-week trials comparing escitalopram were invited to participate in a 24-week, open-label, flexible-dos study (n=526) of escitalopram. Inclusion and exclusion criteria as for the previous trials, with the added requirement that the p participated in and completed one of the three 8-week trials wit 72 hours. All patients, regardless of treatment received in the s trials, were given escitalopram 10 milligrams (mg) daily for 4 we weeks of treatment, the dose could be increased to 20 mg daily patient's response was unsatisfactory. The primary endpoint of study was improvement in Hamilton Rating Scale for Anxiety (H Baseline HAMA scores in the placebo-treated group from the le were higher than in those patients who had been treated with e the lead-in trials. However, within 4 weeks of open-label escital treatment, the improvement had equalized between the two gro remained similar throughout the rest of the study. Of the patien 56.8% completed the extension study. For the intent-to-treat (IT (n=521), the mean change in HAMA score at 24 weeks was -3. and 76% of patients were considered responders and 49% rem (Davidson et al, 2005).

2) Escitalopram was effective in the prevention of relapse of genera disorder (GAD) in a clinical trial that began with a 12-week, open-lab (n=491) followed by a double-blind, randomized treatment period (n between 24 and 76 weeks. Patients included were those between th and 65 with a primary diagnosis of GAD and a Hamilton Rating Sca (HAMA) score of 20 or greater. Those with a diagnosis of major dep disorder, panic disorder, social anxiety disorder, bipolar disorder, ea disorders, suicidal ideations, psychoses, and substance abuse diso excluded. Patients were given escitalopram 10 milligrams (mg) daily week of the open-label period, then doses were increased to 20 mg remainder of the 12-week period. At 12 weeks, responders were ra continue escitalopram 20 mg daily or placebo for the maintenance p

double-blind period ended on the same date for all patients (24 to 7
treatment), then was followed by a 2-week taper. The primary endp
to relapse during the double-blind period, as defined by an increase
total score of 15 or greater or investigator-determined lack of efficac
HAMA total score at the beginning of the open-label period was 27.
standard deviation (SD). At the start of the double-blind period, the
total score for the placebo group was 5 +/-3.1, and the mean HAMA
for the escitalopram group was 5.7 +/-2.9. Escitalopram was benefic
to placebo with regard to time to relapse (p less than 0.001; log-ranl
Escitalopram was associated with decreased relapse compared to p
versus 56%, respectively; p less than 0.001). The hazard ratio for re
4.04 (95% confidence interval (CI), 2.75 to 5.94). The change in tota
score from the beginning of the double-blind period to the end of 24
decrease of 0.83 in the escitalopram group and an increase of 0.39
group (treatment difference, -1.22; 95% CI, -2.28 to -0.17). The mos
side effects reported during the open-label period of treatment with
include nausea (24.2%), headache (16.7%), ejaculation dysfunction
dizziness (11.6%), fatigue (11.2%), insomnia (11%), and dry mouth
most common side effects reported during the double-blind portion
were headache (escitalopram, 11.2%; placebo, 3.7%), rhinitis (escit
13.9%; placebo, 5.9%), and upper respiratory tract infections (escita
placebo, 2.7%), and the withdrawal rate for adverse effects was sim
the two groups (escitalopram, 7%; placebo, 8.5%) (Allgulander et al

a) Geriatric Populations

1) Treatment with escitalopram in older adults (60 years o
generalized anxiety disorder (GAD) was associated with im
cumulative clinical response rates in anxiety symptoms an
role functioning compared to placebo, in a 12-week, rando
double-blind, placebo-controlled, phase 2 study (n=179); h
statistical significance was observed only in the modified ir
analysis. Patients with a principal diagnosis of GAD accorc
Diagnostic and Statistical Manual of Mental Disorders, Fou
(DSM-IV) criteria, and clinically significant anxiety sympton
a score of 17 or greater in the Hamilton Anxiety Rating Sca
total anxiety score range from 0 to 56) were enrolled. Patie
excluded from the study if they had a history of lifetime psy
bipolar disorder, dementia, increased suicide risk, medical
ongoing psychotherapy, and current antidepressant or anx
(with the exception of benzodiazepine use equivalent to lo
milligrams/day (mg/day)). Eligible patients were randomize
fashion to receive escitalopram 10 mg orally daily (mean a
7.4 years (yr); n=85) or matching placebo (mean age, 72.2
n=92) for 12 weeks. Patients who did not achieve a clinical
after 4 weeks of escitalopram 10 mg orally daily were give
escitalopram dose of 20 mg orally daily, as tolerated. Outc
defined as changes in symptoms of anxiety on the Clinical
Impressions Improvement Scale (CGI-I), HARS, Penn Stat
Questionnaire (PSWQ), and role functioning. The primary
a response defined as CGI-I of 1 (very much improved) or
improved). In the modified intent-to-treat (ITT) analysis am
participants who provided at least 1 follow-up data point (n
response was higher in the escitalopram arm (60%; 95% C
71%) compared with the placebo arm (45%; 95% CI, 36%
p=0.048). However, in the ITT analysis (n=179), the respor
statistically different between the escitalopram and placebo
arms (57%; 95% CI, 46% to 67% vs 45%; 95% CI, 35% to
Overall, cumulative incidence of response was higher in th
escitalopram arm versus placebo arm (mean response rate
CI, 58% to 80% vs 51%; 95% CI, 40% to 62%, respectively
Treatment with escitalopram also significantly improved the
activity limitations subscale scores compared to placebo. F
somnolence (41.1%) were the most common adverse effec
with escitalopram and appeared to be dose-related (Lenze

4.5.A.3 Major depressive disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (age 12 years and old
Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence fa
Recommendation: Adult, Class IIa; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENC

b) Summary:

Indicated for the acute and maintenance treatment of major de disorder in adults and adolescents age 12 years and older (Pro LEXAPRO(R) Oral solution, Oral tablets, 2009).

Escitalopram has been more effective than placebo in alleviatir of major depression in adults (Burke et al, 2002b; Gorman et al Wade et al, 2002; Montgomery et al, 2001a; Anon, 2000; Wade Burke, 2000a; Gorman, 2001a).

Escitalopram was not statistically better than placebo in the trea major depressive disorder (MDD) among pediatric patients age years (n=261) (Wagner et al, 2006); however, in a multicenter, randomized, placebo-controlled study (n=316), escitalopram wa more effective than placebo among adolescent patients with M al, 2009).

The efficacy of escitalopram for maintenance treatment of majc disorder in adolescents age 12 to 17 years was extrapolated fr (Prod Info LEXAPRO(R) Oral solution, Oral tablets, 2009).

c) Adult:

1) Randomized studies (published and unpublished) have reported greater efficacy of escitalopram 10 or 20 milligrams (mg) daily comp placebo in the treatment of major depressive disorder, based on imp the Montgomery Asberg Depression Rating Scale (MADRS), the Cli Impressions (CGI) scale, and the Hamilton Depression Rating Scale (Burke et al, 2002b; Gorman et al, 2002b; Wade et al, 2002; Montg 2001a; Anon, 2000; Wade et al, 2001b; Burke, 2000a; Gorman, 200 these studies appeared to involve the same patient populations, wit reinterpretation of data; others were the same population with varie treatment. The three published studies were all of short duration (8 et al, 2002b; Gorman et al, 2002b; Wade et al, 2002). Differences ir of escitalopram (10 and 20 mg) relative to placebo at endpoint in the depression were statistically significant and amounted to decreases points on the MADRS (Burke et al, 2002b; Wade et al, 2002).

2) In studies providing response rates (50% reduction in MADRS s compared to baseline) (Burke et al, 2002b; Gorman et al, 2002b; W 2002; Wade et al, 2001b; Gorman, 2001a), 42% to 44% of patients placebo with 56% to 61% responding to escitalopram 10 or 20 millig this difference reached statistical significance in favor of escitalopra

3) In direct comparisons (unpublished studies), escitalopram 10 or has not been statistically superior to citalopram 20 or 40 mg daily (G 2001a; Burke, 2001b; Montgomery et al, 2001c). However, in an an pooled data from placebo-controlled trials, escitalopram 10 or 20 mg statistically significant (p less than 0.05) decrease in Montgomery A Depression Rating Scale scores compared to citalopram 40 mg dail weeks, but not at weeks 2, 4, or 8 (Gorman et al, 2002b).

4) In a randomized, double-blind study involving patients with majo disorder of at least one month in duration (n=366), Montgomery Asb Depression Rating scale (MADRS), Clinical Global Impression (CGI Hamilton Rating Scale for Depression (HAMD) scores were improve significantly greater extent with escitalopram 10 or 20 milligrams (m placebo. This difference was first noted at one week on the mood ite HAMD scale and on the CGI scale. At week 2 there was also a stati significant difference noted on the MADRS and HAMD scales; impr remained statistically significant in favor of escitalopram throughout of therapy. Discontinuation of treatment due to adverse events was frequent in the 20-mg group compared to 10 mg daily or placebo gr al, 2002b).

d) Pediatric:

1) In a multicenter, double-blind, randomized, placebo-controlled st escitalopram was significantly more effective than placebo in the tre adolescent patients with major depressive disorder (MDD). Adolesc diagnosed with MDD as defined by the Diagnostic and Statistical M Mental Disorders (DSM-IV) criteria and Kiddie Schedule for Affectiv

and Schizophrenia for School-Age Children - Present and Lifetime v
current MDD episode of at least 12 weeks duration, a score of at lea
Children's Depression Rating Scale-Revised (CDRS-R) at both scre
baseline visits, a Clinical Global Impressions-Severity (CGI-S) Scale
least 4 at baseline, a Kaufman Brief Intelligence Test score of 80 or
eligible for the study. There was a 2-week screening period and all p
received single-blind placebo during the second week. Following the
period, eligible patients were randomized to receive escitalopram 10
milligrams/day (mg/day) for the first 3 weeks (n=158; mean age, 14.
years (yr)) or placebo (n=158; mean age, 14.5 +/- 1.5 yr). After 3 or
escitalopram dose could be adjusted to 20 mg/day or remain at 10 m
patients developed intolerance at higher doses. Baseline characteri
similar between the escitalopram arm (mean duration of depressive
+/- 17.4 months; antidepressant naive, 81.3%) and the placebo arm
duration of depressive episode, 16.5 +/- 15.4 months; antidepressa
85.4%). The mean baseline CDRS-R scores (57.6 vs 56; p=0.034) a
scores (4.6 vs 4.4; p=0.007) indicated greater severity of depressio
escitalopram arm compared with the placebo arm, but the difference
clinically significant. A total of 81.3% (126 of 154) of patients in the e
group completed the 8 weeks of treatment compared to 84.7% (133
patients who received placebo. The mean dose of escitalopram was
mg/day and 68.4% patients who received escitalopram had a dose
compared to 76.4% of patients in the placebo arm. Based on the int
analysis, patients who received escitalopram experienced a greater
in the CDRS-R scores at week 8 (primary endpoint) compared with
received placebo (mean +/- standard error of mean, -22.1 +/- 1.22 v
1.27; difference, -3.356; 95% CI, -6.226 to -0.486; p=0.22). Addition
change from baseline to week 8 for the CGI-S scores (secondary en
greater for the patients who received escitalopram compared with p
+/- 0.11 vs 1.4 +/- 0.12; difference, -0.37; 95% CI, -0.64 to -0.1; p=0
Escitalopram was associated with a higher incidence of insomnia (1
6.4%), nausea (10.3% vs 8.3%) and influenza-like symptoms (7.1%
Relative to escitalopram, placebo was associated with a higher incid
menstrual cramps (15.2% vs 10.9%) and inflicted injury (13.4% vs 9
al, 2009).

2) In an 8-week, multicenter, double-blind, randomized, placebo-co
among children and adolescents aged 6 to 17 years with major dep
disorder (n=261; 6 to 11 years, n=104; 12 to 17 years, n=157), escit
not statistically better than placebo in outcome measures. All patien
12.3 +/- 3 years) were free of other psychiatric disorders, of whom 5
female. Patients were randomly assigned to either escitalopram 10
(mg) once daily for the first 4 weeks, followed flexible dosing of 10 t
(n=129) or matching placebo (n=132). The median dose of escitalop
+/- 2.3 mg per day. Baseline Children's Depression Rating Scale-Re
R) scores were 54.5 for escitalopram-treatment patients and 56.6 fo
treated patients, with higher scores indicating worsening of depress
the intent-to-treat analysis using the last observation-carried-forwar
approach, the improvement from baseline at week 8 in the CDRS-R
(primary outcome) was similar between the escitalopram and the pl
(mean change, -21.9 vs -20.2; p=0.31). Escitalopram was not statis
than placebo in Clinical Global Impressions-Improvement (CGI-I) (p
Clinical Global Impressions-Severity (CGI-S) (p=0.057), and Childre
Assessment Scale (CGAS) Compliance (p=0.065) scores. In the su
analysis among adolescents aged 12 to 17 years (n=157) using the
approach, escitalopram demonstrated significant improvements fro
compared with placebo in CGI-I (2.4 vs 2.8; p=0.038), CGI-S (-1.5 v
and CGAS scores (15.7 vs 10; p=0.005). Compliance rates were no
different, at 77.9% and 86.5% for the escitalopram and the placebo
respectively. Headache (22.9% vs 21.8%), abdominal pain (10.7% v
nausea (7.6% vs 4.5%) were more frequently associated with escita
placebo. Suicidal ideation and intent were reported in one escitalop
patients and 2 placebo-treated patients, none of which was success
et al, 2006).

4.5.A.4 Mixed anxiety and depressive 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 EVIDENC

b) Summary:
Effective in treating anxiety in patients with major depression in studies (Burke et al, 2002b; Lydiard, 2001c)

c) Adult:
1) Escitalopram 10 or 20 milligrams (mg) daily was reported to be s placebo in treating both anxiety and depression in outpatients with r depression in an 8-week, placebo-controlled, double-blind study. Th statistically significant decreases in anxiety scores relative to placeb treatment groups; 1.1 points (p=0.04) for the 10 mg escitalopram gr points (p less than 0.01) for the 20 mg escitalopram group. These d represented the change from baseline to endpoint (week 8) as mea Hamilton Rating Scale for Anxiety (Burke et al, 2002b).
2) In an unpublished, 8-week, placebo-controlled studies, escitalop milligrams (mg) daily was reported to be superior to placebo in treat anxiety and depression in outpatients with major depression. Antian were demonstrated by improvements in the anxiety subscale of the Depression Rating Scale (HAMD), the inner tension component of t Montgomery-Asberg Depression Rating Scale (MADRS), and the H Anxiety Scale (HAMA). Doses of 20 mg tended to be more effective Combined data for both doses indicated antianxiety and antidepress comparable to citalopram 20 or 40 mg daily; slightly faster improven symptoms was seen with escitalopram versus citalopram, although statistically significant (Lydiard, 2001c).

4.5.A.5 Obsessive-compulsive 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 EVIDENC

b) Summary:
In patients with obsessive-compulsive disorder, continued treat escitalopram during a 24-week, randomized, double-blind, plac phase maintained clinical response observed after 16 weeks of treatment, and yielded higher relapse prevention than placebo al, 2007).
In a 24-week, randomized, double-blind study (n=466), treatme escitalopram 20 milligrams (mg) per day was more effective tha and achieved comparable efficacy to paroxetine in treating adu to-severe obsessive-compulsive disorder (Stein et al, 2007).

c) Adult:
1) General Information
a) Treatment with oral escitalopram was more effective than pl treating adult moderate-to-severe obsessive-compulsive disord 24-week, randomized, double-blind study (n=466) (Stein et al, 2 study also employed paroxetine as an active-comparator and e efficacy was comparable to that observed with paroxetine. Com effects included nausea, headache, and fatigue among the acti arms. In another study in adults with moderate-to-severe OCD, weeks of open-label treatment with escitalopram 10 or 20 mg/d responders randomized to 24 weeks of continued treatment wit escitalopram at the same doses during the subsequent double- maintained clinical response and had lower relapse rates (52% compared to placebo (Fineberg et al, 2007). Notably, exclusion with other primary or axis I psychiatric disorders and/or significa comorbidity in both studies may limit the generalizability of thes

2) Clinical Trials
a) Twenty-four weeks of continued treatment with escitalopram randomized, double-blind, placebo-controlled phase maintained response observed after 16 weeks of open-label treatment and higher relapse prevention in patients with obsessive compulsive (OCD). Patients with moderate-to-severe OCD diagnosed acco

DSM-IV (Third Revision) criteria (aged 18 to 65 years; mean, 3
were required to have a Yale-Brown Obsessive Compulsive Sc
total score of 20 or higher, with an OCD duration of at least 1 y
symptoms for at least 6 months, and no other primary psychiat
significant somatic comorbidity. Patients (n=468; mean +/- stan
(SD) Y-BOCS total score, 26.4 +/- 3.7) were first enrolled in a 1
open-label phase, receiving oral escitalopram 10 mg/day for th
and then titrated up to 20 mg/day based on tolerability and effic
was fixed from weeks 12 to 16. Of the 374 patients completing
phase, 320 who responded to treatment (ie, had a 25% or grea
from baseline Y-BOCS total score; mean +/- SD Y-BOCS total
weeks, 15 +/- 8.5) were entered into the double-blind phase an
to receive either escitalopram 10 or 20 mg/day (n=163) or place
for 24 weeks. Escitalopram was tapered off in patients assigne
as well as in the escitalopram group at the end of the study (we
of patients in the escitalopram group received the 20 mg/day d
the double-blind phase, trained raters assessed patients using
National Institute of Mental Health-Obsessive Compulsive Scal
OCS), and Clinical Global Impressions-Severity of Illness (CGI-
Improvement of Illness (CGI-I) every 2 weeks until week 8 and
weeks. Relapse was defined as an increase in the Y-BOCS tot
or greater, or lack of efficacy based on the investigator's judgm
Meier survival analysis revealed that the primary efficacy meas
relapse of OCD from the start of the double-blind phase (baseli
significantly in favor of escitalopram compared to placebo (p les
log-rank test). The relapse rate was significantly higher in the p
compared to the escitalopram group (52% vs 23%; p less than
yielding an estimated hazard ratio of 2.74 (p less than 0.001). A
significant between-group difference in Y-BOCS total score was
week 4 of the double-blind phase, which was maintained throug
While the mean +/- SD Y-BOCS total scores in the placebo gro
from 11.2 +/- 5.3 at baseline to 14.8 +/- 7.5, Y-BOCS total scor
escitalopram group were essentially unchanged (10.8 +/- 5.4 at
10.7 +/- 7.3 at 24 weeks), yielding an adjusted mean change (p
escitalopram) of -3.67 (95% confidence interval, -4.91 to 2.42).
secondary efficacy measures, the mean NIMH-OCS, CGI-S, ar
scores in the escitalopram group, all of which had reduced sign
baseline during the open-label phase, remained either unchang
decreased compared to values at randomization. In the placebo
measures were increased at week 24 compared to randomizati
adjusted mean change from randomization was statistically sig
favor of escitalopram for all measures. Of the 20% (n=94/468)
who withdrew from the study during the open-label phase, 28 p
withdrew due to adverse events. During the double-blind phase
rates were comparable between the groups (escitalopram, 7.9%
8.9%). Adverse events occurred in 39% of escitalopram-treated
compared to 31.6% of placebo-treated patients, with the majori
being mild to moderate. Despite the taper, discontinuation effec
(5.7% vs 0.6%; p less than 0.001) and dizziness (15.9% vs 0.6%
frequently reported in the placebo group during the first 2 week
double-blind phase (p less than 0.001 for both) (Fineberg et al,

b) Treatment with oral escitalopram 20 milligrams (mg) per day
effective than placebo and achieved comparable efficacy to pa
treating adult moderate to severe obsessive-compulsive disord
24-week, randomized, double-blind study (n=466). Outpatients
years (mean, 38 years) with a primary diagnosis of OCD accor
DSM-IV (Third Revision) criteria, with a Yale-Brown Obsessive
Scale (Y-BOCS) total score of 20 or higher, an OCD duration o
year and stable symptoms for at least 6 months, and no other c
psychiatric disorders were included. Patients were randomized
either escitalopram 10 mg/day (n=116) or 20 mg/day (n=116), p
mg/day (n=119), or placebo (n=115) for 24 weeks, followed by
taper period. Trained raters assessed efficacy primarily using th
total score every 2 weeks until week 12 and every 4 weeks sub
Secondary efficacy measures included the National Institute of
Health-Obsessive Compulsive Scale (NIMH-OCS), and Clinical
Impressions-Severity of Illness (CGI-S) and Improvement of Illn

Response was defined as a score of 2 or less on the CGI-I, and reduction in the Y-BOCS total score at week 12 and 24; remiss score of 1 or 2 on the CGI-S, and a Y-BOCS total score of 10 o weeks 12 and 24. At baseline, the mean +/- standard deviation total scores were 27.7 +/- 4.2, 26.6 +/- 3.7, 26.6 +/- 3.9, and 27 placebo, escitalopram 10 mg/day, escitalopram 20 mg/day, and 40 mg/day groups, respectively. Compared to placebo, the mea Y-BOCS total score from baseline to week 12 (primary efficacy statistically significant for the escitalopram 20 mg/day group (m difference, -3.21; 95% confidence interval (CI), -5.19 to -1.23; p 0.01) and the paroxetine group (mean difference, -2.47; 95% C 0.51; p less than 0.05). For the escitalopram 20 mg/day group, treatment difference from placebo in Y-BOCS total scores eme 6 (p less than 0.05) and continued through week 24 (p less tha Analysis of the per-protocol population revealed statistically sig +/- SD changes from baseline to week 12 in Y-BOCS total scor to placebo (-8.46 +/- 0.76; n=97) for the escitalopram 10 mg/da 0.78; p less than 0.01; n=92), escitalopram 20 mg/day (-12.14 - than 0.001; n=95), and the paroxetine 40 mg/day groups (-11.6 less than 0.01; n=90). For the escitalopram 20 mg/day group, a responder status and remitter status from placebo emerged at week 12, respectively, based on the Y-BOCS total score criteria other secondary endpoints, all active treatment groups showed significant improvement versus placebo in NIMH-OCS, CGI-S, scores at both weeks 12 and 24. Of 131 study withdrawals, a s higher proportion of patients withdrew from the placebo group (lack of efficacy compared to the escitalopram 20 mg/day (6.1% paroxetine 40 mg/day (7.7%) groups (p less than 0.05 for both) (19% to 27%), headache (17% to 22%), and fatigue (12% to 19 most commonly reported adverse events in the active treatmen (Stein et al, 2007).

4.5.A.6 Panic 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 EVIDENC

b) Summary:

Reduced panic attack frequency in patients with panic disorder 2003)

c) Adult:

1) Escitalopram treatment reduced panic attack frequency in patien disorder. In a randomized, double-blind, placebo-controlled, flexible multicenter study, patients with panic disorder with or without agora received escitalopram (n=128; mean dose, 10.8 milligrams (mg)/day (n=119; mean dose, 21.3 mg/day), or placebo for 10 weeks. Panic a frequency in escitalopram-treated patients was significantly reduced baseline to endpoint as compared with patients who received placel 0.32, respectively; p=0.04). Additionally, the percentage of patients escitalopram group with zero panic attacks at endpoint as compared approached statistical significance (50% vs 38%, respectively; p=0.(citalopram group was not statistically different from placebo on eithe measures. However, patients in both the escitalopram and citalopra show significant improvements in numerous other efficacy measure placebo including, Panic and Agoraphobia Scale total score, Clinica Impression- Improvement (CGI-I) and -Severity of Illness (CGI-S) sc Phobic avoidance score, Patient Global Evaluation score, and Qual Enjoyment and Satisfaction Questionnaire score (p less than or equ values). The most commonly reported adverse events included hea mouth, nausea, insomnia, fatigue, dizziness, and somnolence (Stah

4.5.A.7 Trichotillomania

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 EVIDENC

b) Summary:

Treatment with escitalopram led to significant improvement in s trichotillomania in adult women (mean age, 32.5 years) in a sm open-label, prospective trial (n=20) (Gadde et al, 2007)

c) Adult:

1) In a small, 12-week, open-label, prospective trial (n=20), treatme escitalopram led to significant improvement in symptoms of trichotill adult women. Enrollees (mean age, 32.5 years; 17 Caucasian) had DSM-IV-TR diagnosis of trichotillomania and were required to have or higher on the National Institute of Mental Health (NIMH) trichotillo severity scale (TSS) and 4 or higher on the NIMH trichotillomania in scale (TIS). Patients with a history of mania, hypomania, schizophre psychotic disorders, with a primary diagnosis of obsessive-compuls or those with recent (4 weeks prior) use of antidepressants or other medications were excluded. Study patients received escitalopram 1 (mg) orally once daily in the evening. Based on clinical response an the dose was increased in 10-mg increments at 4-week intervals up maximum dose of 30 mg/day by week 8. Patients kept diaries detail pulling behavior prior to study initiation and maintained them during study duration. Assessments were conducted every 2 weeks using Massachusetts General Hospital (MGH) Hair Pulling scale, clinician rated Clinical Global Impression improvement scale (CGI-I). The TS (range, 0 to 25), assessing the frequency of hair pulling, resistance, urge, distress, and interference, was the primary efficacy measure. a clinician-rated CGI-I score of 1 (very much improved) or 2 (much i at least 50% reduction in TSS total score were classified as respond baseline, most study patients displayed hair pulling from more than the scalp being the most common site (n=16). The mean +/- standa duration of trichotillomania was 15.3 +/- 2.1 years, and an equal nur patients displayed relaxation- and stress-associated trichotillomania The mean +/- SE escitalopram dose was 21.9 +/- 2.1 mg/day. Base intention-to-treat (ITT) analysis (including all patients with at least 1 assessment), 50% (8/16) of patients were responders. Of the 8 resp were rated as very much improved and 5 were rated as much impro the clinician- and patient-rated CGI-I. In the ITT population, the mea total score decreased over time from 15.4 +/- 0.9 at baseline to 9.4 week 12 (p less than 0.0001); scores were similar among study com (n=12; 15.8 +/- 1 at baseline to 7.5 +/- 1.2 at week 12; p less than 0 Among secondary outcomes, significant improvements occurred in +/- 0.3 to 3.3 +/- 0.4; p less than 0.0001) and MGH hair pulling scale to 10.6 +/- 1.2; p less than 0.0015) scores for the ITT set. Results w among study completers. Specific predictors of response were not e this small study set. Treatment-emergent adverse events were mos included nausea (n=6), insomnia (n=4), fatigue (n=2), decreased lib orgasmic dysfunction (n=2). Bruising, which resolved after discontin was reported in 1 patient (Gadde et al, 2007).

4.6 Comparative Efficacy / Evaluation With Other Therapies

Citalopram

Duloxetine

Paroxetine

4.6.A Citalopram

Depression

Mixed anxiety and depressive disorder

4.6.A.1 Depression

a) Direct placebo-controlled comparisons of escitalopram 10 or 20 millig daily and citalopram 20 or 40 mg daily in patients with major depression revealed a trend toward the superiority of escitalopram in improving sym although this did not reach statistical significance (Gorman et al, 2002a; et al, 2001a; Burke et al, 2002a). In all studies, improvements from base escitalopram versus placebo tended to be greater than citalopram versu leading the investigators to indicate greater efficacy of escitalopram; hov statistical superiority of escitalopram versus citalopram for baseline impr not demonstrated. Using placebo-effect versus baseline comparisons, th action of escitalopram was judged faster than that of citalopram; statistic between escitalopram and citalopram were not applied.

b) In pooled data from three 8-week, placebo-controlled studies compar 20 to 40 mg daily and escitalopram 10 to 20 mg daily in patients with ma disorder, improvement of Montgomery Asberg Depression Rating Scale scores was significantly greater with escitalopram versus placebo after c whereas borderline significance (p=0.068) versus placebo was seen for week 4. Similar trends were reported for Clinical Global Impressions (CG scores. In patients completing 8 weeks of treatment, MADRS scores had at least 50% in 59%, 53%, and 41% of patients receiving escitalopram, c and placebo, respectively; MADRS response rates for both escitalopram citalopram were significantly greater compared to placebo, although ther significant difference between active drug groups (Gorman et al, 2002a)

4.6.A.2 Mixed anxiety and depressive disorder

a) In unpublished, 8-week placebo-controlled studies, escitalopram 10 c milligrams (mg) daily was comparable in efficacy to citalopram 20 or 40 r treating both anxiety and depression in outpatients with major depressio 2001). A trend toward faster improvement of anxiety symptoms was see escitalopram, although this was not statistically significant. Adverse-effe provided only for escitalopram.

4.6.A.3 Adverse Effects

a) In one large study (N=491) adverse effects occurred in 71%, 79%, 86 of patients treated with placebo, escitalopram 10 mg daily, escitalopram and citalopram 40 mg daily, respectively; corresponding incidences of th discontinuation due to adverse effects were 2.5%, 4.2%, 10.4%, and 8.8 no significant statistical difference in the number of adverse effects betw and escitalopram 10 mg daily. There was also no significant statistical di the number of adverse effects reported for escitalopram 20 mg daily and 40 mg daily, but both groups had statistically (p less than 0.01) higher ra treatment-emergent adverse effects than placebo or escitalopram 10 mg et al, 2002a).

4.6.B Duloxetine

4.6.B.1 Major depressive disorder

a) In an 8-week randomized, double-blind, placebo- and active-compara multicenter, noninferiority trial in adult patients (n=684) with major depre (MDD), onset of efficacy for duloxetine 60 milligrams (mg) daily was at le onset for escitalopram 10 mg daily, and patients in both active treatment more likely to meet onset criteria than placebo patients. Patients aged 1 older (range, 18 to 79 years), meeting the DSM-IV criteria for MDD and Montgomery-Asberg Depression Rating Scale (MADRS) total score of 2 and a Clinical Global Impression Scale-Severity (CGI-S) score of 4 or gr included. Patients were randomized to receive either duloxetine 60 mg c mean age, 41.1 years; mean baseline Hamilton Rating Scale for Depres Maier subscale score, 17.6), escitalopram 10 mg daily (n=274; mean ag mean baseline HAMD score, 17.8), or placebo (n=137; mean age, 42.5 baseline HAMD score, 17.7) during an 8-week, acute treatment period. efficacy (primary endpoint) was defined as achieving a 20% or greater d HAMD score by week 2 that was sustained for the remainder of the acut period. In the intent-to-treat analysis, the probability of meeting efficacy was similar in the duloxetine and escitalopram groups (42.6% vs 35.2%, difference, 7.4%; 95% confidence interval (CI), -1.3% to 16.2%; p=0.097 patients in both groups were more likely to achieve efficacy onset compa placebo patients (21.5%; duloxetine vs placebo, p less than 0.001; escit

placebo, p=0.008). The noninferiority of duloxetine to escitalopram was
following a per-protocol analysis. In an analysis for the main treatment e
data from all visits were pooled, a significantly greater proportion of dulo
patients achieved efficacy onset vs escitalopram patients (p=0.026), and
proportion of patients in both active treatment groups achieved efficacy
placebo patients (p less than or equal to 0.018 for both). The median tim
was significantly shorter among duloxetine-treated patients than both es
and placebo-treated patients (23 days vs 41 days vs 55 days, respective
vs escitalopram, p=0.032; duloxetine vs placebo, p less than 0.001), and
to onset did not differ between escitalopram and placebo patients (p=0.0
probability of achieving a treatment response (secondary endpoint) by w
as a 50% or greater improvement in HAMD total score, was similar amo
duloxetine (48.7%), escitalopram (45.3%), and placebo (36.9%) groups,
probability of remission (HAMD total score of 7 or less) also did not diffe
groups (40.1% vs 33% vs 27.7%, respectively). The 191 subjects who fa
complete the study were evenly distributed among the groups, and a sim
percentage in each group discontinued due to adverse effects. Nausea
commonly caused discontinuation among duloxetine patients compared
escitalopram patients (2.9% vs 0.4%, respectively; p=0.02). Both nausea
mouth occurred more often in duloxetine patients compared to escitalop
placebo patients and at a rate greater than 10% (nausea, 23.8% vs 12%
mouth, 21.6% vs 10.9% vs 10.9%; p less than 0.05 for all). Although this
focused on the acute 8-week treatment period, subjects completing this
continued with blinded treatment for an additional 6 months (Nierenberg
During the 6-month extension phase, the duloxetine dose ranged from 6
mg/day and the escitalopram dose ranged from 10 to 20 mg/day; placeb
responders from the acute treatment phase were assigned in a double-b
active treatment. Among the 431 patients (63%) continuing on in the ext
there were no significant differences in antidepressant efficacy between
and escitalopram groups based on HAMD total scores. The probability o
was 70% and 75% among the duloxetine and escitalopram groups, resp
(p=0.44). The only statistically significant difference between the groups
HAMD sleep subscale, where escitalopram-treated patients had greater
in insomnia than duloxetine-treated patients (mean change from baselin
1.55; p less than 0.05). Although discontinuation rates over the 8-month
higher in the duloxetine group vs escitalopram (62% vs 55%; p=0.02), ra
discontinuation due to adverse events were similar (12.8% vs 12%, resp
(Pigott et al, 2007).

b) In a randomized, double-blind, fixed-dose, noninferiority trial (n=294)
duloxetine was at least as effective as escitalopram for the long term tre
major depressive disorder (MDD), escitalopram was superior in acute tre
study included outpatients aged 18 to 73 years old with MDD according
(Third Revision) criteria, with a Montgomery-Asberg Depression Rating S
(MADRS) total score of 26 or greater, and with a Clinical Global Impress
Severity (CGI-S) score of 4 or greater were included. With the exception
compulsive disorder, posttraumatic stress disorder, or panic disorder, pa
secondary, current, comorbid anxiety disorder were included. Study pati
randomized to receive either duloxetine 60 milligrams (n=151) or escitalo
(initial dose, 10 mg/day; increased after 2 weeks; n=143) orally once dai
weeks. At baseline, the MADRS scores were 32.1 +/- 4.4 and 32.5 +/- 4.
duloxetine and escitalopram groups, respectively. At the end of the 24 w
mean change from baseline in MADRS score in the intent-to-treat popul
endpoint) for escitalopram and duloxetine were -23.4 and -21.7, respecti
(p=0.055). Based on a per-protocol analysis (n=287), the between-group
(escitalopram minus duloxetine) in MADRS scores at 24 weeks was 0.67
confidence interval (CI), -1.06 to 2.41; p not significant), which met the p
noninferiority criteria (ie, upper limit of the one-sided CI did not include 2
Furthermore, superiority of escitalopram was evident (ie, upper limit of th
CI did not include zero) at week 8 and week 24 based on a between-gro
differences of 2.54 (95% CI, p=0.011) and 2.21 (p=0.027), respectively,
per-protocol population. At 24 weeks, 81.6% (n=115) of escitalopram-tre
were considered to be responders (ie, 50% or greater decrease from ba
MADRS total score) compared with 73% (n=112) of duloxetine-treated p
Among secondary endpoints, escitalopram was significantly more effecti
duloxetine in CGI-I (p=0.039) score reduction from baseline to week 8. E
also was significantly better than duloxetine in the Sheehan Disability Sc
work score reduction at week 24, and SDS total score reduction at week

less than 0.05 for all). Significantly more patients on duloxetine reported (12.6% vs 4.9%) and constipation (8.6% vs 2.8%) compared to escitalop almost twice the withdrawal rate due to adverse events in the duloxetine vs 9%; p less than 0.05) (Wade et al, 2007).

4.6.C Paroxetine

4.6.C.1 Generalized anxiety disorder

a) In a randomized, double-blind, multi-center trial involving patients (m approximately 37 years) with moderate to severe generalized anxiety dis treatment with either escitalopram (10 to 20 milligrams (mg) per day), or (20 to 50 mg per day) lead to improvements over time in all efficacy mea however, escitalopram was better tolerated. The primary efficacy endpoi change in Hamilton Anxiety Scale (HAMA) total score from baseline to w intent -to-treat (ITT) population. Mean baseline HAMA scores were 23.7 standard error of the mean (SEM) for the escitalopram-treated patients (23.4 +/- 0.4 SEM for the paroxetine-treated patients (n=61). Upon analys data, there were no statistically significant differences between treatmen week 8 or week 24. At week 24, mean changes in HAMA scores were -1 SEM and -13.3 +/- 1 SEM for the escitalopram and paroxetine groups, re The proportions of patients who met the response criterion (Clinical Glob Impressions of Improvement (CGI-I) of 1 or 2) at week 8 were 65% for e and 55.7% for paroxetine and at week 24 were 78.3% and 62.3%, respe differences were not statistically significant. A greater proportion of patie with paroxetine withdrew from the study due to adverse events compare receiving escitalopram (22.6% vs. 6.6%, respectively; p=0.02). While no adverse event was reported as the reason for discontinuation of escitalo by more than one patient, headache, insomnia, and nausea each lead to discontinuation of paroxetine in 2 or more patients. Upper respiratory tra and diarrhea were reported more frequently with escitalopram than with (14.8% vs. 4.8% and 21.3% vs. 8.1%, respectively). Insomnia (25.8% vs constipation (14.5% vs. 1.6%), ejaculation disorder (30% vs. 14.8%), an (26.2% vs. 5.9%) and decreased libido (22.6% vs. 4.9%) occurred more the paroxetine group compared to the escitalopram group, respectively. incidence of treatment emergent adverse events was 88.7% for paroxeti for escitalopram (Bielski et al, 2005).

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