DRUGDEX® Evaluations

FLUOXETINE HYDROCHLORIDE/OLANZAPINE

0.0 Overview

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

2) Dosing Information
- **a)** Adult
  - **1)** Bipolar disorder, depressed phase
    - **a)** initial, olanzapine 6 mg/ fluoxetine 25 mg ORALLY once daily each evening (Prod Info SYMBYAX(R) oral
    - **b)** usual range, olanzapine 6 to 12 mg/fluoxetine 25 to 50 mg ORALLY once daily each evening (Prod Info S
  - **2)** Major depressive disorder, Treatment resistant
    - **a)** initial, olanzapine 6 mg/ fluoxetine 25 mg ORALLY once daily each evening (Prod Info SYMBYAX(R) oral
    - **b)** usual range, olanzapine 6 to 18 mg/fluoxetine 25 to 50 mg ORALLY once daily each evening (Prod Info S

3) Contraindications
- **a)** concomitant use of pimozide, MAOIs, or thioridazine (Prod Info SYMBYAX(R) oral capsule, 2009)

4) Serious Adverse Effects
- **a)** Death
- **b)** Depression, Worsening
- **c)** Diabetic ketoacidosis
- **d)** Dyskinesia
- **e)** Hyponatremia
- **f)** Mania
- **g)** Neuroleptic malignant syndrome
- **h)** Pulmonary eosinophilia
- **i)** Seizure
- **j)** Suicidal thoughts
- **k)** Suicide
- **l)** Violent behavior

5) Clinical Applications
- **a)** FDA Approved Indications
  - **1)** Bipolar disorder, depressed phase
  - **2)** Major depressive disorder, Treatment resistant

1.0 Dosing Information

Drug Properties

Storage and Stability

Adult Dosage

Pediatric Dosage

1.1 Drug Properties

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

1.2 Storage and Stability

A) Preparation
- **1)** Oral
  - **a)** The combination of olanzapine/fluoxetine should be administered in the evening. While food has no appre
    fluoxetine given individually, the effect of food on the absorption of the combination has not been studied (Pr

B) Symbyax(TM) capsules should be stored at 25 degrees Celsius (77 degrees Fahrenheit); excursions permitted to
Fahrenheit). Keep tightly closed and protect from moisture (Prod Info Symbyax(TM), 2003b).

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 Oral route

Bipolar disorder, depressed phase

Major depressive disorder, Treatment resistant

1.3.1.A.1 Bipolar disorder, depressed phase

a) The recommended initial dose for the acute treatment of depressive episodes associated with bipolar (mg)/fluoxetine 25 mg orally once daily each evening. The usual dose range is olanzapine 6 to 12 mg/flu oral capsule, 2009).

1.3.1.A.2 Major depressive disorder, Treatment resistant

a) The recommended initial dose in the acute treatment of treatment-resistant major depressive disorde previous trials of antidepressant therapy is olanzapine 6 milligrams (mg)/fluoxetine 25 mg orally once dai olanzapine 6 to 18 mg/fluoxetine 25 to 50 mg (Prod Info SYMBYAX(R) oral capsule, 2009).

B) The safety of doses greater than olanzapine 18 milligrams (mg) and fluoxetine 75 mg per day have not been e capsule, 2009).

1.3.2 Dosage in Renal Failure

A) Dose adjustments based upon renal impairment is not routinely required, although the possibility exists that pa accumulate higher levels of fluoxetine metabolites (Prod Info SYMBYAX(R) oral capsule, 2009).

1.3.3 Dosage in Hepatic Insufficiency

A) A reduced starting dose of olanzapine 3 to 6 milligrams (mg)/ fluoxetine 25 mg should be considered for patier individual pharmacokinetic profiles of olanzapine and fluoxetine, the pharmacokinetics of olanzapine/fluoxetine ma (Prod Info SYMBYAX(R) oral capsule, 2009).

1.3.4 Dosage in Geriatric Patients

A) Based on the individual pharmacokinetic profiles of olanzapine and fluoxetine, the pharmacokinetics of the cor Caution should be used in dosing the elderly, especially if there are other factors that might additively influence dr sensitivity (female gender, geriatric age, nonsmoking status). Dose escalation should be performed with caution ir capsule, 2009).

B) In a study involving 24 healthy subjects, the mean elimination half- life of olanzapine was about 1.5 times grea age) than in non-elderly subjects (65 years of age or under) (Prod Info SYMBYAX(R) oral capsule, 2009).

1.3.6 Dosage in Other Disease States

A) A reduced starting dose of olanzapine 3 to 6 milligrams (mg)/ fluoxetine 25 mg should be used for patients wit patients with hepatic impairment, or in slow CYP2D6 metabolizers, patients who exhibit a combination of factors t (female gender, geriatric age, nonsmoking status). Dose escalation should be performed with caution in these pat 2009).

B) A reduced dose is recommended in women during the third trimester of pregnancy due to the risk of adverse e Info SYMBYAX(R) oral capsule, 2009).

1.4 Pediatric Dosage

1.4.1 Normal Dosage

1.4.1.A Oral route

1) Safety and effectiveness of the combination of olanzapine and fluoxetine in pediatric patients have not be capsule, 2009).

2.0 Pharmacokinetics

Drug Concentration Levels

ADME

2.2 Drug Concentration Levels

A) Therapeutic Drug Concentration

1) Bipolar disorder, plasma concentrations are not used clinically.

B) Time to Peak Concentration

1) ORAL, capsule: olanzapine, 4 hours, fluoxetine, 6 hours (Prod Info Symbyax(TM), 2003a).

a) Following a single oral 12 mg/50 mg dose of olanzapine/fluoxetine, peak plasma concentrations of olanza 6 hours, respectively (Prod Info Symbyax(TM), 2003a).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption

A) Bioavailability

1) Oral, capsule: Olanzapine, 60%; fluoxetine 100% (Lemberger et al, 1985a; Prod Info Symbyax(TM), 2003

a) Olanzapine: extensive first-pass metabolism, with approximately 40% of the dose metabolized before Symbyax(TM), 2003a).

B) Effects of Food

1) none (Prod Info Symbyax(TM), 2003a).

a) The effect of food on the absorption and bioavailability of the combination of olanzapine and fluoxetin olanzapine of fluoxetine were not affected by food. It is unlikely that there would be a significant food effe Info Symbyax(TM), 2003a). The absorption of fluoxetine is delayed but not decreased in the presence of

2.3.2 Distribution

A) Distribution Sites

1) Protein Binding

a) Olanzapine, 93%; fluoxetine 94.5% (Prod Info Symbyax(TM), 2003a).

1) Olanzapine is 93% bound to plasma proteins over the concentration range of 7 to 1100 ng/mL, b glycoprotein (Prod Info Symbyax(TM), 2003a).

2) Over the concentration range from 200 to 1000 ng/mL, approximately 94.5% of fluoxetine is bou albumin and alpha-1-glycoprotein (Prod Info Symbyax(TM), 2003a; Lemberger et al, 1985a; Aronoff

B) Distribution Kinetics

1) Volume of Distribution

a) Olanzapine, 1000 L (Prod Info Symbyax(TM), 2003a); fluoxetine, 1000 to 7200 L (Aronoff et al, 1984)

1) The corresponding volume of distribution for norfluoxetine ranged from 700 to 5,700 L. No relatio fluoxetine or its metabolite and renal function has been observed (Aronoff et al, 1984).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics

1) LIVER, extensive for both olanzapine and fluoxetine (Prod Info Symbyax(TM), 2003a).

a) Olanzapine: extensive first-pass metabolism, with approximately 40% of the dose metabolized before Symbyax(TM), 2003a).

B) Metabolites

1) OLANZAPINE

a) 10-N-glucuronide is present at steady state at 44% of the olanzapine concentration (Prod Info Symby

b) 4'-N-desmethyl olanzapine (inactive) is present at steady state at 31% of the olanzapine concentratio

2) FLUOXETINE

a) Fluoxetine is metabolized primarily via N-demethylation to the active metabolite, norfluoxetine (Lemb Glucuronide conjugates are also found but in small quantities (Lemberger et al, 1985a).

b) Extensive metabolizers with respect to cytochrome P450 2C19 (CYP2C19) showed lower maximum

levels of norfluoxetine (p less than 0.001) after a 40 milligram dose of fluoxetine than did poor metabolize
Oral clearance by poor metabolizers was 55% lower than oral clearance by extensive metabolizers (p les

2.3.4 Excretion

A) Kidney

1) Renal Excretion (%)

a) Olanzapine, 57% (Prod Info Symbyax(TM), 2003a); fluoxetine, 60% (Lemberger et al, 1985a)

1) OLANZAPINE: About 7% of the olanzapine dose was recovered in the urine as unchanged drug, (Prod Info Symbyax(TM), 2003a)

2) FLUOXETINE: The primary route of fluoxetine elimination appears to be hepatic metabolism to i Info Symbyax(TM), 2003a)

3) Only 2.5 to 5.0% of an oral fluoxetine dose is recovered as unchanged drug; 10% is excreted as Aronoff et al, 1984). Conjugated metabolites, fluoxetine glucuronide and norfluoxetine glucuronide, (Lemberger et al, 1985a).

B) Other

1) PLASMA CLEARANCE

a) 25 L/hr (Prod Info Symbyax(TM), 2003a)

1) The apparent plasma clearance ranges from 12 to 47 L/hr (Prod Info Symbyax(TM), 2003a)

2) OTHER EXCRETION

a) Feces: olanzapine 30% (Prod Info Symbyax(TM), 2003a); fluoxetine, 12% (Lemberger et al, 1985a)

2.3.5 Elimination Half-life

A) Parent Compound

1) ELIMINATION HALF-LIFE

a) olanzapine, 30 hours (Prod Info Symbyax(TM), 2003a); fluoxetine, 4 to 6 days, chronic administration (R), 2001ai; Lemberger et al, 1985a).

1) OLANZAPINE

a) The olanzapine half-life ranges from 21 to 54 hours (mean 30 hours) (Prod Info Symbyax(TM

2) FLUOXETINE

a) Following acute administration, the elimination half-life of fluoxetine is 1 to 3 days (Prod Info 2002).

b) The mean half-life of fluoxetine among extensive metabolizers with respect to cytochrome P450 2C19 among poor metabolizers with the CYP2C19*2 or CYP2C19*3 mutation, mean half-life was 62 hours (Liu

B) Metabolites

1) Norfluoxetine, 4 to 16 days (Prod Info Prozac(R), 2001ai; Lemberger et al, 1985a).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING

1) Oral (Capsule)

Suicidality and Antidepressant Drugs -

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in child studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of fl antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk w adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with ages who are started on antidepressant therapy should be monitored appropriately and observed closely for changes in behavior. Families and caregivers should be advised of the need for close observation and comm hydrochloride/olanzapine is not approved for use in pediatric patients.

Increased Mortality in Elderly Patients with Dementia-Related Psychosis - .

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of d trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of d 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, th about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varie cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational stud

drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findin
may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. F
approved for the treatment of patients with dementia-related psychosis (Prod Info SYMBYAX(R) oral capsule

3.1 Contraindications

A) concomitant use of pimozide, MAOIs, or thioridazine (Prod Info SYMBYAX(R) oral capsule, 2009)

3.2 Precautions

A) elderly with dementia-related psychosis (unapproved use); increased risk of death; most deaths were attributed to sudden death) or infections (eg, pneumonia) (Prod Info SYMBYAX(R) oral capsule, 2009)
B) suicidal ideation and behavior or worsening depression; increased risk, particularly in children, adolescents, and y during the first few months of therapy or following changes in dosage (Prod Info SYMBYAX(R) oral capsule, 2009)
C) abnormal bleeding has been reported, including life-threatening hemorrhages; increased risk with concomitant use affect coagulation (Prod Info SYMBYAX(R) oral capsule, 2009)
D) abrupt withdrawal; serious discontinuation symptoms have been reported (Prod Info SYMBYAX(R) oral capsule, 2
E) allergic reactions including anaphylaxis, rash, and systemic reactions possibly related to vasculitis may occur; may SYMBYAX(R) oral capsule, 2009)
F) body weight increases may occur; monitoring recommended (Prod Info SYMBYAX(R) oral capsule, 2009)
G) bipolar disorder; increased risk of precipitation of a mixed/manic episode (Prod Info SYMBYAX(R) oral capsule, 2
H) cardiovascular or cerebrovascular disease, conditions that predispose patients to hypotension (eg, dehydration, h concomitant antihypertensive drug use; increased risk of orthostatic hypotension, bradycardia, and syncope (Prod Info
I) concomitant serotonergic drug use (serotonin precursors (tryptophan), SSRIs, serotonin-norepinephrine reuptake in Info SYMBYAX(R) oral capsule, 2009)
J) conditions that may contribute to elevated body temperature (eg, strenuous exercise, extreme heat exposure, dehy disrupt body temperature regulation and increase risk of hyperthermia (Prod Info SYMBYAX(R) oral capsule, 2009)
K) diabetes mellitus, preexisting disease or risk factors, or patients with borderline increased blood glucose level; incr recommended (Prod Info SYMBYAX(R) oral capsule, 2009)
L) dyslipidemia (abberations in cholesterol, triglycerides, HDL, and LDL) has been reported; monitoring recommende
M) elderly patients, especially elderly women are at increased risk of tardive dyskinesia (Prod Info SYMBYAX(R) oral
N) glaucoma, narrow-angle; condition may be exacerbated due to cholinergic antagonism (Prod Info SYMBYAX(R) or
O) hepatic impairment, preexisting conditions associated with limited hepatic functional reserve, or concomitant use o impairment and reduce fluoxetine clearance (Prod Info SYMBYAX(R) oral capsule, 2009)
P) hyperglycemia (some extreme cases associated with ketoacidosis or hyperosmolar coma or death) has been repo SYMBYAX(R) oral capsule, 2009)
Q) hyponatremia may occur; elderly or volume-depleted patients, and concomitant diuretic use may increase risk; dis develops (Prod Info SYMBYAX(R) oral capsule, 2009)
R) increased duration of therapy and/or higher cumulative doses; increased risk of tardive dyskinesia (Prod Info SYM
S) neuroleptic malignant syndrome, potentially fatal; has been reported in association with olanzapine therapy; immed oral capsule, 2009)
T) paralytic ileus, history; condition may be exacerbated due to cholinergic antagonism (Prod Info SYMBYAX(R) oral
U) prostatic hypertrophy; condition may be exacerbated due to cholinergic antagonism (Prod Info SYMBYAX(R) oral
V) seizure disorder, history, or conditions which lower seizure threshold (Prod Info SYMBYAX(R) oral capsule, 2009)
W) serotonin syndrome has been reported, including fatalities; monitoring recommended (Prod Info SYMBYAX(R) ora
X) tardive dyskinesia, potentially irreversible, may occur (Prod Info SYMBYAX(R) oral capsule, 2009)
Y) use of fluoxetine/olanzapine within 14 days of MAOI discontinuation (Prod Info SYMBYAX(R) oral capsule, 2009)
Z) use of MAOI or thioridazine within 5 weeks of fluoxetine/olanzapine discontinuation (Prod Info SYMBYAX(R) oral c
AA) volume-depleted, elderly, or concurrent diuretic therapy; increased risk of hyponatremia (Prod Info SYMBYAX(R)

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

Reproductive Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

Bradyarrhythmia

Cardiovascular finding

Edema

Orthostatic hypotension

Peripheral edema

QT interval - finding

Tachycardia

3.3.1.A Bradyarrhythmia

1) In a clinical pharmacology study of olanzapine/fluoxetine, 3 healthy subjects were discontinued from the tr hypotension and bradycardia that occurred 2 to 9 hours following a single 12-mg/50-mg dose of olanzapine/fl combination of hypotension and bradycardia (and also accompanied by sinus pause) have been observed in various formulations of olanzapine (one oral, two intramuscular) (Prod Info SYMBYAX(R) oral capsule, 2009)

3.3.1.B Cardiovascular finding

1) Olanzapine/fluoxetine should be used with particular caution in patients with known cardiovascular diseas heart failure, or conduction abnormalities), cerebrovascular disease, or conditions that would predispose pati and treatment with antihypertensive medications) (Prod Info SYMBYAX(R) oral capsule, 2009).

3.3.1.C Edema

1) Incidence: 3% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea 3% of patients who received fluoxetine/olanzapine (n=771) compared with 0% of patients who received place capsule, 2009).

3.3.1.D Orthostatic hypotension

1) Incidence: 4% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In the olanzapine/fluoxetine-controlled clinical studies across all indications, there were no significant diffe receiving combination therapy compared to olanzapine, fluoxetine, and placebo groups. Orthostatic systolic b occurred in 4% (28/705), 2.3% (19/831), 4.5% (18/399), and 1.8% (8/442) of the olanzapine/fluoxetine, olanz respectively. In controlled clinical studies, the incidence of patients with a decrease in orthostatic pulse of 20 with a decrease in orthostatic systolic blood pressure of 20 mmHg or greater was 0.3% (2/706) in the olanzap olanzapine group, 0% in the fluoxetine group, and 0.2% (1/445) in the placebo group. The incidence of synco 0.4% (3/771) compared to placebo (0.2%, 1/477)(Prod Info SYMBYAX(R) oral capsule, 2009).

3) In a clinical pharmacology study of olanzapine/fluoxetine, 3 healthy subjects were discontinued from the tr

hypotension and bradycardia that occurred 2 to 9 hours following a single 12-mg/50-mg dose of olanzapine/fl
combination of hypotension and bradycardia (and also accompanied by sinus pause) have been observed in
various formulations of olanzapine (one oral, two intramuscular) (Prod Info SYMBYAX(R) oral capsule, 2009)

3.3.1.E Peripheral edema

1) Incidence: 9% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea
occurred in 9% of patients who received fluoxetine/olanzapine (n=771) compared with 0% of patients who re
oral capsule, 2009).

3.3.1.F QT interval - finding

1) The mean increase in QTc interval for olanzapine/fluoxetine-treated patients (4.4 msec) in clinical studies
treated (-0.8 msec), olanzapine-treated patients (-0.3 msec), and fluoxetine-treated patients (1.7 msec). Ther
patients treated with olanzapine/fluoxetine, placebo, olanzapine, or fluoxetine in the incidence of QTc outliers
(R) oral capsule, 2009).

3.3.1.G Tachycardia

1) Tachycardia has occurred in olanzapine/fluoxetine-treated patients in premarketing clinical studies (Prod I

3.3.2 Dermatologic Effects

3.3.2.A Erythema multiforme

1) Erythema multiforme has been reported with olanzapine or fluoxetine monotherapy, but was not observed
premarketing clinical studies (Prod Info SYMBYAX(R) oral capsule, 2009).

3.3.3 Endocrine/Metabolic Effects

Bicarbonate level - finding

Body temperature above normal

Diabetes mellitus

Diabetic ketoacidosis

Hypercholesterolemia

Hyperglycemia

Hyperprolactinemia

Hypoalbuminemia

Hyponatremia

Hypophosphatemia

Serum triglycerides raised

Weight gain

3.3.3.A Bicarbonate level - finding

1) Incidence: 14.1% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In olanzapine/fluoxetine clinical studies (including treatment resistant depression, depressive episodes as
depressive disorder with psychosis, or sexual dysfunction), low bicarbonate level occurred at a greater freque
olanzapine/fluoxetine-treated patients compared to placebo (14.1% vs 8.8%) (Prod Info SYMBYAX(R) oral ca

3.3.3.B Body temperature above normal

1) Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic drugs
olanzapine/fluoxetine for patients who will be experiencing conditions which may contribute to an elevation in
strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or bein

(R) oral capsule, 2009).

3.3.3.C Diabetes mellitus

1) Summary

a) As with other atypical antipsychotics, hyperglycemia has been reported in patients on olanzapine. Th nonfasting levels, from baseline to the average of the 2 highest serum concentrations was 15 mg/dL, dur Effectiveness in patients treated for a median olanzapine-exposure duration of 9.2 months. Olanzapine i is difficult to assess the relationship because of an increased risk of diabetes mellitus in patients with sch diabetes mellitus in the general population. In general, epidemiological studies show that atypical antipsy hyperglycemia. Olanzapine appears to have a greater risk of glucose abnormalities compared with other oral capsule, 2009).

b) The risks and benefits of olanzapine/fluoxetine hydrochloride should be considered prior to prescribin diabetes mellitus or in patients with borderline increased blood glucose levels (fasting 100 to 126 mg/dL monitoring of blood glucose is recommended. For patients with risk factors for diabetes mellitus, fasting l initiation and periodically during olanzapine/fluoxetine therapy. All patients should be monitored for signs polyuria, polyphagia, and weakness). Fasting blood glucose should be tested if symptoms of hyperglyce discontinuation of olanzapine/fluoxetine; however, some patients may continue to need antidiabetic thera Info SYMBYAX(R) oral capsule, 2009).

2) New onset diabetes mellitus (DM) has been reported with the administration of olanzapine. At least 25 fat olanzapine-induced diabetic ketoacidosis (Torrey & Swalwell, 2003; Goldstein et al, 1999; Lindenmayer & Pa

3) A 51-year-old woman with schizoaffective disorder and type 2 diabetes (stabilized on metformin 1 gram tw developed hyperglycemia, without weight gain, when an episode of elevated mood and psychosis was treate risperidone for 4 weeks but did not respond. Chlorpromazine also was not effective. Olanzapine, titrated to 3(symptoms. Her blood glucose then began to increase, although her diet was controlled by the hospital. Oral h maximum and she was started on actrapid insulin. Glucose levels remained unstable until olanzapine was ta hypoglycemic medications were reduced to previous levels and actrapid insulin was discontinued. Zuclopenth schizoaffective disorder. The patient showed no significant weight gain during treatment with olanzapine, whi effect on glucose regulation (Ramankutty, 2002).

4) A 27-year-old man developed signs of diabetes mellitus (polydipsia, polyphagia, nausea and vomiting, hy olanzapine for treatment of schizophrenia. He was treated with insulin, and his dose of olanzapine was increa valproic acid, which he had taken for 3 years. After 3 months, insulin therapy was replaced by pioglitazone 3(control. Olanzapine therapy was not discontinued because of the risk of psychotic worsening (Seaburg et al,

5) A 45-year-old obese man developed elevated fasting glucose 1 year after his treatment for schizophrenia to 25 mg/day). Six months later, he was treated with glyburide 1.25 mg/day. Over the next 6 months, glycosy weight began to increase. Five months later, he complained of diarrhea and weight loss. His glyburide dose v symptoms (polyuria, polydipsia, and diaphoresis), his glyburide dosage was increased to 10 mg twice daily, i replaced by risperidone. Six weeks after discontinuation of olanzapine, the patient's glycosylated hemoglobin glyburide was reduced to 1.25 mg/day, and his weight stabilized. Five months later, his diabetes was well-co

6) Olanzapine-induced glucose dysregulation has been reported as an adverse effect, possibly due to drug-i with a severe exacerbation of type 2 diabetes in a 51-year-old woman with a major depressive disorder and s with sertraline and haloperidol decanoate. After 4 weeks, sertraline was replaced by fluoxetine due to continu haloperidol was replaced by olanzapine due to persistent auditory and visual hallucinations. Prior to initiation well-controlled by diet (glycosylated hemoglobin 6.5%, baseline fasting blood glucose 89 to 132 mg/dL). Twe control diminished and continued to worsen despite treatment with glipizide, metformin, and diet. At week 26, due to inadequate antidepressant response. At week 35 (fasting blood glucose 120 to 461 mg/dL, glycosylate 70/30) was initiated and titrated to 70 units per day. Olanzapine was tapered during weeks 39 and 40 and dis therapy was stopped, the patient's fasting blood glucose levels had decreased to within 85 and 163 mg/dL. B been reduced to 45 units/day NPH 70/30 (Bettinger et al, 2000).

7) Cases of new-onset diabetes mellitus (DM) were reported that developed after initiation of olanzapine trea months (mean 26 weeks; median 20 weeks) after olanzapine initiation. Two cases presented with diabetic ke DM and 4 patients experienced weight gain while on olanzapine. Olanzapine was eventually discontinued in treatment for DM was still required (Goldstein et al, 1999).

3.3.3.D Diabetic ketoacidosis

1) Summary

a) As with other atypical antipsychotics, diabetic ketoacidosis or hyperosmolar coma, including death, ha Olanzapine is implicated in glucose abnormalities; however, it is difficult to assess the relationship becau patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. I atypical antipsychotics increase the risk of treatment-emergent hyperglycemia. Olanzapine appears to ha compared with other atypical antipsychotics (Prod Info SYMBYAX(R) oral capsule, 2009).

b) The risks and benefits of olanzapine/fluoxetine hydrochloride should be considered prior to prescribin diabetes mellitus or in patients with borderline increased blood glucose levels (fasting 100 to 126 mg/dL monitoring of blood glucose is recommended. For patients with risk factors for diabetes mellitus, fasting l initiation and periodically during olanzapine/fluoxetine therapy. All patients should be monitored for signs polyuria, polyphagia, and weakness). Fasting blood glucose should be tested if symptoms of hyperglyce discontinuation of olanzapine/fluoxetine; however, some patients may continue to need antidiabetic thera Info SYMBYAX(R) oral capsule, 2009).

2) Diabetic coma has been reported with olanzapine or fluoxetine monotherapy, but was not observed in ola

premarketing clinical studies (Prod Info SYMBYAX(R) oral capsule, 2009).
3) Olanzapine-induced ketoacidosis has been reported, including one near-fatal case in a 44-year-old Africa patient had taken olanzapine 25 mg/day for approximately 1 month (Straker et al, 2002).
4) Diabetic ketoacidosis following 3 months of olanzapine therapy was reported in a 31-year-old man with nc patient was started on insulin and olanzapine was discontinued. Fifteen days later his insulin requirements de the patient has remained metabolically stable, free of diabetic symptoms (Gatta et al, 1999).
5) Diabetic ketoacidosis has been reported with the administration of olanzapine. At least 25 fatalities have b induced diabetic ketoacidosis (Torrey & Swalwell, 2003; Goldstein et al, 1999; Lindenmayer & Patel, 1999).
6) A 50-year-old African American man developed diabetic ketoacidosis after receiving 8 months of olanzapi olanzapine 30 mg daily with divalproex 750 mg twice daily. He began insulin therapy but after the olanzapine normal (Lindenmayer & Patel, 1999).
7) A 39-year-old man developed diabetic ketoacidosis after receiving olanzapine 10 mg for a treatment-refra previous laboratory evidence of diabetes. His body mass index was high at 40 kg/m(2). He was admitted with hyperglycemia (6 mmol/L), and acidosis. His HbA1c was 14.7%. He was maintained on insulin 3 times daily. requirements decreased after 15 days. His blood glucose and HbA1c became normal (Gatta et al, 1999).

3.3.3.E Hypercholesterolemia

1) Summary
a) Significant increases in total cholesterol have been observed during treatment with olanzapine/fluoxe total cholesterol from baseline was 12.1 mg/dL in olanzapine/fluoxetine-treated patients compared with 4 patients and a decrease of 5.5 mg/dL in placebo-treated patients (statistically significant), in an analysis duration. Baseline and follow-up lipid monitoring of lipids is recommended in patients on olanzapine (Pro
2) Incidence: up to 36% (Prod Info SYMBYAX(R) oral capsule, 2009)
3) In an analysis of 7 placebo-controlled monotherapy studies of up to 12 weeks duration, the mean increase 12.1 mg/dL in olanzapine/fluoxetine-treated patients compared with 4.8 mg/dL in olanzapine monotherapy-tre placebo-treated patients. The table below provides the frequency and degree of increase of nonfasting choles with treatment up to 12 weeks(Prod Info SYMBYAX(R) oral capsule, 2009):

Nonfasting Total Cholesterol In Adults With Treatment Up to 12 weeks			
Change from Baseline	Treatment Arm	N	Portion of Patients
Increase by 40 mg/dL or more	olanzapine/fluoxetine	685	35% *
	olanzapine	749	22.7%
	placebo	390	9%
Normal to High	olanzapine/fluoxetine	256	8.2% *
	olanzapine	279	2.9%
	placebo	175	1.7%
Borderline to High	olanzapine/fluoxetine	213	36.2% *
	olanzapine	261	27.6%
	placebo	111	9.9%
KEY: mg/dL = milligrams/deciliter; Normal = less than 200 mg/dL; Borderline = 200 mg/dL to less than 240 mg/dL; High = 240 mg/dL or greater; * = statistically significant compared to placebo and olanzapine			

4) In long-term olanzapine/fluoxetine studies of at least 48 weeks, changes in nonfasting total cholesterol fro (n=150) and changes from borderline to high occurred in 56.6% (n=143) of patients. The mean change in nor (Prod Info SYMBYAX(R) oral capsule, 2009).
5) In an analysis of 5 placebo-controlled monotherapy studies of up to 12 weeks duration, olanzapine-treate fasting total cholesterol of 5.3 mg/dL compared to decreases from baseline of 6.1 mg/dL for placebo-treated least 48 weeks, patients had increases from baseline in mean fasting total cholesterol of 5.6 mg/dL. In an ana therapy, the mean nonfasting total cholesterol did not increase further after approximately 4 to 6 months. The of increase of fasting cholesterol and LDL cholesterol (Prod Info SYMBYAX(R) oral capsule, 2009):

Fasting Total Cholesterol In Adults					
		Up to 12 weeks exposure		At least 48 weeks exposure	
Change from Baseline	Treatment Arm	N	Portion of Patients	N	Portion of Patients
Increase by 40 mg/dL or more	olanzapine	745	21.6%	489	32.9%
	placebo	402	9.5%	NA	NA
Normal to High	olanzapine	392	2.8%	283	14.8%
	placebo	207	2.4%	NA	NA
Borderline to High	olanzapine	222	23%	125	55.2%
	placebo	112	12.5%	NA	NA
KEY: mg/dL = milligrams/deciliter; Normal = less than 200 mg/dL; Borderline = 200 mg/dL to less than 240 mg/dL; High = 240 mg/dL or greater; NA = Not Applicable					

Fasting Low-Density-Lipoprotein Cholesterol In Adults			

		Up to 12 weeks exposure		At least 48 weeks exposure	
Change from Baseline	Treatment Arm	N	Portion of Patients	N	Portion of Patients
Increase by 30 mg/dL or more	olanzapine	536	23.7% *	483	39.8%
	placebo	304	14.1%	NA	NA
Normal to High	olanzapine	154	0%	123	7.3%
	placebo	82	1.2%	NA	NA
Borderline to High	olanzapine	302	10.6%	284	31%
	placebo	173	8.1%	NA	NA
KEY: mg/dL = milligrams/deciliter; Normal = less than 100 mg/dL; Borderline = 100 mg/dL to less than 160 mg/dL; High = 160 mg/dL or greater; NA = Not Applicable					

6) In an analysis of 3 placebo-controlled monotherapy studies of up to 6 weeks duration in adolescents, olan baseline in mean fasting total cholesterol of 12.9 mg/dL and LDL cholesterol compared to increases from bas cholesterol of 1.3 mg/dL and 1 mg/dL for placebo-treated patients, respectively. In long-term olanzapine stud increases from baseline in mean fasting total cholesterol and LDL cholesterol of 5.5 mg/dL and 5.4 mg/dL, re cholesterol of 4.5 mg/dL. The tables below provide the frequency and degree of increase of fasting total chol (R) oral capsule, 2009):

Fasting Total Cholesterol In Adolescents					
		Up to 6 weeks exposure		At least 24 weeks exposure	
Category Change from Baseline	Treatment Arm	N	Portion of Patients	N	Portion of Patients
Increase by 40 mg/dL or more	olanzapine	138	14.5%	122	14.8%
	placebo	66	4.5%	NA	NA
Normal to High	olanzapine	87	6.9%	78	7.7%
	placebo	43	2.3%	NA	NA
Borderline to High	olanzapine	36	38.9%	33	57.6
	placebo	13	7.7%	NA	NA
KEY: mg/dL = milligrams/deciliter; Normal = less than 170 mg/dL; Borderline = 170 mg/dL to less than 200 mg/dL; High = 200 mg/dL or greater ; NA = Not Applicable					

Fasting Low-Density-Lipoprotein Cholesterol In Adolescents					
		Up to 6 weeks exposure		At least 24 weeks exposure	
Category Change from Baseline	Treatment Arm	N	Portion of Patients	N	Portion of Patients
Increase by 30 mg/dL or more	olanzapine	137	17.5%	121	22.3%
	placebo	63	11.1%	NA	NA
Normal to High	olanzapine	98	5.1%	92	10.9%
	placebo	44	4.5%	NA	NA
Borderline to High	olanzapine	29	48.3% *	21	47.6%
	placebo	9	0%	NA	NA
KEY: mg/dL = milligrams/deciliter; Normal = less than 110 mg/dL; Borderline = 110 mg/dL to less than 130 mg/dL; High = 130 mg/dL or greater; NA = Not Applicable					

7) Patients (n=25) receiving olanzapine were found to have increases in body weight and serum triglyceride receiving olanzapine (mean dose 13.8 mg) had their weight, cholesterol, and triglycerides measured at basel mean of 5.4 kg. Cholesterol levels increased by only 3 mg/dL while triglyceride levels increased by 60 mg/dL with weight change (p less than 0.02).

8) After an average of 16 months of olanzapine therapy, 9 patients had marked increases in triglyceride leve increased from a mean of 170 mg/dL to a mean of 240 mg/dL. Five patients had at least a 50% increase in le unchanged. The patients had a mean weight gain of 10 kg.

3.3.3.F Hyperglycemia

1) Summary

a) As with other atypical antipsychotics, hyperglycemia has been reported in patients on olanzapine. In a which were placebo-controlled, with treatment duration up to 12 weeks, olanzapine/fluoxetine was assoc glucose compared to placebo (8.65 mg/dL vs -3.86 mg/dL) . The mean increase of serum glucose (fastin average of the 2 highest serum concentrations was 15 mg/dL, during Clinical Antipsychotic Trials of Inte median olanzapine-exposure duration of 9.2 months. Olanzapine is implicated in glucose abnormalities; because of an increased risk of diabetes mellitus in patients with schizophrenia and the increasing incide population. In general, epidemiological studies show that atypical antipsychotics increase the risk of trea

appears to have a greater risk of glucose abnormalities compared with other atypical antipsychotics (Pro
b) The risks and benefits of olanzapine/fluoxetine hydrochloride should be considered prior to prescribin
diabetes mellitus or in patients with borderline increased blood glucose levels (fasting 100 to 126 mg/dL
monitoring of blood glucose is recommended. For patients with risk factors for diabetes mellitus, fasting l
initiation and periodically during olanzapine/fluoxetine therapy. All patients should be monitored for signs
polyuria, polyphagia, and weakness). Fasting blood glucose should be tested if symptoms of hyperglycer
discontinuation of olanzapine/fluoxetine; however, some patients may continue to need antidiabetic thera
Info SYMBYAX(R) oral capsule, 2009).

2) Incidence: baseline normal, 2.3%; baseline borderline-normal, 34.1% (Prod Info SYMBYAX(R) oral capsu

3) The mean changes in random glucose concentrations were an increase of 8.65 mg/dL in olanzapine/fluox
3.86 mg/dL (statistically significant), in an analysis of 7 controlled clinical studies, 2 of which were placebo-co
In patients with normal random glucose levels (less than 140 mg/dL) and baseline borderline random glucose
mg/dL) treated with olanzapine/fluoxetine, 2.3% and 34.1% (statistically significant compared with placebo), r
greater. In comparison, 0.3% and 3.6%, respectively, of the placebo-treated patients had high glucose levels.
concentration increases were patients with glucose dysregulation at baseline defined as: diagnosis with diabe
with antidiabetic agents, or baseline random glucose concentrations of 200 mg/dL or greater, and/or a baseli
These patients had a greater mean increase in glycosylated hemoglobin (Prod Info SYMBYAX(R) oral capsu

4) In a study of healthy volunteers, patients who received olanzapine (n=22) for 3 weeks had a mean increas
compared to baseline . Placebo-treated patients (n=19) had a mean increase in fasting blood glucose compa
SYMBYAX(R) oral capsule, 2009).

5) Data for fasting glucose are limited for olanzapine/fluoxetine. However for olanzapine monotherapy the m
mg/dL in olanzapine-treated adults compared with 0.17 mg/dL in placebo-treated patients, in an analysis of 5
to 12 weeks (Prod Info SYMBYAX(R) oral capsule, 2009).

6) The mean change in fasting glucose for olanzapine-treated patients was 4.2 mg/dL (n=487), and mean ch
at least 48 weeks was 5.9 mg/dL (n=425). In analyses of patients who completed 9 to 12 months of olanzapir
nonfasting glucose levels continue to increase over time (Prod Info SYMBYAX(R) oral capsule, 2009).

7) The mean changes in fasting glucose levels were an increase of 2.68 mg/dL in olanzapine-treated adoles
placebo-treated adolescents (statistically significant), in an analysis of 3 placebo-controlled trials of adolescer
duration of 6 weeks in schizophrenia trials or 3 weeks in bipolar disorder trials. The mean change in fasting g
weeks was 3.1 mg/dL. In adolescents with normal fasting glucose levels (less than 100 mg/dL) and baseline
less than 126 mg/dL) treated with olanzapine, 0% (0 out of 124) and 14.3% (2 out of 14), respectively, had hi
comparison, 1.9% (1 out of 53) and 0% (0 out of 13), respectively, of the placebo-treated patients had high gl
capsule, 2009).

3.3.3.G Hyperprolactinemia

1) Incidence: up to 61.1% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) Olanzapine/fluoxetine elevates prolactin levels as with other drugs that antagonize dopamine D2 receptor
impotence have been reported in patients receiving prolactin-elevating compounds. In clinical studies of olan
concentrations were observed in 27.6% of the olanzapine/fluoxetine-treated adults compared to 4.8% of plac
plasma prolactin concentrations were reported in 34% of adults treated with olanzapine compared to 13.1% c
from clinical studies including 8136 adults treated with olanzapine, potentially associated clinical manifestatio
gynecomastia of males was 0.2% (8/4896), and breast enlargement of females were 0.06% (2/3240) (Prod In

3) In a single 8-week randomized, double-blind, fixed-dose study comparing olanzapine 10 mg/day (n=199),
incidence of treatment-emergent prolactin elevation greater than 24.2 ng/mL in females or greater than 18.77
31.2% at 10 mg, 42.7% at 20 mg, and 61.1% at 40 mg per day (Prod Info SYMBYAX(R) oral capsule, 2009).

4) In placebo-controlled olanzapine monotherapy studies in adolescent patients with schizophrenia or bipola
compared to baseline occurred in 47.4% of the adolescents treated with olanzapine compared to 6.8% of pla
adolescents, gynecomastia occurred in 2.4% of males (7/286) and galactorrhea occurred in 1.8% of females
2009).

3.3.3.H Hypoalbuminemia

1) Incidence: 2.7% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In olanzapine/fluoxetine clinical studies (including treatment resistant depression, depressive episodes as
depressive disorder with psychosis, or sexual dysfunction), low albumin level occurred at a greater frequency
olanzapine/fluoxetine-treated patients compared to placebo (2.7% vs 0.3%) (Prod Info SYMBYAX(R) oral cap

3.3.3.I Hyponatremia

1) Hyponatremia (headache, difficulty concentrating, memory impairment, confusion, weakness, and unstead
use, with some serious or acute cases resulting in hallucination, syncope, seizure, coma, respiratory arrest, a
110 mmol/L, which was reversible upon discontinuation, have been reported with olanzapine/fluoxetine. The
secretion may have been one possible etiology. Older patients and patients taking diuretics or who were othe
hyponatremia. Drug discontinuation is recommended in patients who develop symptomatic hyponatremia (Pr

3.3.3.J Hypophosphatemia

1) Incidence: 1.9% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In olanzapine/fluoxetine clinical studies (including treatment resistant depression, depressive episodes as
depressive disorder with psychosis, or sexual dysfunction), low inorganic phosphorus level occurred at a grea
olanzapine/fluoxetine-treated patients compared to placebo (1.9% vs 0.3%) (Prod Info SYMBYAX(R) oral cap

3.3.3.K Serum triglycerides raised

1) Summary

a) Elevations in serum triglycerides have been observed, at times a greater than 500 mg/dL increase, du hydrochloride. Baseline and follow-up lipid monitoring of lipids is recommended in patients on olanzapine capsule, 2009).

2) Incidence: up to 70% (Prod Info SYMBYAX(R) oral capsule, 2009)

3) The table below provides the frequency and degree of increase of nonfasting triglycerides in adults on ola of up to 12 weeks(Prod Info SYMBYAX(R) oral capsule, 2009):

Nonfasting Triglycerides In Adults on Olanzapine/Fluoxetine			
Category Change from Baseline	Treatment Arm	N	P
Increase by 50 mg/dL or more	olanzapine/fluoxetine	174	6
	olanzapine	172	7
Normal to High	olanzapine/fluoxetine	57	0
	olanzapine	58	0
Borderline to High	olanzapine/fluoxetine	106	1
	olanzapine	103	8
KEY: mg/dL = milligrams/deciliter; Normal = less than 150 mg/dL; borderline = 150 mg/dL to less than 5(mg/dL or greater			

4) In an analysis of 5 placebo-controlled olanzapine monotherapy studies of up to 12 weeks duration, the me by 20.8 mg/dL in olanzapine-treated patients compared to decreases from baseline of 10.7 mg/dL for placebo studies of at least 48 weeks, patients had increases from baseline in mean fasting triglycerides of 18.7 mg/dL who had at least one change in triglycerides from normal or borderline to high was greater in long-term studie median exposure of 9.2 months in phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (C olanzapine-treated patients was 40.5 mg/dL. The table below provides the frequency and degree of increase SYMBYAX(R) oral capsule, 2009):

Fasting Triglycerides In Adults on Olanzapine-Monotherapy					
		Up to 12 weeks exposure		At least 48 weeks exposure	
Category Change from Baseline	Treatment Arm	N	Portion of Patients	N	Portion of Patients
Increase by 50 mg/dL or more	olanzapine	745	39.6%	487	61.4%
	placebo	402	26.1%	NA	NA
Normal to High	olanzapine	457	9.2%	293	32.4%
	placebo	251	4.4%	NA	NA
Borderline to High	olanzapine	135	39.3%	75	70.7%
	placebo	65	20%	NA	NA
Increase by 40 mg/dL or more	olanzapine	745	21.6%	489	32.9
	placebo	402	9.5%	NA	NA
KEY: mg/dL = milligrams/deciliter; Normal = less than 150 mg/dL; Borderline = 150 mg/dL to less than 200 mg/dL; High = 200 mg/dL or greater; NA = Not Applicable					

5) In an analysis of 3 placebo-controlled olanzapine monotherapy studies of up to 6 weeks duration in adoles increases from baseline in mean fasting triglycerides of 28.4 mg/dL compared to a decrease of 1.1 mg/dL for olanzapine studies of at least 24 weeks, adolescents had increases from baseline in mean fasting triglyceride frequency and degree of increase of fasting triglycerides(Prod Info SYMBYAX(R) oral capsule, 2009):

Fasting Triglycerides In Adolescents					
		Up to 6 weeks exposure		At least 24 weeks exposure	
Category Change from Baseline	Treatment Arm	N	Portion of Patients	N	Portion of Patients
Increase by 50 mg/dL or more	olanzapine	138	37%	122	45.9%
	placebo	66	15.2%	NA	NA
Normal to High	olanzapine	67	26.9%	66	36.4%
	placebo	28	10.7%	NA	NA
Borderline to High	olanzapine	37	59.5%	31	64.5
	placebo	17	35.3%	NA	NA
KEY: mg/dL = milligrams/deciliter; Normal = Normal = less than 90 mg/dL; Borderline = 90 mg/dL to less than 130 mg/dL; High = 130 mg/dL or greater; NA = Not Applicable					

6) Random triglyceride levels of 1000 mg/dL or more have been reported during postmarketing reports with c

SYMBYAX(R) oral capsule, 2009).
7) Patients (n=25) receiving olanzapine were found to have increases in body weight and serum triglycerides receiving olanzapine (mean dose 13.8 mg) had their weight, cholesterol, and triglycerides measured at basel mean of 5.4 kg. Cholesterol levels increased by only 3 mg/dL while triglyceride levels increased by 60 mg/dL with weight change (p less than 0.02).
8) After an average of 16 months of olanzapine therapy, 9 patients had marked increases in triglyceride leve increased from a mean of 170 mg/dL to a mean of 240 mg/dL. Five patients had at least a 50% increase in le unchanged. The patients had a mean weight gain of 10 kg.

3.3.3.L Weight gain

1) Summary
a) Weight gain is associated with olanzapine use. Weight gain (greater than 7% of their baseline weight) olanzapine/fluoxetine long term (median days of exposure, 448) with the mean weight gain of 6.7 kg. For change was +4 kg and -0.3 kg for olanzapine/fluoxetine and placebo-treated patients, respectively, in an which were placebo-controlled. Regular monitoring of weight should be performed. Before initiating olanz to the potential consequences of weight gain (Prod Info SYMBYAX(R) oral capsule, 2009).
2) Incidence: 25% (Prod Info SYMBYAX(R) oral capsule, 2009)
3) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea occurred in 25% of patients who received fluoxetine/olanzapine (n=771) compared with 3% of patients who re (R) oral capsule, 2009).
4) In a single 8-week randomized, double-blind, fixed-dose study comparing olanzapine 10 mg/day (n=199), mean baseline to endpoint increase in weight was 1.9 kg, 2.3 kg, and 3 kg, respectively, with significant differ SYMBYAX(R) oral capsule, 2009).
5) The mean weight change was +4 kg and -0.3 kg for olanzapine/fluoxetine and placebo-treated patients, re studies, 2 of which were placebo-controlled. After a median duration of 6 weeks, 22% of olanzapine/fluoxetin patients (statistically significant) gained at least 7% of their baseline weight. After a median duration of 8 wee compared with 0% of placebo-treated patients (statistically significant) gained at least 15% of their baseline w difference in the amount gained. The discontinuation rate due to weight gain was 2.5% and 0% in the olanzap respectively.(Prod Info SYMBYAX(R) oral capsule, 2009).
6) The table below provides the adult weight gain observed in olanzapine treated patients from 86 clinical ola capsule, 2009) :

	Olanzapine-Monotherapy Trials in Adults		
Amount Gained	6 weeks	6 months	12 months
	n=7465	n=4162	n=1345
0 kg gain or loss of weight	26.2%	24.3%	20.8%
0 to 5 kg (0 to 11 lb)	57%	36%	26%
greater than 5 to 10 kg (11 to 22 lb)	14.9%	24.6%	24.2%
greater than 10 to 15 kg (22 to 33 lb)	1.8%	10.9%	14.9%
greater than 15 to 20 kg (33 to 44 lb)	0.1%	3.1%	8.6%
greater than 20 to 25 kg (44 to 55 lb)	0%	0.9%	3.3%
greater than 25 to 30 kg (55 to 66 lb)	0%	0.2%	1.4%
greater than 30 kg (greater than 66 lb)	0%	0.1%	0.8%
Key: kg = kilograms; lb = pounds			

7) Weight gain (greater than 7% of their baseline weight) occurred in 66% of patients treated with olanzapine 448) with the mean weight gain of 6.7 kg. Discontinuation due to weight gain in long-term exposure (48 week olanzapine/fluoxetine-treated patients. In long-term olanzapine monotherapy studies, the mean weight gain w 64% of patients who gaining at least 7% of their baseline weight. Discontinuation due to weight gain occurred long-term olanzapine monotherapy studies (Prod Info SYMBYAX(R) oral capsule, 2009).
8) An average weight gain of 4.6 kg in olanzapine-treated adolescents and 0.3 kg in placebo-treated adolesc controlled trials of adolescents (under the age of 18 years) treated with monotherapy olanzapine for a mediar 4 weeks, 40.6% of olanzapine-treated compared with 9.8% of placebo-treated patients gained at least 7% of 19 weeks, 7.1% of olanzapine-treated compared with 2.7% of placebo-treated patients gained at least 15% o due to weight gain was 1% and 0% in the olanzapine and placebo treated patients, respectively (Prod Info SY
9) In long-term (24 weeks or more) olanzapine studies, 89% of adolescents gained at least 7% of their basel the mean weight gain of 11.2 kg. Baseline body mass index (BMI) did not affect the amount gained. Discontir occurred in 2.2% of olanzapine-treated patients(Prod Info SYMBYAX(R) oral capsule, 2009).
10) The table below provides the adolescent weight gain with olanzapine treated patients from 6 clinical olan capsule, 2009) :

Olanzapine-Monotherapy Trials in Adolescents	
Amount Gained	6 weeks
	n=243
0 kg gain or loss of weight	2.9%
0 to 5 kg (0 to 11 lb)	47.3%
greater than 5 to 10 kg (11 to 22 lb)	42.4%
greater than 10 to 15 kg (22 to 33 lb)	5.8%
greater than 15 to 20 kg (33 to 44 lb)	0.8%
greater than 20 to 25 kg (44 to 55 lb)	0.8%
greater than 25 to 30 kg (55 to 66 lb)	0%
greater than 30 to 35 kg (66 to 77 lb)	0%
greater than 35 to 40 kg (77 to 88 lb)	0%
greater than 40 kg (greater than 88 lb)	0%
Key: kg = kilograms; lb = pounds	

11) Weight gain (39.8%) and increased appetite (32%) were reported following the administration of olanzap and 46.1 mg/day, respectively (Corya et al, 2003a).
12) Adolescent patients taking olanzapine experienced greater weight gain and increased in body mass inde retrospective study involving 103 patients younger than 18 years of age. Patients received olanzapine (n=50, mean daily dose 510.9 mg) for at least 2 weeks. Weight and height were measured at baseline and 14 or mo baseline in the olanzapine group was 3.8 kg (p less than 0.001) compared to 0.03 kg in the quetiapine group. showed slight, but significant, increases in height from baseline (0.006 meters, p=0.042 and 0.006 meters, p for baseline differences, the mean weight change between groups was significant (3.4 kg, p less than 0.001). the olanzapine group (p less than 0.001) compared to a decreased of 0.2 kg/m(2) in the quetiapine group. Af difference in change in BMI was significant (0.9 kg/m(2), p=0.008) (Patel et al, 2004).
13) Excessive appetite was seen more commonly with olanzapine therapy than with haloperidol (24% versus was also associated with a clinically significant greater increase in weight over haloperidol therapy (p less tha that body mass index was the predominant predictor of weight gain. Patients with a low prestudy body mass olanzapine treatment. Treatment effect on weight change was consistent between male and female patients
14) A prospective, multicenter, observational study showed that olanzapine treatment of outpatients (n=2128 group of patients (n=821) receiving a variety of other antipsychotic drug therapies. Drugs used in the control sertindole, zuclopenthixol, fluphenazine, thioridazine, perphenazine, pimozide, clozapine, pipotiazine, sulpirid clothiapine, and lorazepam. Overall, olanzapine had a significantly lower incidence of adverse events than th 0.001). Somnolence and weight gain occurred significantly more frequently in olanzapine-treated patients. Ak hypertonia, and tremor were significantly higher in the control group. Abnormal ejaculation and impotence oc control group. Over a 6-month period, fewer olanzapine-treated patients received a concomitant anticholinerg control group (36% versus 58%, p less than 0.001) (Gomez et al, 2000).

3.3.4 Gastrointestinal Effects

Abdominal distension

Constipation

Diarrhea

Dysphagia

Flatulence

Gastrointestinal hemorrhage

Increased appetite

Nausea

Xerostomia

3.3.4.A Abdominal distension

1) Incidence: 2% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea occurred in 2% of patients who received fluoxetine/olanzapine (n=771) compared with 0% of patients who re oral capsule, 2009).

3.3.4.B Constipation

1) Constipation was associated with olanzapine/fluoxetine in premarketing clinical studies (Prod Info SYMBY

3.3.4.C Diarrhea

1) Incidence: 12.5% (Corya et al, 2003a)

2) Dry mouth (37.1%), nausea (15.7%), and diarrhea (12.5%) have occurred following the administration of o of 7.5 and 46.1 milligrams/day, respectively (Corya et al, 2003a).

3.3.4.D Dysphagia

1) Antipsychotic drug use has been associated with esophageal dysmotility and aspiration. Olanzapine/fluox Alzheimer's disease due to the risk of aspiration pneumonia, a common cause of morbidity and mortality in th SYMBYAX(R) oral capsule, 2009).

3.3.4.E Flatulence

1) Incidence: 3% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea in 3% of patients who received fluoxetine/olanzapine (n=771) compared with 1% of patients who received pla capsule, 2009).

3.3.4.F Gastrointestinal hemorrhage

1) Serotonin norepinephrine reuptake inhibitors (SNRIs) and SSRIs, including fluoxetine, may increase the ri aspirin, NSAIDs, warfarin and other anticoagulants may increase this risk. Case reports and epidemiological design, have demonstrated an association between use of drugs that interfere with serotonin reuptake and th anticoagulant effects, including increased bleeding, have been reported with SNRIs or SSRIs when given cor warfarin 20 mg did not affect olanzapine pharmacokinetics. Likewise, single doses of olanzapine did not affec reactions associated with SNRIs and SSRIs use have ranged from ecchymoses, hematomas, epistaxis and p Patients receiving warfarin therapy should be carefully monitored when olanzapine/fluoxetine is initiated or di capsule, 2009).

2) Case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic Subsequent epidemiological studies, both of the case-control and cohort design, have demonstrated an asso interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. The same epidemiolo a nonsteroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding. Patients should be associated with the concomitant use of olanzapine/fluoxetine with NSAIDs, aspirin, or other drugs that affect capsule, 2009).

3.3.4.G Increased appetite

1) Incidence: 20% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea occurred in 20% of patients who received fluoxetine/olanzapine (n=771) compared with 4% of patients who re (R) oral capsule, 2009).

3.3.4.H Nausea

1) Incidence: 15.7% (Corya et al, 2003a)

2) Dry mouth (37.1%), nausea (15.7%), and diarrhea (12.5%) have occurred following the administration of o of 7.5 and 46.1 milligrams/day, respectively (Corya et al, 2003a).

3.3.4.I Xerostomia

1) Incidence: 15% to 37.1%(Prod Info SYMBYAX(R) oral capsule, 2009; Corya et al, 2003a)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea in 15% of patients who received fluoxetine/olanzapine (n=771) compared with 6% of patients who received p capsule, 2009).

3) Dry mouth (37.1%), nausea (15.7%), and diarrhea (12.5%) have occurred following the administration of o of 7.5 and 46.1 milligrams/day, respectively (Corya et al, 2003a).

3.3.5 Hematologic Effects

Aplastic anemia

Decreased hemoglobin

Lymphocytopenia

Neutropenia

3.3.5.A Aplastic anemia

1) Aplastic anemia has been reported with olanzapine or fluoxetine monotherapy, but was not observed in ol premarketing clinical studies (Prod Info SYMBYAX(R) oral capsule, 2009).

3.3.5.B Decreased hemoglobin

1) Incidence: 2.6% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In olanzapine/fluoxetine clinical studies (including treatment resistant depression, depressive episodes as depressive disorder with psychosis, or sexual dysfunction), low hemoglobin level occurred at a greater freque olanzapine/fluoxetine-treated patients compared to placebo (2.6% vs 0%) (Prod Info SYMBYAX(R) oral caps

3.3.5.C Lymphocytopenia

1) Incidence: 1.9% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In olanzapine/fluoxetine clinical studies (including treatment resistant depression, depressive episodes as depressive disorder with psychosis, or sexual dysfunction), low lymphocytes level occurred at a greater frequ olanzapine/fluoxetine-treated patients compared to placebo (1.9% vs 0%) (Prod Info SYMBYAX(R) oral caps

3.3.5.D Neutropenia

1) Neutropenia has been reported with olanzapine or fluoxetine monotherapy, but was not observed in olanz premarketing clinical studies (Prod Info SYMBYAX(R) oral capsule, 2009).

3.3.6 Hepatic Effects

Cholestatic hepatitis

Decreased bilirubin level

Hepatitis

Increased liver function test

3.3.6.A Cholestatic hepatitis

1) Incidence: rare (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In the postmarketing period, there have been rare reports of hepatitis and very rare cases of cholestatic o capsule, 2009).

3) Jaundice and cholestatic jaundice have been reported with olanzapine or fluoxetine monotherapy, but was patients during premarketing clinical studies (Prod Info SYMBYAX(R) oral capsule, 2009).

3.3.6.B Decreased bilirubin level

1) Incidence: 15.3% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In olanzapine/fluoxetine clinical studies (including treatment resistant depression, depressive episodes as depressive disorder with psychosis, or sexual dysfunction), low total bilirubin level occurred at a greater frequ olanzapine/fluoxetine-treated patients compared to placebo (15.3% vs 3.9%) (Prod Info SYMBYAX(R) oral ca

3.3.6.C Hepatitis

1) Incidence: rare (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In the postmarketing period, there have been rare reports of hepatitis and very rare cases of cholestatic o capsule, 2009).

3.3.6.D Increased liver function test

1) Incidence: 2% to 3.4% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) As with olanzapine, asymptomatic elevations of hepatic transaminases (ALT (SGPT), AST (SGOT), and G observed with olanzapine/fluoxetine. In the olanzapine/fluoxetine-controlled database, ALT (SGPT) elevation of the normal range) were observed in 3.4% (20/586) of patients exposed to olanzapine/fluoxetine compared 3.5% (23/665) of olanzapine-treated patients. The difference between olanzapine/fluoxetine and placebo was olanzapine/fluoxetine patients who started normal at baseline and had increases in ALT 5 times or more of th jaundice and 4 had transient elevations greater than 200 IU/L (Prod Info SYMBYAX(R) oral capsule, 2009).

3) In olanzapine placebo-controlled studies, clinically significant ALT elevations (3 times the upper limit or gr (6/243) of patients exposed to olanzapine compared with 0% (0/115) of the placebo patients. None of these p patients, liver enzymes decreased toward normal despite continued treatment, and in 2 others, enzymes dec remaining 2 patients, one, seropositive for hepatitis C, had persistent enzyme elevations for 4 months after di follow-up to determine if enzymes normalized (Prod Info SYMBYAX(R) oral capsule, 2009).

4) Within the larger olanzapine premarketing database of about 2400 patients with baseline ALT less than or to greater than 200 international units/L was 2% (50/2381). None of these patients experienced jaundice or o and most had transient changes that tended to normalize while olanzapine treatment was continued. Among approximately 1% (23/2500) discontinued treatment due to transaminase increases (Prod Info SYMBYAX(R)

3.3.7 Immunologic Effects

3.3.7.A Immune hypersensitivity reaction

1) In premarketing controlled clinical studies, the overall incidence of rash or allergic events in treated patien (5.2% (25/477)). The majority of the cases of rash and/or urticaria were mild; however, three patients disconti severity, and two due to allergic events, one of which included face edema). In fluoxetine US clinical studies, developed various types of rashes and/or urticaria (Prod Info SYMBYAX(R) oral capsule, 2009).

2) Among the cases of rash and/or urticaria reported in premarketing clinical studies, almost a third were witl and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with ras carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients expe completely (Prod Info SYMBYAX(R) oral capsule, 2009).

3) In fluoxetine premarketing clinical studies, 2 patients are known to have developed a serious cutaneous s unequivocal diagnosis, but 1 was considered to have a leukocytoclastic vasculitis, and the other, a severe de variously to be a vasculitis or erythema multiforme. Other patients have had systemic syndromes suggestive fluoxetine, systemic events, possibly related to vasculitis, have developed in patients with rash. Although thes the lung, kidney, or liver. Death has been reported to occur in association with these systemic events (Prod I

4) Anaphylactoid events, including bronchospasm, angioedema, and urticaria alone and in combination, hav inflammatory processes of varying histopathology and/or fibrosis, have been reported rarely. These events ha symptom. Whether these systemic events and rash have a common underlying cause or are due to different Furthermore, a specific underlying immunologic basis for these events has not been identified. Upon the app phenomena for which an alternative etiology cannot be identified, the drug should be discontinued (Prod Info

3.3.8 Musculoskeletal Effects

Arthralgia

Muscle rigidity

Pain, Extremity

3.3.8.A Arthralgia

1) Incidence: 4% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea 4% of patients who received fluoxetine/olanzapine (n=771) compared with 1% of patients who received place capsule, 2009).

3.3.8.B Muscle rigidity

1) Incidence: 2% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea stiffness occurred in 2% of patients who received fluoxetine/olanzapine (n=771) compared with 1% of patient SYMBYAX(R) oral capsule, 2009).

3.3.8.C Pain, Extremity

1) Incidence: 3% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea occurred in 3% of patients who received fluoxetine/olanzapine (n=771) compared with 1% of patients who re oral capsule, 2009).

3.3.9 Neurologic Effects

Asthenia

Central nervous system finding

Dizziness

Dyskinesia

Hypersomnia

Impaired cognition

Lethargy

Sedated

Seizure

Somnolence

Tremor

3.3.9.A Asthenia

1) Incidence: 3% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea 3% of patients who received fluoxetine/olanzapine (n=771) compared with 1% of patients who received place capsule, 2009).

3.3.9.B Central nervous system finding

1) Cerebrovascular adverse events (eg, stroke, transient ischemic attack), including fatalities, were reported patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher inciden treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatm (Prod Info SYMBYAX(R) oral capsule, 2009).

2) Somnolence (47.7%), headache (22.3%), asthenia (19.3%), tremor (18.8%), anxiety (13.9%), dizziness (1 (11.6%) were reported following the administration of olanzapine/fluoxetine combination at mean doses of 7.5 al, 2003a).

3.3.9.C Dizziness

1) Incidence: 1.6% to 6.6%

2) In a single 8-week randomized, double-blind, fixed-dose study comparing olanzapine 10 mg/day (n=199), dizziness was reported at 2.6%, 1.6%, and 6.6%, respectively, with significant differences between 20 vs 40 2009).

3.3.9.D Dyskinesia

1) A syndrome of potentially irreversible, involuntary, dyskinetic movements (tardive dyskinesia) may develo Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndr in their potential to cause tardive dyskinesia is unknown. The risk of developing tardive dyskinesia and the lik believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs adminis syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses or treatment (Prod Info SYMBYAX(R) oral capsule, 2009).

2) The incidence of dyskinetic movement in olanzapine/fluoxetine-treated patients was infrequent. The mean Scale (AIMS) across clinical studies involving olanzapine/fluoxetine-treated patients decreased from baseline prescribed in a manner that is most likely to minimize the risk of tardive dyskinesia. If signs and symptoms of olanzapine/fluoxetine, drug discontinuation should be considered. However, some patients may require treatr presence of the syndrome. The need for continued treatment should be reassessed periodically (Prod Info SY

3) Dyskinesia has been reported with olanzapine or fluoxetine monotherapy, but was not observed in olanza premarketing clinical studies (Prod Info SYMBYAX(R) oral capsule, 2009).

3.3.9.E Hypersomnia

1) Incidence: 5% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea occurred in 5% of patients who received fluoxetine/olanzapine (n=771) compared with 1% of patients who rec oral capsule, 2009).

3.3.9.F Impaired cognition

1) Sedation-related adverse events were commonly reported with olanzapine/fluoxetine treatment, occurring olanzapine/fluoxetine patients compared with 10.9% in placebo patients. Sedation-related adverse events (sc discontinuation in 2% (15/771) of patients during controlled clinical studies. As with any CNS-active drug, olan judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, inclu certain that olanzapine/fluoxetine therapy does not affect them adversely (Prod Info SYMBYAX(R) oral capsu

3.3.9.G Lethargy

1) Incidence: 3% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea 3% of patients who received fluoxetine/olanzapine (n=771) compared with 1% of patients who received place capsule, 2009).

3.3.9.H Sedated

1) Incidence: 8% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea 8% of patients who received fluoxetine/olanzapine (n=771) compared with 4% of patients who received place capsule, 2009).

3.3.9.I Seizure

1) Incidence: 0.2% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) Seizures occurred in 0.2% (4/2547) of olanzapine/fluoxetine-treated patients during open-label clinical stu olanzapine/fluoxetine studies. Seizures have also been reported with both olanzapine and fluoxetine monothe used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure thres may be more prevalent in a population of greater than or equal to 65 years of age (Prod Info SYMBYAX(R) o

3) There have been rare reports of prolonged seizures in patients on fluoxetine receiving electroconvulsive tl studies establishing the benefit of the combined use of ECT and fluoxetine (Prod Info SYMBYAX(R) oral caps

3.3.9.J Somnolence

1) Incidence: 14% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea occurred in 14% of patients who received fluoxetine/olanzapine (n=771) compared with 6% of patients who re (R) oral capsule, 2009).

3.3.9.K Tremor

1) Incidence: 9% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea 9% of patients who received fluoxetine/olanzapine (n=771) compared with 3% of patients who received place capsule, 2009).

3.3.10 Ophthalmic Effects

3.3.10.A Blurred vision

1) Incidence: 5% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea occurred in 5% of patients who received fluoxetine/olanzapine (n=771) compared with 2% of patients who rec oral capsule, 2009).

3.3.12 Psychiatric Effects

Depression, Worsening

Disturbance in thinking

Disturbance of attention

Feeling nervous

Mania

Restlessness

Suicidal thoughts

Suicide

Violent behavior

3.3.12.A Depression, Worsening

1) All patients being treated with antidepressants for any indication should be monitored appropriately and ol and unusual changes in behavior, in particular during the first few months or at times of dose increase or dec 2009).

3.3.12.B Disturbance in thinking

1) Incidence: 2% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea occurred in 2% of patients who received fluoxetine/olanzapine (n=771) compared with 1% of patients who re oral capsule, 2009).

3.3.12.C Disturbance of attention

1) Incidence: 5% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea attention occurred in 5% of patients who received fluoxetine/olanzapine (n=771) compared with 1% of patient SYMBYAX(R) oral capsule, 2009).

3.3.12.D Feeling nervous

1) Incidence: 2% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea occurred in 2% of patients who received fluoxetine/olanzapine (n=771) compared with 1% of patients who re oral capsule, 2009).

3.3.12.E Mania

1) In the two controlled bipolar depression studies there was no statistically significant difference in the incid depressive reaction) between olanzapine/fluoxetine- and placebo-treated patients. In one of the studies, the i olanzapine/fluoxetine-treated patients compared to (3% (5/184)) in placebo-treated patients. In the other stud in olanzapine/fluoxetine-treated patients compared to (8% (15/193)) in placebo-treated patients. This limited olanzapine/fluoxetine in the treatment of bipolar depression makes it difficult to interpret these findings until a the cyclical nature of bipolar disorder, patients should be monitored closely for the development of symptoms olanzapine/fluoxetine (Prod Info SYMBYAX(R) oral capsule, 2009).

3.3.12.F Restlessness

1) Incidence: 4% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea occurred in 4% of patients who received fluoxetine/olanzapine (n=771) compared with 1% of patients who re oral capsule, 2009).

3.3.12.G Suicidal thoughts

1) Adult and pediatric patients being treated with antidepressants for major depressive disorder (MDD) and o who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness) restlessness), hypomania, or mania may be at risk of suicidal ideation and behavior (suicidality). In pooled an of 9 antidepressants including over 4400 pediatric patients with MDD, obsessive compulsive disorder (OCD), suicidal behavior or ideation during the first few months of therapy was demonstrated in children, adolescents receiving antidepressants as compared with placebo. However, pooled analyses of 295 short-term (median d 11 antidepressants including over 77,000 adults with MDD or other psychiatric disorders did not demonstrate antidepressants compared to placebo in adults beyond age 24 years. Further, there was a reduction in risk o placebo in adults aged 65 years and older. The risk of suicidality was most consistently observed in the trials signs of risk emerging from trials in other psychiatric indications, such as OCD and social anxiety disorder. N however, there were suicides in the adult trials. The risk of suicidality during longer-term use (ie, beyond seve known. However, placebo-controlled maintenance trials in adults with depression indicate that antidepressan Info SYMBYAX(R) oral capsule, 2009).

3.3.12.H Suicide

1) The possibility of a suicide attempt is inherent in bipolar disorder and may persist until significant remissio should accompany drug therapy. Prescriptions for olanzapine/fluoxetine should be written for the smallest qu in order to reduce the risk of overdose. There were reports of suicides during clinical trials in adults, but the n about drug effect on suicide (Prod Info SYMBYAX(R) oral capsule, 2009).

3.3.12.I Violent behavior

1) Violent behaviors have been reported with olanzapine or fluoxetine monotherapy, but was not observed in premarketing clinical studies (Prod Info SYMBYAX(R) oral capsule, 2009).

3.3.13 Renal Effects

Glycosuria

Increased uric acid level

Serum blood urea nitrogen raised

3.3.13.A Glycosuria

1) Incidence: 4.4% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In an analysis of 6 controlled clinical studies, glycosuria were reported at 4.4% in patients treated with ola receiving placebo (Prod Info SYMBYAX(R) oral capsule, 2009).

3.3.13.B Increased uric acid level

1) Incidence: 2.9% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In olanzapine/fluoxetine clinical studies (including treatment resistant depression, depressive episodes as depressive disorder with psychosis, or sexual dysfunction), elevated uric acid level occurred at a greater freq olanzapine/fluoxetine-treated patients compared to placebo (2.9% vs 0.5%) (Prod Info SYMBYAX(R) oral cap

3.3.13.C Serum blood urea nitrogen raised

1) Incidence: 2.8% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In olanzapine/fluoxetine clinical studies (including treatment resistant depression, depressive episodes as depressive disorder with psychosis, or sexual dysfunction), elevated urea nitrogen level occurred at a greater olanzapine/fluoxetine-treated patients compared to placebo (2.8% vs 0.8%) (Prod Info SYMBYAX(R) oral cap

3.3.14 Reproductive Effects

Erectile dysfunction

Sexual dysfunction

3.3.14.A Erectile dysfunction

1) Incidence: 2% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea occurred in 2% of patients who received fluoxetine/olanzapine (n=771) compared with 1% of patients who re oral capsule, 2009).

3.3.14.B Sexual dysfunction

1) In the pool of controlled olanzapine/fluoxetine studies, there were higher rates of treatment-emergent adv anorgasmia, impotence and abnormal ejaculation in the olanzapine/fluoxetine group than in the placebo grou discontinuation in the olanzapine/fluoxetine group. In the controlled studies that contained a fluoxetine arm, t ejaculation in the olanzapine/fluoxetine group were less than the rates in the fluoxetine group. None of the di study (n=560), decreased libido occurred in 11.4% of patients following the administration of olanzapine/fluox milligrams/day, respectively (Prod Info SYMBYAX(R) oral capsule, 2009; Corya et al, 2003a).

2) Sexual dysfunction, including priapism, has been reported with all SSRIs. While it is difficult to know the p the use of SSRIs, physicians should routinely inquire about such possible side effects (Prod Info SYMBYAX(

3.3.15 Respiratory Effects

Pulmonary eosinophilia

Respiratory finding

Sinusitis

3.3.15.A Pulmonary eosinophilia

1) Eosinophilic pneumonia has been reported with olanzapine or fluoxetine monotherapy, but was not obser during premarketing clinical studies (Prod Info SYMBYAX(R) oral capsule, 2009).

3.3.15.B Respiratory finding

1) Pharyngitis (10.4%), rhinitis (22.1%), and dyspnea have been reported in olanzapine/fluoxetine-treated pa

3.3.15.C Sinusitis

1) Incidence: 2% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea 2% of patients who received fluoxetine/olanzapine (n=771) compared with 1% of patients who received place capsule, 2009).

3.3.16 Other

Death

Fatigue

Fever

Neuroleptic malignant syndrome

Pain

Serotonin syndrome

3.3.16.A Death

1) Incidence: 3.5% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In olanzapine placebo-controlled clinical trials of elderly patients with dementia-related psychosis, the inci
significantly higher than the placebo group (3.5% vs 1.5%, respectively)(Prod Info SYMBYAX(R) oral capsule

3) Sudden unexpected death has been reported with olanzapine or fluoxetine monotherapy, but was not obs
during premarketing clinical studies (Prod Info SYMBYAX(R) oral capsule, 2009).

4) Results of a population-based, retrospective cohort study demonstrated that the use of conventional antip
risk for death than atypical antipsychotics when administered to elderly patients (aged 66 years and older) wi
and conventional versus atypical antipsychotic use pair-wise comparisons were made. A total of 27,259 matc
cohort was stratified based on place of residence (community versus long-term care facilities). In order to adj
propensity score matching was used. The primary outcome of the study was all-cause mortality. The risk for
days after the antipsychotic medications were initially dispensed. There was a statistically significant increase
new use of atypical antipsychotic medications compared with nonuse in both the community-dwelling cohort
confidence interval (CI), 1.02 to 1.70); absolute risk difference, 0.2 percentage point) and long-term care coh
absolute risk difference, 1.2 percentage points). For both cohorts, the risk associated with atypical antipsycho
death associated with conventional antipsychotics was even greater than the risk identified with atypical antip
community-dwelling cohort was 1.55 (95% CI, 1.19 to 2.02) and 1.26 (95% CI, 1.04 to 1.53) for the long-term
was 1.1 percentage points). The risk appeared to persist to 180 days for both groups. Some important limitati
unmeasured confounders may influence the results and cause of death could not be examined (Gill et al, 200

5) Results of a population-based, retrospective cohort study demonstrated comparable to possibly greater ris
conventional antipsychotic medications in the elderly (aged 65 years and older) compared with atypical antips
patients with cancer and included only new users of antipsychotic medications. The primary study outcome w
confounders was measured based on healthcare utilization data within 6 months before the initiation of antips
patients identified, 12,882 and 24,359 received conventional and atypical antipsychotic medications, respecti
group within the first 180 days was 14.1% compared with 9.6% in the atypical drug group (unadjusted mortali
to 1.56). In the multi-variable analysis which controlled for potential confounders, the adjusted mortality ratio f
conventional versus atypical drug therapy was 1.32 (95% CI, 1.23 to 1.42). When the most frequently prescri
compared with risperidone, the mortality ratio associated with haloperidol was 2.14 (95% CI, 1.86 to 2.45) an
there was no difference associated with olanzapine. The increased mortality risk for conventional versus atyp
higher (above median) doses were used (mortality ratio 1.67; 95% CI, 1.5 to 1.86) and also during the first 40
1.42 to 1.8). Confirmatory analyses consisting of multi-variable Cox regression, propensity score, and instrum
the study (Schneeweiss et al, 2007).

3.3.16.B Fatigue

1) Incidence: 12% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea
12% of patients who received fluoxetine/olanzapine (n=771) compared with 2% of patients who received plac
capsule, 2009).

3) In a single 8-week randomized, double-blind, fixed-dose study comparing olanzapine 10 mg/day (n=199),
fatigue was reported at 1.5%, 2.1%, and 6.6%, respectively, with significant differences between 10 vs 40 an
capsule, 2009).

3.3.16.C Fever

1) Incidence: 2% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea
2% of patients who received fluoxetine/olanzapine (n=771) compared with 1% of patients who received place
capsule, 2009).

3.3.16.D Neuroleptic malignant syndrome

1) Neuroleptic malignant syndrome (NMS) has been reported in association with administration of antipsych manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic in tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosph acute renal failure. Management of NMS should include immediate discontinuation of antipsychotic drugs and therapy, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious are available. There is no general agreement about specific pharmacological treatment regimens for NMS (P

3.3.16.E Pain

1) Incidence: 2% (Prod Info SYMBYAX(R) oral capsule, 2009)

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and trea of patients who received fluoxetine/olanzapine (n=771) compared with 1% of patients who received placebo (2009).

3.3.16.F Serotonin syndrome

1) The development of a potentially life-threatening serotonin syndrome or neuroleptic malignant syndrome (serotonin norepinephrine reuptake inhibitor (SNRIs) and SSRIs alone but particularly with concomitant use of drugs which impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine anta include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, tachycardia, lab neuromuscular aberrations (eg, hyperreflexia, incoordination) and/or gastrointestinal symptoms (eg, nausea, most severe form can resemble NMS, which includes hyperthermia, muscle rigidity, autonomic instability with mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like s olanzapine/fluoxetine with MAOIs for depression is contraindicated. Further, concomitant use of olanzapine/fl agonist (triptans) is clinically warranted, and its use is not recommended with SNRIs, SSRIs, or tryptophan. T concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued imme supportive symptomatic treatment should be initiated (Prod Info SYMBYAX(R) oral capsule, 2009).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) Fluoxetine

a) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info PROZAC(R) oral capsu (All Trimesters)

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

b) Australian Drug Evaluation Committee's (ADEC) Category: C(Batagol, 1999)

1) Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing ha without causing malformations. These effects may be reversible. Accompanying texts should be consulte

See Drug Consult reference: PREGNANCY RISK CATEGORIES

c) Crosses Placenta: Yes

d) Clinical Management

1) A large, population-based study found no increased risk of malformations in infants exposed to select exposed infants were more likely to require treatment in a special or intensive care unit (Malm et al, 2005 20 weeks of gestation has been associated with an increased risk of persistent pulmonary hypertension (of prospectively collected data suggests antenatal use of selective serotonin-reuptake inhibitor (SSRI) ar prolongation in exposed neonates (Dubnov-Raz et al, 2008). There was no significant association betwe risks of birth defects, including congenital heart defects, according to a later population-based case-cont to fluoxetine and other SSRI and selective serotonin and norepinephrine reuptake inhibitors (SNRI), late symptoms of SSRI and SNRI toxicity or withdrawal syndrome (Prod Info PROZAC(R) oral capsules, dela the dangers of failing to treat major depression are obvious, and in each case, these dangers must be w effects (Nulman et al, 1997; Lamberg, 1999). In pregnant patients diagnosed with obsessive compulsive behavioral therapy has proven inadequate (Anon, 2000; Altshuler et al, 1996a).

e) Literature Reports

1) A study of prospectively collected data suggests antenatal use of selective serotonin-reuptake inhibito interval prolongation in exposed neonates. Between January 2000 and December 2005, researchers co antidepressants (paroxetine (n=25), citalopram (n=13), fluoxetine (n=12), fluvoxamine (n=1), and venlafa 52 matched neonates with no exposure. Prolonged QTc is defined as an interval of greater than 460 mill cited by authorities in both pediatric cardiology and neonatology). A pediatric cardiologist blinded to drug (ECGs) using standard statistical analyses. ECG recordings revealed markedly prolonged mean QTc int unexposed neonates (mean; 409 +/- 42 msec versus 392 +/- 29 msec, p=0.02). The mean uncorrected C neonates (mean; 280 +/- 31 msec versus 261 +/- 25 msec, p less than 0.001). Ten percent (n=5) of expo interval prolongation (greater than 460 msec) compared to none of the unexposed neonates. The longes Raz et al, 2008).

2) Data from the case-controlled National Birth Defects Prevention Study (NBDPS), which included data 2002, indicated that early maternal exposure (defined as treatment with any SSRI from 1 month before t associated with anencephaly in 9 exposed infants out of 214 (adjusted odds ratio (OR), 2.4; 95% confide craniosynostosis in 24 exposed infants out of 432 (adjusted OR 2.5; 95% CI, 1.5 to 4.0; P less than 0.00 181 (adjusted OR 2.8; 95% CI, 1.3 to 5.7; P=0.005). However, early exposure did not significantly increa other birth defects. The most commonly used SSRIs reported by control mothers were sertraline, fluoxet 2007).

3) In a prospective longitudinal study (n=201), discontinuation of antidepressant medication in women w euthymic at the start of pregnancy increased the chance for relapse of major depression compared to wo However, neonatal exposure, particularly in the third trimester, to fluoxetine and other selective serotonir norepinephrine reuptake inhibitors (SNRIs) has led to complications requiring prolonged hospitalization, findings have included cyanosis, apnea, seizures, tremor, and constant crying, and the clinical scenario i careful assessments of potential risks and benefits of treatment must be conducted prior to using fluoxet trimester (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

4) A case-control study found that the use of selective serotonin reuptake inhibitors (SSRIs) after 20 we increased risk of persistent pulmonary hypertension of the newborn (PPHN). Fluoxetine, paroxetine, and carry this increased risk. A total of 377 women who had infants with PPHN were matched to 836 women determined by telephone interview within 6 months of birth. After adjusting for other covariates, SSRI use an odds ratio of 6.1 (95% CI 2.2-16.8; p=0.001) of delivering an infant with PPHN relative to no use durir gestation and non-SSRI antidepressants use at any gestation time was not associated with increased ris in the general population is about 0.1 to 0.2%. According to this study, infants exposed to SSRIs after 20 0.6 to 1.2% (Chambers et al, 2006).

5) A population-based study of 1782 pregnant women exposed to selective serotonin reuptake inhibitors perinatal outcome except for treatment in the neonatal intensive or special care unit, particularly with thir derived from a government project involving 4 birth or medication registries in Finland, women who had a SSRI during the period of one month before pregnancy and the day pregnancy ended were compared to purchases during the same peripartum period. The mean age of both cohorts was 30 years (+/- 7). There times as many pregnancies induced by artificial reproductive techniques in the SSRI group compared to gestation and birth weight were lower (p less than 0.001) in the SSRI group. Malformations, however, we 0.4). Purchases of SSRIs (citalopram, fluoxetine, paroxetine, sertraline and fluvoxamine) were more com with 525 women purchasing fluoxetine during the first trimester, 232 during the second trimester, 239 du When compared to first trimester exposure, treatment in a special or intensive care unit was more comm trimester (11.2% and 15.7%, respectively; p = 0.009). Even after adjusting for confounding variables, this 1.6; 95% CI 1.1 to 2.2) (Malm et al, 2005).

6) In a prospective clinical trial designed to evaluate the pharmacokinetics of fluoxetine and norfluoxetin pregnancy outcomes were found to be similar in both the control and treated groups. The study compare 50 mg per day during pregnancy and lactation to 10 women in the control group who were not exposed t hepatic blood flow, increased volume of distribution and decreased binding to plasma proteins, trough pl norfluoxetine were low. At delivery, umbilical vein concentrations were 65% and 72% of the maternal cor postnatal period, plasma concentrations of fluoxetine and norfluoxetine were still elevated, likely due to t capacity and CYP2D6 enzyme activity. There were no fetal malformations or difference in birth weights b at fifteen minutes were lower in the fluoxetine group (Heikkinen et al, 2003).

7) In one study assessing the direct effects of fluoxetine on infant outcome at birth (Chambers et al, 199 to fluoxetine in the third trimester may be at an increased risk for perinatal complications such as respira jitteriness. These neonates may have had difficulty clearing the drug due to its long half-life. Depending c and patient may consider tapering the dose of fluoxetine to discontinue 10 to 14 days prior to delivery to 1999).

8) Based on analyses of independently collected data and that obtained through the Motherisk Program function, temperament and general behavior in children exposed prenatally to fluoxetine as compared to Nulman & Koren, 1996; Nulman et al, 1997). However, among infants who were exposed to either fluoxe gestation, those born to mothers with uncontrolled depressive symptoms showed lower cognitive and lar who were well-controlled (Nulman et al, 2002).

9) An increased risk for central nervous system serotonergic symptoms was observed during the first fo selective serotonin reuptake inhibitors (SSRI) during the third trimester of pregnancy. In a controlled, pro milligrams/day of either citalopram (n=10) or fluoxetine (n=10) while pregnant were compared to a contro ranged from 7 to 41 weeks. Newborns in the SSRI group had a lower Apgar score at 15 minutes as com The only significant difference observed in the vital signs of the newborns was a higher heart rate in the controls (mean, 153 vs 141 beats per minute; p=0.049). Serotonergic symptom scores in the first 4 days group than in the control group (total score, 121 vs 30, respectively; p=0.008). Tremor, restlessness, and Myoclonus was reported in one infant exposed to fluoxetine. Significantly lower cord blood 5-hydroxyindo in the SSRI-exposed infants as compared with the control group (mean, 63 mmol/L vs 77 mmol/L; p=0.0 was observed between the serotonergic symptom score and the umbilical vein 5-HIAA concentrations in control group (p=0.007). Although not statistically significant, mean umbilical cord serum prolactin conce infants than in control infants at the time of birth (Laine et al, 2003).

2) Olanzapine

a) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info ZYPREXA(R) oral table disintergating tablets, 2008) (All Trimesters)

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

b) Australian Drug Evaluation Committee's (ADEC) Category: B3(Australian Drug Evaluation Committee, 19

1) Drugs which have been taken by only a limited number of pregnant women and women of childbearir malformation or other direct or indirect harmful effects on the human fetus having been observed. Studie increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

c) Crosses Placenta: Yes

d) Clinical Management

1) There is insufficient evidence to clearly establish the safety of olanzapine during pregnancy and it is r only if the potential benefit justifies the potential risk to the fetus (Prod Info ZYPREXA(R) oral tablets, IM disintergating tablets, 2008). Limited data to date do not suggest an increased risk of major malformatior Goldstein et al, 2000); notably, schizophrenic women may have higher prevalence rates of social and life drug use, low socioeconomic status) associated with risky neonatal outcomes (Patton et al, 2002). Patie bipolar disorder should be maintained on medication therapy throughout gestation, as these patients anc (Altshuler et al, 1996).

e) Literature Reports

1) A prospective, observational study of 54 women (mean age, 30.7 years), recruited from the Emory W antipsychotic medication during pregnancy, showed permeability of the placental barrier. Outcomes were blood samples taken at delivery and through data collected from maternal reports and medical records. F umbilical cord to maternal plasma concentrations) showed a significant difference between antipsychotic 46.8%-97.5%) being the highest, followed by haloperidol 65.5% (95% CI, 40.3%-90.7%), risperidone 49. 24.1% (95% CI, 18.7%-29.5%), showing the lowest placental passage ratio. There was a greater frequer 0.23), low birth weights (30.8%, p=less than 0.07), and neonatal intensive care admission (30.8%, p=less (Newport et al, 2007).

2) There are no adequate and well-controlled studies with olanzapine use during pregnancy. Seven preg olanzapine, which resulted in 2 normal births, 1 neonatal death due to cardiovascular defect, 3 therapeut Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008). F pregnancies, there was no increase in risk of spontaneous abortion, stillbirth, prematurity, or major malfo utero (Goldstein et al, 2000). Analysis of expanded data from this latter report produced similar conclusic 71.9% resulted in normal births, 12.5% in spontaneous abortions, 2.1% in premature deliveries, 3.1% in Goldberg, 2002). From an ongoing study to assess the fetal safety of atypical antipsychotics, interim resu olanzapine, or quetiapine had the following outcomes: 20 live births with no malformations, 3 spontaneou abortions (McKenna et al, 2003).

3) Occasional spontaneous case reports of in utero exposure to olanzapine have produced viable newb established (Mendhekar et al, 2002; Nagy et al, 2001; Littrell et al, 2000; Kirchheiner et al, 2000). A case (cord blood) level of 11 nanograms (ng)/mL compared with 34 ng/mL in the maternal plasma drawn befo olanzapine 15 mg during pregnancy. During gestation, the maternal olanzapine plasma levels were betw development with the only complication being gestational diabetes which was resolved with diet. Delivery score of 10/10/10) developed normally during the first 6 months (Aichhorn et al, 2008).

4) In another case report, a 37-year-old woman with a 7-year history of paranoid schizophrenia gave birt olanzapine 25 mg/day starting at week 8 until week 32 when she discontinued it against medical advice. 3 months preceding her pregnancy (Lim, 2001). An isolated case of maternal use of up to 20 mg of olanz 23rd week of gestation until 10 days prior to delivery has been reported. In this case, a healthy baby was and 9-10 at 5 minutes; at 3 months of age, the infant showed age-appropriate milestones (Mendhekar et day exposure from the 18th week of pregnancy through delivery and during breastfeeding also exists. De suspicious motor development at 7 months of age, the infant showed no abnormal findings at 11 months

B) Breastfeeding

1) Fluoxetine

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

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

1) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant ris potential benefits of drug treatment against potential risks before prescribing this drug during breastfeedi

c) Clinical Management

1) Fluoxetine and its active metabolite, norfluoxetine, appear in breast milk and the oral dose available t mcg/kg/day for fluoxetine (Burch & Wells, 1992), and 40 mcg/kg/day for fluoxetine plus norfluoxetine (Ta recommendation that fluoxetine not be used by women while breastfeeding (Prod Info PROZAC(R) oral 2008), many women choose to do so. The American Academy of Pediatrics considers antidepressants to (Anon, 2001). There is insufficient data available to safely recommend use of fluoxetine by nursing moth infant should be monitored for anorexia, weight loss, irritability, and insomnia. The long-term effects of ex (SSRIs) via breast milk on the cognitive development of the infant have not been determined.

d) Literature Reports

1) A number of cases have been reported in which fluoxetine was used to treat postpartum depression i or composition was observed. While increased infant irritability during maternal fluoxetine treatment has after exposure to fluoxetine during nursing (Epperson et al, 2003; Burch & Wells, 1992; Isenberg, 1990).

2) In a study of 14 mother-infant pairs, the mean total infant exposure was estimated as 6.81% (3.36% f 9 infants with blood samples, 5 and 7 had detectable concentrations of fluoxetine and norfluoxetine, resp had withdrawal symptoms described as uncontrollable crying, irritability, and poor feeding. Symptoms in plasma concentrations of fluoxetine and/or norfluoxetine. One mother also used methadone, and 4 infan authors recommend caution especially during the early neonatal period and in infants exposed in utero to

3) A 1996 cohort study involved 11 infants nursed by 10 mothers. Although limited by maternal perceptio infants were reported by the mothers (Taddio et al, 1996).

4) One study described 4 nursing mothers, taking 20 to 40 mg of fluoxetine per day, in which the Bayley development of the infants. None of the infants exhibited any neurological abnormality (Taddio et al, 199

5) The manufacturer reports a maternal plasma concentration of 295 nanograms/mL for fluoxetine plus concentration of 70.4 nanograms/mL. No adverse effects in the nursing infant were reported. In another

340 nanograms/mL of fluoxetine and 208 nanograms/mL of norfluoxetine on the second day of breastfee not reported. The infant developed crying, sleep disturbance, vomiting, and watery stools (Prod Info PRO capsules, solution, 2008).

6) No clinically significant changes in platelet 5-hydroxytryptamine (5-HT) transport were reported in 11 the study) exposed to fluoxetine through maternal breast milk. Determinations of whole-blood 5-HT, fluox both infants and mothers prior to initiating fluoxetine doses of 20 mg to 40 mg per day. Post-exposure le maternal plasma concentrations of fluoxetine were 125 nanograms/mL, and norfluoxetine were 142 nanc fluoxetine levels below 1 nanograms/mL, and the mean infant plasma concentration of norfluoxetine was post-fluoxetine 5-HT levels were 157 nanograms/mL and 23 nanograms/mL, respectively. The mean infa were 217 nanograms/mL and 230 nanograms/mL, respectively. Baley Scale scores were determined for revealing that 6 infants were within one standard deviation of the mean on mental and motor developme most exclusively breastfed infants will not likely experience changes in platelet 5-HT levels upon materna

2) Olanzapine

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

1) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant ris potential benefits of drug treatment against potential risks before prescribing this drug during breastfeedi

b) Clinical Management

1) Limited data from studies of nursing mothers treated with olanzapine have demonstrated that olanzap ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008; Gardi report described jaundice, cardiomegaly, somnolence, and a heart murmur in the infant of a mother rece remained after bottle-feeding was initiated on day 7 of life. Another case from the same report demonstra maternal olanzapine doses at 2 months of age (Goldstein et al, 2000a). Undetectable infant olanzapine p olanzapine levels of 32.8 to 39.5 nanograms/mL were reported in another case (Kirchheiner et al, 2000a excreted in human breast milk, it is recommended that women treated with olanzapine should not breast injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).

c) Literature Reports

1) In a study of healthy, nursing women, olanzapine was excreted in breast milk. The estimated mean in maternal olanzapine dose (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) ora mothers receiving 5 to 20 mg/day of olanzapine, the median infant dose ingested through breast milk wa analysis of milk and plasma samples from five nursing mothers treated with olanzapine 2.5 mg to 10 mg 0.84. This compared to a theoretical value of 0.38 that was determined using the known pharmacokinetic consumption of 0.15 L/kg/day and assuming 100% bioavailability, relative infant dose was estimated to b dose (Croke et al, 2002). In a case report, breast milk was collected by an electric pump and olanzapine chromatography. The findings indicated that olanzapine was excreted in the breast milk in relatively sma ratio was 0.42 at steady state (Ambresin et al, 2004).

2) Limited data from cases of olanzapine exposure via breast milk fail to affirm or eliminate the potential case described an infant exposed in utero to olanzapine (maternal dose 5 mg/day) who was born with ca murmur. However, jaundice and sedation continued despite the initiation of bottle-feeding on day seven exposed at two months of age (maternal dose 10 mg/day) had no adverse effects (Goldstein et al, 2000a infant olanzapine plasma levels (less than 2 ng/mL) despite maternal steady-state trough levels of 32.8 t olanzapine doses of 10 mg daily throughout pregnancy and during breastfeeding (Kirchheiner et al, 2000

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Food Combinations

3.5.1 Drug-Drug Combinations

Abciximab

Acecainide

Aceclofenac

Acemetacin

Acenocoumarol

Activated Charcoal

Ajmaline

Alclofenac

Almotriptan

Alprazolam

Amiodarone

Amisulpride

Amitriptyline

Amoxapine

Anagrelide

Ancrod

Anisindione

Antithrombin III Human

Aprindine

Ardeparin

Aripiprazole

Arsenic Trioxide

Aspirin

Astemizole

Atomoxetine

Azimilide

Belladonna

Belladonna Alkaloids

Benoxaprofen

Bepridil

Betel Nut

Bivalirudin

Bretylium

Bromfenac

Bufexamac

Bupropion

Buspirone

Cannabis

Carbamazepine

Carbamazepine

Carprofen

Celecoxib

Certoparin

Chloral Hydrate

Chloroquine

Chlorpromazine

Cilostazol

Ciprofloxacin

Clarithromycin

Clomipramine

Clonixin

Clopidogrel

Clopidogrel

Clorgyline

Clozapine

Cyclobenzaprine

Cyproheptadine

Dalteparin

Danaparoid

Defibrotide

Dehydroepiandrosterone

Dehydroepiandrosterone

Delavirdine

Dermatan Sulfate

Desipramine

Desirudin

Desvenlafaxine

Dexfenfluramine

Dexketoprofen

Dextromethorphan

Diazepam

Dibenzepin

Diclofenac

Dicumarol

Diflunisal

Digitoxin

Digoxin

Dihydroergotamine

Dipyridamole

Dipyrone

Disopyramide

Dofetilide

Dolasetron

Doxepin

Droperidol

Droxicam

Duloxetine

Eletriptan

Enflurane

Enoxaparin

Epoprostenol

Eptifibatide

Ergoloid Mesylates

Ergonovine

Ergotamine

Erythromycin

Eszopiclone

Etodolac

Etofenamate

Etoricoxib

Felbinac

Fenbufen

Fenfluramine

Fenoprofen

Fentiazac

Flecainide

Floctafenine

Fluconazole

Flufenamic Acid

Fluphenazine

Flurbiprofen

Fluvoxamine

Fondaparinux

Foscarnet

Fosphenytoin

Frovatriptan

Furazolidone

Galantamine

Gemifloxacin

Ginkgo

Halofantrine

Haloperidol

Haloperidol

Halothane

Heparin

Hydroquinidine

Hydroxytryptophan

Ibuprofen

Ibutilide

Iloperidone

Iloprost

Imipramine

Indomethacin

Indoprofen

Insulin Aspart, Recombinant

Insulin Detemir

Insulin Glargine, Recombinant

Insulin Glulisine

Insulin Human Inhaled

Iproniazid

Isocarboxazid

Isoflurane

Isoxicam

Isradipine

Ketoprofen

Ketorolac

Lamifiban

Levodopa

Levomethadyl

Levomethadyl

Lexipafant

Lidoflazine

Linezolid

Lithium

Lithium

Lorcainide

Lornoxicam

Meclofenamate

Mefenamic Acid

Mefloquine

Meloxicam

Meperidine

Mesoridazine

Methylergonovine

Methylphenidate

Methysergide

Metoprolol

Milnacipran

Mirtazapine

Mirtazapine

Moclobemide

Morniflumate

Nabumetone

Nadroparin

Naproxen

Naratriptan

Nebivolol

Nialamide

Niflumic Acid

Nimesulide

Nortriptyline

Octreotide

Oxaprozin

Parecoxib

Pargyline

Parnaparin

Paroxetine

Pentamidine

Pentazocine

Pentosan Polysulfate Sodium

Phenelzine

Phenindione

Phenprocoumon

Phenylalanine

Phenylbutazone

Phenytoin

Pimozide

Pirazolac

Pirmenol

Piroxicam

Pirprofen

Prajmaline

Probucol

Procainamide

Procarbazine

Prochlorperazine

Propafenone

Propranolol

Propyphenazone

Proquazone

Quetiapine

Quinidine

Rasagiline

Reviparin

Risperidone

Ritonavir

Ritonavir

Rizatriptan

Rofecoxib

Selegiline

Sematilide

Sertindole

Sibrafiban

Sibutramine

Sotalol

Spiramycin

St John's Wort

St John's Wort

Sulfamethoxazole

Sulfinpyrazone

Sulindac

Sulodexide

Sultopride

Sumatriptan

Suprofen

Tamoxifen

Tamsulosin

Tapentadol

Tedisamil

Telithromycin

Tenidap

Tenoxicam

Terfenadine

Tetrabenazine

Tetrabenazine

Thioridazine

Tiaprofenic Acid

Ticlopidine

Tinzaparin

Tipranavir

Tirofiban

Tolmetin

Toloxatone

Tramadol

Tramadol

Tranylcypromine

Trazodone

Trifluoperazine

Trimethoprim

Trimipramine

Tryptophan

Valdecoxib

Vasopressin

Venlafaxine

Warfarin

Xemilofiban

Ziprasidone

Zolmitriptan

Zolpidem

Zomepirac

Zotepine

3.5.1.A Abciximab

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; release capsules, solution, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 200

7) Probable Mechanism: unknown

3.5.1.B Acecainide

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

2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class prolong the QTc interval is not recommended (Allen et al, 2002; Prod Info Tikosyn(TM) dofetilide capsules, 1 been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001a).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that pro recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.C Aceclofenac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in

7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.D Acemetacin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.E Acenocoumarol

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2 (R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wl (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally was discontinued. The next day the patient presented to the hospital with left-sided weakness and later c interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.F Activated Charcoal

1) Interaction Effect: decreased bioavailability of olanzapine
2) Summary: Activated charcoal reduces the maximum concentration and area under the concentration-time Zyprexa(R), 1999b). This drug interaction may make activated charcoal useful in cases of olanzapine overdo
3) Severity: minor
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Do not administer activated charcoal and olanzapine concomitantly.
7) Probable Mechanism: binding of olanzapine in the gut

3.5.1.G Ajmaline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class prolong the QTc interval is not recommended (Prod Info Quinaglute Dura-tabs(R), 1999). Fluoxetine has dem (Prod Info Prozac(R), 2001z).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class Ia antiarrhythmic agents and agents that pro recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.H Alclofenac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of up than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.I Almotriptan

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Concomitant use of almotriptan and selective serotonin reuptake inhibitors (SSRI's) has been r incoordination (Prod Info Axert(TM), 2001). Concurrent use of a triptan and an SSRI may result in serotonin s Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart be body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that trip that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin s combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administratio
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of a triptan, such as almotriptan, and an SSRI may result in a life- Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be pr are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms hyperthermia, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

8) Literature Reports

a) Concomitant administration of fluoxetine and almotriptan is well tolerated and fluoxetine has only a m concentration (Cmax). Other almotriptan pharmacokinetics are not significantly affected. A randomized, healthy volunteers has been conducted. Subjects received each of the following treatments with a minim 20 mg fluoxetine capsules on day 1 to 8 and one dose almotriptan 12.5 mg on day 8, (2) one dose of alm days 1 through 7. Peak almotriptan concentrations were 18% higher following concomitant administratio administration alone. This difference was statistically significant (p equal 0.023). Mean almotriptan area u oral clearance were borderline statistically different between treatment groups. Mean half-life was not sta During fluoxetine coadministration, Tmax was shorter, suggesting that the absorption rate of almotriptan author concludes that based on the results of this study and the lack of effect of fluoxetine on almotriptar can be safely used concomitantly in migraine management (Fleishaker et al, 2001).

3.5.1.J Alprazolam

1) Interaction Effect: an increased risk of alprazolam toxicity (somnolence, dizziness, ataxia, slurred speech,

2) Summary: Coadministered fluoxetine increases alprazolam serum concentrations (Greenblatt et al, 1992a interaction is thought to be inhibition by fluoxetine of the cytochrome P453A4 isoenzyme (CYP3A4), which is metabolism. Some benzodiazepines (lorazepam, oxazepam) are metabolized by glucuronidation rather than choice for fluoxetine and benzodiazepine cotherapy.

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Monitor patients for signs and symptoms of alprazolam intoxication (somnolence, d psychomotor impairment). Alprazolam doses may need to be reduced. Alternatively, consider substituting a b oxazepam) that has less potential for interacting with fluoxetine.

7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated alprazolam metabolism

8) Literature Reports

a) Alprazolam serum concentrations were analyzed in a double-blind, placebo-controlled study involving Concurrent administration of alprazolam 1 mg four times a day and fluoxetine 60 mg each morning for fo alprazolam levels and a 21% decrease in the alprazolam elimination rate. The elevated alprazolam conc impairment, but did not affect mood status or sedation.

b) The effect of fluoxetine on the pharmacokinetics of alprazolam was analyzed in a 31-day, double-blin included a 10-day washout period (Greenblatt et al, 1992). Twelve healthy male volunteers were given fl single dose of alprazolam 1 mg on days 3 and 24. Fluoxetine significantly increased the half-life of alpraz decreased its clearance from 61 mL/min to 48 mL/min.

c) Inhibition of alprazolam metabolism by fluoxetine occurs via cytochrome P450 3A4. A randomized, do design was used to assess this potential interaction. Twenty healthy volunteers attended four study sess absence of an SSRI in the first two study sessions; alprazolam/placebo while at steady-state with either was given in the last two study sessions. At each session they received alprazolam 1 mg orally or placeb of alprazolam by 16% and increased the area under the concentration-time curve by 32%. Citalopram di alprazolam were not altered by either SSRI. These findings suggest that citalopram and fluoxetine differe 2002).

3.5.1.K Amiodarone

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

2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class prolong the QTc interval is not recommended (Allen et al, 2002; Prod Info Tikosyn(TM) dofetilide capsules, 1 been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001a).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that pro recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.L Amisulpride

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

2) Summary: Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs know fluoxetine, is not recommended. Several antipsychotic agents have demonstrated QT prolongation including quetiapine (Owens, 2001b), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), and zotepine (Sw

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of fluoxetine and antipsychotics is not recommended

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.M Amitriptyline

1) Interaction Effect: tricyclic antidepressant toxicity (dry mouth, urinary retention, sedation) and an increase

de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and fluoxetine have been shown to prolong the QTc interval a Prozac(R), 2001h; Marshall & Forker, 1982). Even though no formal drug interaction studies have been done coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as fluox 1999). In addition, concurrent use of fluoxetine and TCAs such as desipramine, nortriptyline, and imipramine concentrations (Preskorn et al, 1994a; Preskorn et al, 1994a; Aranow et al, 1989a; Downs et al, 1989a; Gooc
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and a tricyclic antidepressant is not recc
7) Probable Mechanism: decreased tricyclic antidepressant metabolism; additive effects on QT prolongation
8) Literature Reports
a) Fluoxetine increased the level of tricyclic antidepressants (nortriptyline, imipramine, desipramine) in 4 ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients develope constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels (Aranow et al,
b) Fluoxetine statistically and clinically significantly increased desipramine concentrations in 18 healthy added to desipramine (50 mg daily), the mean maximum concentration of desipramine increased by 278 curve increased by 342%. Desipramine trough concentrations continued to be 198% above baseline thre same study compared pharmacokinetics of desipramine when combined with sertraline. The impact of se short-term increases in desipramine plasma concentrations (Preskorn et al, 1994).
c) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations w levels ranged from 109 to 150 ng/mL with oral doses of 300 mg at bedtime prior to fluoxetine therapy. Fc to the regimen, the desipramine serum level increased to 212 ng/mL within five days. The fluoxetine dos and the desipramine serum level was 419 ng/mL after four days. A worsening of depression and severe desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose to 200 mg dai ng/mL within two weeks (Bell & Cole, 1988).
d) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with a 40 mg daily and desipramine 150 mg daily for five weeks; fluoxetine was discontinued and the blood leve ng/mL with resolution of clinical symptoms (Goodnick, 1989).
e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant the patient's measured levels of desipramine had ranged from 148 to 160 ng/mL on a regimen of 300 mg 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a desipramine level of to 200 mg/day; eleven days later, the level was 244 ng/mL; the patient reported decreased energy, impa speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced t days. Eight days later, the desipramine level was 122 ng/mL (Downs et al, 1989).
f) Concomitant administration of fluoxetine and desipramine was reported to result in an increased desip year-old male within 10 days of the addition of fluoxetine to the patient's regimen (Preskorn et al, 1990).

3.5.1.N Amoxapine
1) Interaction Effect: tricyclic antidepressant toxicity (dry mouth, urinary retention, sedation) and an increase de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and fluoxetine have been shown to prolong the QTc interval a Prozac(R), 2001h; Marshall & Forker, 1982). Even though no formal drug interaction studies have been done coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as fluox 1999). In addition, concurrent use of fluoxetine and TCAs such as desipramine, nortriptyline, and imipramine concentrations (Preskorn et al, 1994a; Preskorn et al, 1994a; Aranow et al, 1989a; Downs et al, 1989a; Gooc
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and a tricyclic antidepressant is not recc
7) Probable Mechanism: decreased tricyclic antidepressant metabolism; additive effects on QT prolongation
8) Literature Reports
a) Fluoxetine increased the level of tricyclic antidepressants (nortriptyline, imipramine, desipramine) in 4 ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients develope constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels (Aranow et al,
b) Fluoxetine statistically and clinically significantly increased desipramine concentrations in 18 healthy added to desipramine (50 mg daily), the mean maximum concentration of desipramine increased by 278 curve increased by 342%. Desipramine trough concentrations continued to be 198% above baseline thre same study compared pharmacokinetics of desipramine when combined with sertraline. The impact of se short-term increases in desipramine plasma concentrations (Preskorn et al, 1994).
c) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations w levels ranged from 109 to 150 ng/mL with oral doses of 300 mg at bedtime prior to fluoxetine therapy. Fc to the regimen, the desipramine serum level increased to 212 ng/mL within five days. The fluoxetine dos and the desipramine serum level was 419 ng/mL after four days. A worsening of depression and severe desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose to 200 mg dai ng/mL within two weeks (Bell & Cole, 1988).
d) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with a 40 mg daily and desipramine 150 mg daily for five weeks; fluoxetine was discontinued and the blood leve

ng/mL with resolution of clinical symptoms (Goodnick, 1989).
e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant the patient's measured levels of desipramine had ranged from 148 to 160 ng/mL on a regimen of 300 mg 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a desipramine level of to 200 mg/day; eleven days later, the level was 244 ng/mL; the patient reported decreased energy, impa speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced t days. Eight days later, the desipramine level was 122 ng/mL (Downs et al, 1989).
f) Concomitant administration of fluoxetine and desipramine was reported to result in an increased desip year-old male within 10 days of the addition of fluoxetine to the patient's regimen (Preskorn et al, 1990).

3.5.1.O Anagrelide

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 200
7) Probable Mechanism: unknown

3.5.1.P Ancrod

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2 (R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh cas a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally was discontinued. The next day the patient presented to the hospital with left-sided weakness and later c interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.Q Anisindione

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2((R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients (treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model

c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh cas a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally was discontinued. The next day the patient presented to the hospital with left-sided weakness and later c interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.R Antithrombin III Human

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2((R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients (treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4

corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T
treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only
bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI
dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding
exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee
hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b
subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690
for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva
gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca
a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations.
week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril,
acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv
mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa
was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally
was discontinued. The next day the patient presented to the hospital with left-sided weakness and later d
interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim
warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.S Aprindine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class
prolong the QTc interval is not recommended (Prod Info Tambocor(R) flecainide acetate, 1998). Fluoxetine h
recommended therapeutic dose (Prod Info Prozac(R), 2001w).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class I antiarrhythmic agents and agents that prolo
recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.T Ardeparin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2
(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax
threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig
taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b
warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to
protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl
patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi
mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p
SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients
treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4
corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T
treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only
bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI
dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding
exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee
hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b
subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690
for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva
gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca
a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Clair
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations.
week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril,
acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was gi
mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa
was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationall
was discontinued. The next day the patient presented to the hospital with left-sided weakness and later
interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regi
warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.U Aripiprazole

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

3.5.1.V Arsenic Trioxide

1) Interaction Effect: cardiotoxicity (QT interval prolongation, torsades de pointes, cardiac arrest)
2) Summary: Arsenic trioxide and fluoxetine have been shown to prolong the QTc interval at the recommend
2001a; Prod Info Prozac(R), 2001u). Even though no formal drug interaction studies have been done, arseni
drugs which are also known or have the potential to prolong the QTc interval, including fluoxetine (Prod Info
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of arsenic trioxide and fluoxetine is not recommende
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports

a) QT/QTc prolongation should be expected during treatment with arsenic trioxide and torsade de pointe
reported. Over 460 ECG tracings from 40 patients with refractory or relapsed APL treated with arsenic tri
Sixteen of 40 patients (40%) had at least one ECG tracing with a QTc interval greater than 500 msec. Pr
and 5 weeks after arsenic trioxide infusion, and then returned towards baseline by the end of 8 weeks af
evaluations, women did not experience more pronounced QT prolongation than men, and there was no
2001).

b) QT Prolongation was observed on the electrocardiogram (ECG) of a 52- year-old man who had been
followed by 40 milligrams/day thereafter) for depression for 3 months. An ECG just before the start of flu
The QT interval returned to normal within 10 days of discontinuing fluoxetine treatment (Varriale, 2001).

3.5.1.W Aspirin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control an
use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding event
hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008;
release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for
oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 200
7) Probable Mechanism: unknown

3.5.1.X Astemizole

1) Interaction Effect: cardiotoxicity (QT interval prolongation, torsades de pointes, cardiac arrest)
2) Summary: It is theoretically possible that an interaction might occur between astemizole and fluoxetine be
cytochrome P450 system. Astemizole is metabolized by CYP3A4. Fluoxetine is known to be a potent inhibito
P450 enzymes, including CYP3A4 (Riesenman, 1995a). Coadministered fluoxetine may inhibit astemizole cl
serum concentrations and potential astemizole toxicity. The manufacturer of astemizole recommends avoidin
Hismanal(R), 1998). In addition, fluoxetine has been shown to prolong the QTc interval at the recommended
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical

6) Clinical Management: Concomitant use of astemizole and fluoxetine is not recommended.
7) Probable Mechanism: possible inhibition of astemizole P450 metabolism by fluoxetine and/or additive effe
8) Literature Reports
a) Astemizole has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod drug interaction studies have been done, the coadministration of astemizole and other drugs known to pr not recommended.

3.5.1.Y Atomoxetine
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations
2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hy atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as f observed in poor metabolizers. In extensive metabolizers treated with fluoxetine, the area under the concentr 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than ator
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with flu
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by fluoxeti

3.5.1.Z Azimilide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class prolong the QTc interval is not recommended (Allen et al, 2002; Prod Info Tikosyn(TM) dofetilide capsules, 19 been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that pro recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AA Belladonna
1) Interaction Effect: excessive anticholinergic activity (severe dry mouth, constipation, decreased urination,
2) Summary: The anticholinergic activity of the active alkaloids present in belladonna may predispose the pa with olanzapine. Belladonna contains L-hyoscyamine, atropine, and scopolamine with a total alkaloid content roots (Blumenthal et al, 1998). Because belladonna is typically available as a homeopathic preparation, the c is unknown. Caution is advised.
3) Severity: minor
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Excessive anticholinergic activity may be manifested by dry mouth, constipation, ur mydriasis, blurred vision, elevated temperature, muscular weakness, and sedation. If such effects are noted, In severe cases, paralytic ileus, confusion, psychoses, agitation, delusions, delirium, and paranoia may be er and hypertension. In severe cases, immediate medical attention should be obtained.
7) Probable Mechanism: additive anticholinergic effect

3.5.1.AB Belladonna Alkaloids
1) Interaction Effect: excessive anticholinergic activity (severe dry mouth, constipation, decreased urination,
2) Summary: The anticholinergic activity of the active alkaloids present in belladonna may predispose the pa with olanzapine. Belladonna contains L-hyoscyamine, atropine, and scopolamine with a total alkaloid content roots (Blumenthal et al, 1998). Because belladonna is typically available as a homeopathic preparation, the c is unknown. Caution is advised.
3) Severity: minor
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Excessive anticholinergic activity may be manifested by dry mouth, constipation, ur mydriasis, blurred vision, elevated temperature, muscular weakness, and sedation. If such effects are noted, In severe cases, paralytic ileus, confusion, psychoses, agitation, delusions, delirium, and paranoia may be er and hypertension. In severe cases, immediate medical attention should be obtained.
7) Probable Mechanism: additive anticholinergic effect

3.5.1.AC Benoxaprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate

4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.AD Bepridil

1) Interaction Effect: cardiotoxicity (QT interval prolongation, torsades de pointes, cardiac arrest)
2) Summary: Both bepridil and fluoxetine have been shown to prolong the QTc interval at therapeutic doses (R), 2000). Even though no formal drug interaction studies have been done, the coadministration of bepridil a Vascor(R), 2000).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of bepridil and fluoxetine is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AE Betel Nut

1) Interaction Effect: increased extrapyramidal side effects of olanzapine (difficulty with movement or abnorm
2) Summary: Case reports have described increased extrapyramidal side effects when betel nut was chewe fluphenthixol for schizophrenia (Deahl, 1989a). The extrapyramidal effects were not improved with anticholine betel nut discontinuation (Deahl, 1989a). A similar effect may occur if betel nut is chewed with concomitant ol betel nut has been attributed to the arecoline content. When given with peripheral anticholinergics, arecoline muscarinic agonist activity (Nutt et al, 1978a). Case reports suggest the onset of betel nut activity to be withir discontinuation (Deahl, 1989a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: It is unclear to what extent the cholinergic effect of betel nut may increase the incid especially if patients are treated with anticholinergic agents to control these side effects. Deterioration in sym other extrapyramidal movement disorders may be expected. Persons who have been chewing betel nut have help the clinician discover betel nut use.
7) Probable Mechanism: cholinergic effect of betel nut
8) Literature Reports
a) Within 3 weeks of initiating betel nut chewing, a 51-year-old Indian man experienced marked rigidity, been stabilized for the previous 2 years on fluphenazine decanoate depot 50 milligrams (mg) every 3 we twice daily for a mild Parkinsonian tremor. Within one week of discontinuation of betel nut chewing, the p report appears to demonstrate decreased anticholinergic effects of procyclidine when coadministered wi
b) Following betel nut ingestion, a 45-year-old Indian man developed akathisia, tremor and stiffness whi to 20 mg daily of procyclidine. This patient had been previously stabilized on fluphenthixol 60 mg depot e schizoaffective disorder without extrapyramidal side effects. His symptoms resolved over 4 days after dis anticholinergic effects of procyclidine were diminished when betel nut was chewed concomitantly (Deahl
c) High doses (5 mg, 10 mg, and 20 mg) of subcutaneous (SC) arecoline given one hour after SC admi anticholinergic agent methscopolamine increased the heart rate and blood pressure of six patients with H blood pressure occurred at doses of 5 mg, 10 mg (p less than 0.01) and 20 mg (p less than 0.05). Heart less than 0.01), and 10 mg (p less than 0.05). Subjective effects in some patients included tremor, flushi nausea, weakness, and mental changes at the higher doses. No peripheral cholinergic effects were note effect for arecoline (Nutt et al, 1978).
d) A low dose (0.5 mg) of arecoline given intravenously 3 minutes after the peripheral anticholinergic ag major depressive disorder increased their heart rates. The peak heart rate increase in a non-REM portio infusion period was 6.75 +/- 12.9 beats per minute for placebo and 25 +/- 10.3 beats per minute for arec minutes after the arecoline infusion, and the mean heart rate was significantly elevated over placebo fror than 0.05) (Abramson et al, 1985).
e) Though chewing betel nut alone does not significantly increase catecholamine levels, a popular betel chewing betel nut, 4 subjects had only a moderate increase in plasma noradrenaline from 266.2 +/- 105. pg/mL (p equal to 0.0607). Combining betel nut with lime, catechu and Piper betel flower as is commonly norepinephrine in nine subjects from 292.2 +/- 59.5 pg/mL to 375.1 +/- 130.0 pg/mL (p equal to 0.0244) a 102.2 +/- 45.0 pg/mL (p equal to 0.0226). In this group dopamine was also elevated in 8 of 9 subjects, bu

3.5.1.AF Bivalirudin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2
(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax
threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig
taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b
warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to
protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl
patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi
mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p
SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients
treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4
corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively.
treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only
bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI
dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding
exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee
hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b
subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690
for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva
gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca
a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations.
week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril,
acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv
mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa
was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally
was discontinued. The next day the patient presented to the hospital with left-sided weakness and later d
interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim
warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.AG Bretylium

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class
prolong the QTc interval is not recommended (Allen et al, 2002; Prod Info Tikosyn(TM) dofetilide capsules, 19
been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that pro
recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AH Bromfenac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L
CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.AI Bufexamac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L
CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.AJ Bupropion

1) Interaction Effect: increased plasma levels of fluoxetine
2) Summary: Because bupropion inhibits CYP2D6-mediated metabolism it is recommended that fluoxetine, a
cytochrome P450 2D6 isoenzyme, be initiated at the lower end of the dose range when administered concom
(TM), 2003; Prod Info Zyban(R), 2000). Increased plasma concentrations of fluoxetine may result in increase
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of bupropion and fluoxetine should be approached with caution ar
range of fluoxetine. If bupropion is added to the treatment regimen of a patient already receiving fluoxetine, c
Monitor for increased adverse effects including weight gain or loss, anxiety, weakness, or sleeping disturbanc
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated fluoxetine metabolism
8) Literature Reports

a) The concomitant administration of fluoxetine and bupropion was associated with a hyperactive libido
depression. The patient, a 35-year-old woman, initially received treatment with fluoxetine 40 milligrams (
therapy due to suboptimal therapeutic effect. She experienced a diminished libido from the onset of clom
conversion to fluoxetine. Three months after the conversion to fluoxetine, bupropion 100 mg/day was ad
antidote for the sexual dysfunction. Sexual function appeared to normalize 1 month after the start of bup
beginning bupropion, the patient complained of having an exaggerated increase in libido, causing her to
to normal within 2 months of stopping all medication, accompanied by a recurrence of depressive sympt
same time period, producing another reduction in libido yet accompanied by a full remission from depres

3.5.1.AK Buspirone

1) Interaction Effect: worsening of psychiatric symptoms
2) Summary: In a number of case reports, the concomitant use of buspirone and fluoxetine has been reporte
underlying anxiety/or obsessive-compulsive disorder (Bodkin & Teicher, 1989; Tanquary & Masand, 1990; M
patient maintained on fluoxetine who presented with symptoms of serotonin syndrome, including confusion, c
myoclonus after buspirone was added to his drug regimen (Manos, 2000a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: If possible, the combination of fluoxetine and buspirone should be avoided; howeve
worsening of psychiatric symptoms.
7) Probable Mechanism: possible inhibition of buspirone serotonergic effects
8) Literature Reports

a) One of 10 patients with obsessive-compulsive disorder experienced anorgasmia after buspirone (mea
fluoxetine therapy (mean maximum dose, 78 mg daily). The anorgasmia could not be definitely attributed
the two agents. Both fluoxetine and buspirone have reported a low incidence of sexual dysfunction when

1999d; Prod Info Buspar(R), 1994; Jenike et al, 1991).
b) Three cases of potentiation of the antidepressant effects of fluoxetine by buspirone have been report treatment-resistant symptoms of depression, obsessional traits, anxiety, and a history of eating disorder regimen.
c) A case report describes a 37-year-old male patient maintained on fluoxetine 20mg per day who bega augment the actions of fluoxetine. The starting dose of buspirone was gradually increased from 5mg twic five weeks. After five days at this dose, the patient complained of confusion, diaphoresis, incoordination, be serotonin syndrome. The patients symptoms resolved shortly after discontinuation of buspirone (Man

3.5.1.AL Cannabis
1) Interaction Effect: manic symptoms
2) Summary: One case of mania following use of marijuana with fluoxetine therapy has been reported (Stoll proposed, the authors also state the manic symptoms could have resulted from the fluoxetine or marijuana al marijuana and taking fluoxetine or other serotonin reuptake inhibitors.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Caution patients taking selective serotonin reuptake inhibitors to avoid concomitant
7) Probable Mechanism: additive serotonergic stimulation
8) Literature Reports
a) A 21-year-old female presented with mania, agitation, and grandiose delusions following use of mariju taking fluoxetine 20 mg daily for 4 weeks and reported smoking 2 "joints" during a 36-hour period. Over t energy, hypersexuality, pressured speech, and grandiose delusions. Lorazepam and perphenazine were gradually resolved over 4 days. She remained hospitalized for 36 days. Fluoxetine 20 mg every other da One week after discharge, she discontinued fluoxetine due to insomnia and feeling "hyper". These symp fluoxetine. Due to the rapid switch to mania after smoking marijuana with fluoxetine, the manic symptoms fluoxetine and marijuana, though mania could have developed from either fluoxetine or marijuana alone

3.5.1.AM Carbamazepine
1) Interaction Effect: reduced olanzapine efficacy
2) Summary: Carbamazepine induces CYP1A2 mediated oxidation. Concomitant administration of olanzapin increased the clearance of olanzapine by 50% (Prod Info Zyprexa(R), 1999a). Higher daily doses of carbama olanzapine clearance. In a study of 11 healthy volunteers, concurrent administration of olanzapine and carba olanzapine clearance (Lucas et al, 1998). Because patients respond to a relatively wide range of olanzapine of symptom patterns and changes is necessary whenever carbamazepine is added to or withdrawn from olar adjustments will most likely be highly patient specific (Licht et al, 2000a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Monitor patients for olanzapine efficacy. Doses of olanzapine may need to be adjus carbamazepine.
7) Probable Mechanism: induction of cytochrome P450 1A2-mediated olanzapine metabolism
8) Literature Reports
a) A 23-year-old paranoid schizophrenic female was admitted to the hospital for treatment of hallucinatic admission was perphenazine 12 mg daily, but carbamazepine 600 mg daily was initiated for aggressive risperidone 6 mg daily due to akathisia, rigidity, and tremor, but risperidone was also discontinued due to daily was started and her psychiatric symptoms improved over the next three weeks. Because her aggre carbamazepine was discontinued due to lack of efficacy. She had received cotherapy with olanzapine 15 three consecutive weeks. The day prior to carbamazepine discontinuation, the patient's olanzapine seru Over the next few weeks, her olanzapine concentration increased by 114% to 45 ng/mL. The dose of ola corresponding fall in the olanzapine level occurred. This case report suggests that carbamazepine induc through the cytochrome P450 1A2 enzyme system (Licht et al, 2000).

3.5.1.AN Carbamazepine
1) Interaction Effect: carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizur
2) Summary: The addition of fluoxetine to carbamazepine therapy has increased carbamazepine concentrati vision, dizziness, and tremors in some reports (Grimsley et al, 1991a; Gernaat et al, 1991a; Pearson, 1990a) carbamazepine levels have been reported with the addition of fluoxetine (Spina et al, 1993a). Symptoms of s myoclonus, mental status changes) have also been reported with this combination (Dursun et al, 1993a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Due to the potential to increase carbamazepine levels, patients should be monitore fluoxetine is added to therapy. Carbamazepine levels should be considered within two to three weeks of addi adjustments made as indicated.
7) Probable Mechanism: decreased carbamazepine metabolism
8) Literature Reports
a) An interaction between fluoxetine and carbamazepine was reported in six normal volunteers (Grimsle

days, and fluoxetine was added to the regimen on day 7. The addition of fluoxetine 20 mg daily to carbar
the area under the concentration-time curve for both carbamazepine and carbamazepine-epoxide and a
significant changes were observed in absorption, volume of distribution or elimination rate constant, indic
carbamazepine.
b) The effect of fluoxetine 20 mg daily was studied for three weeks in eight epileptic patients who were s
1993). Steady-state plasma levels of carbamazepine and its epoxide metabolite were not significantly ch
results differ from previous reports. The authors speculate that chronic carbamazepine administration ma
decreased levels of fluoxetine, thereby lowering the chances of a metabolic interaction. Unfortunately flu
c) An interaction between fluoxetine and carbamazepine was reported in two patients receiving chronic
daily respectively. Within 7 to 10 days of initiation of fluoxetine 20 mg daily, both patients developed sym
disappeared within two weeks in one patient following carbamazepine dosage reduction by 200 mg daily
with symptom resolution within two weeks (Pearson, 1990).
d) Two cases of parkinsonism were reported after fluoxetine was added to an existing carbamazepine re
developed symptoms three days after fluoxetine 20 mg per day was added to an existing 12-month regin
patient developed cogwheel rigidity, a mask-like face, and a parkinsonian gait. After discontinuation of flu
patient showed only a slight hypertonia of the arms 17 days later. The other patient, a 53-year old woma
fluoxetine 20 mg per day was added to an existing regimen of carbamazepine 200 mg twice daily. The p
per day which was stopped when fluoxetine was added. The patient developed cogwheel rigidity and a n
fluoxetine therapy (Gernaat et al, 1991).
e) A female patient experienced a drug interaction 14 days after she had fluoxetine 20 mg added to a re
patient presented with symptoms of serotonin syndrome, such as uncontrollable shivering, agitation, incc
diaphoresis. The patient also had leukopenia and thrombocytopenia. After discontinuation of fluoxetine, a
hematological abnormalities resolved over the next 72 hours (Dursun et al, 1993).

3.5.1.AO Carprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L
CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.AP Celecoxib

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L
CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.AQ Certoparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2((R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wi (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients (treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh cas a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally was discontinued. The next day the patient presented to the hospital with left-sided weakness and later d interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.AR Chloral Hydrate

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Chloral hydrate and fluoxetine have been shown to prolong the QTc interval at the recommend 2001ac; Young et al, 1986). Even though no formal drug interaction studies have been done, the coadministr is not recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of chloral hydrate and fluoxetine is not recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) QT Prolongation was observed on the electrocardiogram (ECG) of a 52- year-old man who had been followed by 40 milligrams/day thereafter) for depression for 3 months. An ECG just before the start of flu The QT interval returned to normal within 10 days of discontinuing fluoxetine treatment (Varriale, 2001a)

3.5.1.AS Chloroquine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Chloroquine and fluoxetine have been shown to prolong the QTc interval at the recommended Prod Info Aralen(R), 2001). Even though no formal drug interaction studies have been done, the coadministra is not recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of chloroquine and fluoxetine is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AT Chlorpromazine

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

2) Summary: Although citing no data, the manufacturers of some phenothiazines state that concomitant use not recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Inf 2002; Prod Info Thorazine(R), 2002) . Other phenothiazines may have similar effects, though no reports are a the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2003).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of fluoxetine and a phenothiazine is not recommende

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AU Cilostazol

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; release capsules, solution, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 200

7) Probable Mechanism: unknown

3.5.1.AV Ciprofloxacin

1) Interaction Effect: an increased risk of olanzapine toxicity (increased sedation, orthostatic hypotension)

2) Summary: Ciprofloxacin was suspected of inhibiting the metabolism of olanzapine in a 54-year-old female 1A2 (CYP1A2) has been shown in vitro to be responsible for the formation of some of the metabolites of olan inhibitor of CYP1A2. Although olanzapine has a wide therapeutic range and a correlation between plasma co established, this interaction may be clinically significant (Markowitz & DeVane, 1999a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Patients receiving olanzapine and ciprofloxacin concurrently should be monitored fo increased sedation and orthostatic hypotension.

7) Probable Mechanism: inhibition by ciprofloxacin of cytochrome P450 1A2-mediated olanzapine metabolis

8) Literature Reports

a) A 54-year-old female was admitted to the hospital with suicidal ideation and lacerations to her wrists. olanzapine 10 mg at bedtime, nefazodone 100 mg twice daily, atenolol 25 mg daily, levothyroxine 0.25 m Nefazodone was tapered off prior to electroconvulsive therapy, and ciprofloxacin 250 mg twice daily for s tract infection. Immediately before her last dose of ciprofloxacin, the plasma olanzapine concentration wa was discontinued, her olanzapine concentration had decreased by more than 50% to 14.6 ng/mL. Althou effects from her increased olanzapine level, higher doses of ciprofloxacin could potentially cause more ir DeVane, 1999).

3.5.1.AW Clarithromycin

1) Interaction Effect: delirium and psychosis

2) Summary: Delirium and psychosis were reported in a 53-year-old male after clarithromycin was added to t effects are most likely due to accumulation of fluoxetine (Pollak et al, 1995a).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Clarithromycin should be avoided in patients treated with fluoxetine.

7) Probable Mechanism: fluoxetine toxicity due to decreased metabolism

8) Literature Reports

a) Delirium and psychosis were reported in a 53-year-old male after clarithromycin was added to therapy most likely due to accumulation of fluoxetine, because these symptoms have been associated with fluox patient had previously tolerated an inadvertent overdose of nitrazepam without symptoms of delirium and

3.5.1.AX Clomipramine

1) Interaction Effect: an increased risk of seizures

2) Summary: Psychotropic drugs have been shown to reduce the seizure threshold. A case report describes who received treatment with olanzapine and clomipramine concomitantly. This combination resulted in seizur olanzapine and clomipramine. It is advised to use caution when administering olanzapine concomitantly with seizure threshold (Deshauer et al, 2000a).

3) Severity: major

4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: It is advised to use caution when administering olanzapine concomitantly with clom seizure threshold.
7) Probable Mechanism: unknown
8) Literature Reports
a) A 34-year-old male with schizophrenia and obsessive-compulsive disorder (OCD) without any underly following long-term noncompliance. Inpatient olanzapine treatment (20 mg/day) was initiated and positive Patient was discharged and readmitted because of inability to control symptoms. Clomipramine 250 mg and myoclonic jerks were reported which quickly progressed to general motor seizures and postictal som and paroxysmal slowing on the EEG was consistent with seizure activity. Clomipramine and olanzapine were controlled with diazepam 30 mg per day for three days. This pattern repeated upon re-challenge wi clomipramine. Presumably from the temporal relationship between clomipramine and olanzapine adminis suspected that this adverse event is due to an interaction between these two drugs. Clomipramine and o cytochrome P450 isoenzymes 1A2 and 2D6. One theory is that coadministration may result in elevated l mechanism by which this interaction occurs is not yet known, it is advised to use caution when administe clomipramine, or other agents known to lower the seizure threshold (Deshauer et al, 2000).

3.5.1.AY Clonixin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.AZ Clopidogrel

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 200
7) Probable Mechanism: unknown

3.5.1.BA Clopidogrel

1) Interaction Effect: reduction in clinical efficacy of clopidogrel
2) Summary: Clopidogrel is metabolized to its active metabolite by CYP2C19. Concomitant use of CYP2C19 expected to result in reduced levels of the active metabolite, and therefore a reduction the clinical efficacy of inhibitors with clopidogrel is discouraged (Prod Info PLAVIX(R) oral tablet, 2009).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of clopidogrel and fluoxetine is discouraged (Prod Info PLAVIX(R)
7) Probable Mechanism: inhibition of CYP2C19- mediated clopidogrel metabolism by fluoxetine

3.5.1.BB Clorgyline

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental st
2) Summary: Concurrent administration or overlapping therapy with fluoxetine and a monoamine oxidase (M serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Prod Info Prozac(R), 1

1993t; Feighner et al, 1990t; Kline et al, 1989u; Suchowersky & de Vries, 1990u). Concomitant use is contrai
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of fluoxetine and a MAO inhibitor is contraindicated. Wait at least tw
before initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before in
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod
syndrome (Sternbach, 1991v). Serotonin syndrome is a condition of serotonergic hyperstimulation and m
mental status, hyperreflexia, diaphoresis, shivering, and tremor (Sternbach, 1991v). If the syndrome is n
result.
b) It has been suggested that fluoxetine therapy be discontinued for five weeks before beginning therap
one case report describes a 28-year old woman who had discontinued a 2-year fluoxetine regimen for si
tranylcypromine. Over the next few days the patient developed fever, paresthesias, confusion, abdomina
Upon discontinuation of tranylcypromine, the patient's symptoms began to resolve. Blood samples taken
tranylcypromine revealed no presence of fluoxetine; however, the norfluoxetine level was 84 ng/mL (Cop
c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylc
restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressur
one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, ar
adverse reactions.
d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Klir
insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added
rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours
e) Two cases suggestive of an interaction between fluoxetine and selegiline were reported (Suchowersk
episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy.
drugs were discontinued, and no further details were provided. The second case involved diaphoresis, v
occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinuec
Rechallenge with fluoxetine alone occurred without incident.

3.5.1.BC Clozapine
1) Interaction Effect: an increased risk of clozapine toxicity (sedation, seizures, hypotension)
2) Summary: With concurrent administration of fluoxetine, increased serum clozapine concentrations have b
Centorrino et al, 1994a; Centorrino et al, 1996a; Spina et al, 1998a). Certain adverse effects associated with
sedation (Ayd, 1974) and seizures (Haller & Binder, 1990), and might be expected to occur with concurrent u
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor the therapeutic efficacy of clozapine and for any evidence of toxicity, partic
mg or 3.5 mg/kg. Lower clozapine dosage may be required in some clinical situations.
7) Probable Mechanism: inhibition by fluoxetine of N-dealkylation and N-oxidation of clozapine via the cytoch
8) Literature Reports
a) Subjects receiving concurrent clozapine and fluoxetine had 76% higher serum clozapine concentratio
average compared with controls receiving only clozapine. The mean ratio of total drug level (clozapine pl
mean ratio of concentrations to dose was 75% higher in patients receiving clozapine and fluoxetine com
clozapine alone (Centorrino et al, 1994).
b) A study evaluated the serum concentrations of clozapine and norclozapine, the major metabolite, wh
serotonin reuptake inhibitors (SSRIs) fluoxetine, paroxetine, and sertraline. Eighty outpatients receiving c
schizophrenia or major affective disorder, and 40 of these patients were receiving an SSRI in combinatio
receiving fluoxetine, 10 were receiving sertraline, and 16 were receiving paroxetine therapy. Among the
of clozapine and norclozapine were 41.1% and 44.8% higher, respectively, than in matched patients wh
clozapine plus norclozapine concentration to dose was also 37.7% higher in patients receiving SSRIs, in
differences between the three SSRIs were minor, and the study groups were too limited for an accurate
SSRIs (Centorrino et al, 1996).
c) A 44-year-old male receiving fluoxetine and clozapine was found dead in his yard. The dates of the p
remained indicated that he had been taking his medications as prescribed. Autopsy results showed a hig
mcg/mL) and also a high therapeutic norfluoxetine concentration (0.6 mcg/mL). Fluoxetine found in his g
was being taken as directed. The clozapine blood concentration was in the lethal concentration range (4
contents suggested that the clozapine was being taken as prescribed and that the patient had not consu
Other pathological findings included pulmonary edema, visceral vascular congestion, paralytic ileus, gas
consistent with clozapine toxicity. The combined central nervous system, respiratory, and cardiovascular
sufficient to result in the death of this patient, and his death was ruled to be a clozapine overdose due to
d) Ten institutionalized schizophrenic patients stabilized on clozapine therapy for at least one month par
effect of fluoxetine on clozapine pharmacokinetics. Fluoxetine 20 mg once daily was administered for eig
concentrations increased from 348 ng/mL to 550 ng/mL (58%) at week 8. Plasma levels of norclozapine
381 ng/mL). Clozapine N-oxide levels rose from 89 ng/mL at baseline to 128 ng/mL, representing a 38%
and metabolite plasma concentrations were not associated with significant changes in efficacy or safety

3.5.1.BD Cyclobenzaprine

1) Interaction Effect: an increased risk of QT prolongation

2) Summary: Fluoxetine and cyclobenzaprine caused asymptomatic QT prolongation in a female patient. Ho preoperatively to this patient resulted in torsades de pointes and cardiac arrest. The authors of this case repo cyclobenzaprine, which is structurally similar to the tricyclic antidepressants, was inhibited by fluoxetine. Cyto by fluoxetine, and cyclobenzaprine may also be metabolized via this pathway (Michalets et al, 1998a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Clinicians should monitor patients receiving cyclobenzaprine and fluoxetine for card who receive these two agents concurrently should avoid other drugs which are also known to prolong the QT

7) Probable Mechanism: inhibition of cyclobenzaprine metabolism by fluoxetine via the cytochrome P450 he

8) Literature Reports

a) A 59-year-old female patient was receiving fluoxetine 30 mg daily, cyclobenzaprine 10 mg daily, amlo triamterene 37.5 mg/hydrochlorothiazide 25 mg daily. Five days prior to elective Achilles tendon surgery, this finding, she was premedicated for surgery with intravenous droperidol 0.625 mg and metoclopramid surgery, the patient developed ventricular tachycardia consistent with torsades de pointes which progres Immediately following cardioversion, the patient's QTc was 500 msec. All preadmission medications wer postoperative day 1, the QTc was 440 msec and an electrocardiogram showed normal sinus rhythm (Mi

3.5.1.BE Cyproheptadine

1) Interaction Effect: decreased fluoxetine efficacy

2) Summary: Coadministration of cyproheptadine with fluoxetine may result in reduced fluoxetine effectivene postsynaptic serotonin. Concomitant use of cyproheptadine with drugs that possess serotonergic activity (suc or SSRIs) might be expected to result in a pharmacodynamic interaction. Lack of antidepressant efficacy has concomitantly with fluoxetine and paroxetine (Katz & Rosenthal, 1994a; Feder, 1991a; Goldbloom & Kennedy

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Monitor patients for a reduction in fluoxetine efficacy. When cyproheptadine is coad might need to be adjusted upward. In some cases, it may be necessary to withdraw cyproheptadine.

7) Probable Mechanism: unknown; because cyproheptadine is a serotonin antagonist, it may oppose effects

8) Literature Reports

a) Although not consistently reported, decreased antidepressant effects were found in some patients wh therapy (Katz & Rosenthal, 1994; Feder, 1991; Goldbloom & Kennedy, 1991). A 42-year-old woman usir depression, subsequently started cyproheptadine (4 mg per dose) for its antihistaminic properties (Katz & and after four doses of cyproheptadine, she experienced dysphoria, irritability, and suicidal ideation. She On rechallenge, her feelings of dysphoria returned.

b) A 54-year-old woman was using paroxetine 20 mg per day for the treatment of nonpsychotic major de mg twice a day was added to her therapy. Two days later, her depression worsened and she experience psychotic symptoms resolved two days after cyproheptadine was discontinued. She declined to be recha

3.5.1.BF Dalteparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2 (R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI

dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally was discontinued. The next day the patient presented to the hospital with left-sided weakness and later c interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.BG Danaparoid

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2 (R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally was discontinued. The next day the patient presented to the hospital with left-sided weakness and later c interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.BH Defibrotide

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2

(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax
threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig
taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b
warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to
protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl
patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi
mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p
SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients
treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4
corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively.
treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only
bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI
dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding
exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee
hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b
subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690
for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva
gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca
a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations.
week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril,
acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv
mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa
was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally
was discontinued. The next day the patient presented to the hospital with left-sided weakness and later c
interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim
warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.BI Dehydroepiandrosterone
1) Interaction Effect: reduced effectiveness of olanzapine
2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/decil
of patients with psychosis (Howard, 1992a). In case reports, patients have been resistant to antipsychotics w
1992a). Patients being treated with olanzapine should avoid DHEA supplementation.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and olanzapine. If DHE
mg orally per day may be used to normalize DHEA levels.
7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness
8) Literature Reports
a) A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20 mill
carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg. The patient appeared Cush
abdominal hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA)
micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). Dexamethasone 1 mg orally at bedtime resu
The patient appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. A
normal range (328 mcg/dL). The author concluded that elevated DHEA levels were associated with seve
antipsychotic therapy (Howard, 1992).
b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accom
barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory
attention to personal hygiene, agitation, and combativeness. He was diagnosed with chronic paranoid sc
undifferentiated type, and schizoaffective disorder, excited type. He was resistant to daily doses of trifluo
imipramine 100 mg. He was also resistant to combination therapy with chlorpromazine 400 mg with thiot
perphenazine 48 mg with lithium carbonate 1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg d
A seven-day suppression test with dexamethasone 1 mg orally at bedtime resulted in a normal DHEA lev
and the patient was well-oriented, conversational, and was making good eye contact. Once dexamethas

and florid psychosis ensued despite "substantial amounts of psychotropic medications". DHEA increased elevated DHEA levels were associated with florid psychosis resistant to conventional antipsychotic thera

3.5.1.BJ Dehydroepiandrosterone

1) Interaction Effect: development of manic symptoms

2) Summary: A case has been reported in which concomitant dehydroepiandrosterone (DHEA) and sertralin episode in a patient with a history of bipolar disorder (Dean, 2000a). DHEA was also noted to cause mania in history of bipolar disorder (Markowitz et al, 1999). Elevated DHEA levels have been found in patients with me improvement in psychotic symptoms (Howard, 1992b). DHEA possesses proserotonergic activity which may (Majewska, 1995). DHEA is a precursor to androgenic steroids, which in high doses may precipitate mania (M for bipolar disorder or patients with a personal and/or family history of bipolar disorder should not take DHEA drug-herb interaction. Concomitant use of DHEA with selective serotonin reuptake inhibitors (SSRIs) should b precipitation of mania.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and selective serotonin symptoms (i.e. agitation, anger, irritability, aggressive behavior), determine if the patient is using DHEA and c

7) Probable Mechanism: serotonergic activity of dehydroepiandrosterone, possibly increased androgen level

8) Literature Reports

a) A 31-year-old male was admitted following threats to commit suicide and injure family members. He h daily for the previous 2 to 3 weeks for depression. Sertraline had been prescribed 3 years prior when he discontinued after 2 weeks. He had also taken dehydroepiandrosterone (DHEA) 300 mg to 500 mg daily training. Following use of DHEA for a short time, he became more irritable, was not sleeping well, and be members. He also drank alcohol occasionally and reportedly had difficulty controlling his anger when into was treated with valproic acid with the dose titrated to 500 mg twice daily. The combination of DHEA, ser for the developing of the manic episode (Dean, 2000).

3.5.1.BK Delavirdine

1) Interaction Effect: increased trough delavirdine concentrations

2) Summary: Population pharmacokinetic data in 36 patients suggested that coadministration of delavirdine increase in trough delavirdine concentrations (Prod Info Rescriptor(R), 1999). The clinical significance of this

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concurrent use of delavirdine with fluoxetine should be coadministered with caution delavirdine adverse effects.

7) Probable Mechanism: unknown

3.5.1.BL Dermatan Sulfate

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2 (R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model

c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum

reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee
hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b
subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690
for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva
gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca
a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations.
week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril,
acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv
mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa
was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally
was discontinued. The next day the patient presented to the hospital with left-sided weakness and later c
interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim
warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.BM Desipramine

1) Interaction Effect: tricyclic antidepressant toxicity (dry mouth, urinary retention, sedation) and an increase
de pointes, cardiac arrest)

2) Summary: Tricyclic antidepressants (TCAs) and fluoxetine have been shown to prolong the QTc interval a
Prozac(R), 2001h; Marshall & Forker, 1982). Even though no formal drug interaction studies have been done
coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as fluox
1999). In addition, concurrent use of fluoxetine and TCAs such as desipramine, nortriptyline, and imipramine
concentrations (Preskorn et al, 1994a; Preskorn et al, 1994a; Aranow et al, 1989a; Downs et al, 1989a; Gooc

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of fluoxetine and a tricyclic antidepressant is not recc

7) Probable Mechanism: decreased tricyclic antidepressant metabolism; additive effects on QT prolongation

8) Literature Reports

a) Fluoxetine increased the level of tricyclic antidepressants (nortriptyline, imipramine, desipramine) in 4
ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients develope
constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels (Aranow et al,

b) Fluoxetine statistically and clinically significantly increased desipramine concentrations in 18 healthy
added to desipramine (50 mg daily), the mean maximum concentration of desipramine increased by 278
curve increased by 342%. Desipramine trough concentrations continued to be 198% above baseline thre
same study compared pharmacokinetics of desipramine when combined with sertraline. The impact of se
short-term increases in desipramine plasma concentrations (Preskorn et al, 1994).

c) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations w
levels ranged from 109 to 150 ng/mL with oral doses of 300 mg at bedtime prior to fluoxetine therapy. Fo
to the regimen, the desipramine serum level increased to 212 ng/mL within five days. The fluoxetine dos
and the desipramine serum level was 419 ng/mL after four days. A worsening of depression and severe
desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose to 200 mg dai
ng/mL within two weeks (Bell & Cole, 1988).

d) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with a
40 mg daily and desipramine 150 mg daily for five weeks; fluoxetine was discontinued and the blood leve
ng/mL with resolution of clinical symptoms (Goodnick, 1989).

e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant
the patient's measured levels of desipramine had ranged from 148 to 160 ng/mL on a regimen of 300 mg
20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a desipramine level of
to 200 mg/day; eleven days later, the level was 244 ng/mL; the patient reported decreased energy, impa
speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced t
days. Eight days later, the desipramine level was 122 ng/mL (Downs et al, 1989).

f) Concomitant administration of fluoxetine and desipramine was reported to result in an increased desip
year-old male within 10 days of the addition of fluoxetine to the patient's regimen (Preskorn et al, 1990).

3.5.1.BN Desirudin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2
(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax
threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig
taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh

(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally was discontinued. The next day the patient presented to the hospital with left-sided weakness and later c interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.BO Desvenlafaxine

1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental s
2) Summary: Concurrent use of desvenlafaxine and a selective serotonin reuptake inhibitor (SSRI) may resu threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea (Prod Info PRISTIQ(TM) d
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of desvenlafaxine and an SSRI may result in a life-threatening co agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for sy hyperthermia, hyperreflexia, incoordination), especially during treatment initiation and dose increases (Prod I 2008).
7) Probable Mechanism: additive serotonergic effect

3.5.1.BP Dexfenfluramine

1) Interaction Effect: serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Dexfenfluramine is a nonspecific serotonin agonist that both enhances the release of serotonin therapy with dexfenfluramine and another selective serotonin reuptake inhibitor, such as fluoxetine, has the p & Mahowald, 1996). Serotonin syndrome is a hyperserotonergic state characterized by symptoms such as re status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (S be used in combination with fluoxetine (Prod Info Redux(R), 1997).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of dexfenfluramine and fluoxetine may result in an additive increase system, and could result in serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status chan combination with fluoxetine or other serotonin specific reuptake inhibitors.
7) Probable Mechanism: additive serotonergic effects

3.5.1.BQ Dexketoprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.BR Dextromethorphan

1) Interaction Effect: possible dextromethorphan toxicity (nausea, vomiting, blurred vision, hallucinations) or myoclonus, mental status changes)
2) Summary: Fluoxetine strongly inhibits hepatic cytochrome P450IID6 (CYP2D6), the isoenzyme known to & Wrighton, 1993). Fluoxetine inhibits dextromethorphan metabolism (Otton et al, 1993a). With concomitant competitively inhibit each others metabolism, increasing serum levels of both drugs. Serotonin syndrome, cha changes in mental status (Sternbach, 1991e), is a possibility with the combined use of dextromethorphan and reports of serotonin syndrome associated with concurrent paroxetine and dextromethorphan therapy (Skop e
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Caution patients taking fluoxetine that an interaction could occur with dextromethor may be necessary.
7) Probable Mechanism: competitively inhibited metabolism of both agents
8) Literature Reports
a) Therapeutic doses of fluoxetine were found to potently inhibit the metabolism of dextromethorphan, a function (Otton et al, 1993). A 30 mg dose of dextromethorphan hydrobromide was given to 19 patients t addition, dextromethorphan was given to 208 known extensive metabolizers and to 15 known poor meta dextromethorphan metabolism was reduced in the fluoxetine-treated patients, it was more significantly a indicates that patients who are slow metabolizers may be at greater risk for experiencing dextromethorp fluoxetine.
b) A 32-year-old woman experienced visual hallucinations after concomitant use of fluoxetine and dextr fluoxetine 20 mg daily for 18 days prior to taking two doses of dextromethorphan. After each dose of dex and saw bright colors. These effects continued for six to eight hours. Fluoxetine was withdrawn and she
c) A 51-year old male patient with vascular disease following concurrent use of dextromethorphan and p days after self-medication with a dextromethorphan-containing cold product, the patient experienced sho confusion. Upon arrival to the hospital, the patient presented with diaphoresis, tremor, confusion, abdom administration of benzodiazepines and discontinuation of paroxetine, the patient's condition improved an 1994).

3.5.1.BS Diazepam

1) Interaction Effect: higher serum concentrations of diazepam
2) Summary: During coadministration of fluoxetine with diazepam, the fluoxetine area under the concentratio not associated with increased impairment (Lemberger et al, 1988a). Conversely, a controlled study observed performance when diazepam was added to fluoxetine (Moskowitz & Burns, 1988a). The metabolism of diaze may be inhibited by fluoxetine (Riesenman, 1995c; Shen, 1995a; Nemeroff et al, 1996b). Further case report appropriately define the pharmacokinetic effects as well as the degree of psychomotor impairment resulting f
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Although dose adjustments are thought not to be necessary when fluoxetine and di patients for signs and symptoms of excessive diazepam concentrations (sedation, dizziness, ataxia, decreas patients, such as the elderly, it may be safer to give a lower dose of diazepam during combination therapy.
7) Probable Mechanism: inhibition of the hepatic P450 metabolism of diazepam
8) Literature Reports
a) Coadministration of fluoxetine and diazepam resulted in prolonged half-life, reduced plasma clearanc diazepam 10 mg was given alone, after a single dose of oral fluoxetine 60 mg, and after 8 daily doses of demonstrated no effect of fluoxetine on the psychomotor response to diazepam. Thus, although fluoxetir does not appear to be of clinical relevance and dosing adjustments are not required during combined the
b) Combined therapy with diazepam and fluoxetine caused an increase in the half-life of the metabolite clinically significant. Diazepam had no effect on the disposition of fluoxetine or norfluoxetine (Lemberger
c) To date, in-vitro studies have found that diazepam demethylation occurs via P450 1A2, 3A4, 2C9, an metabolized by these enzymes suggests that fluoxetine strongly inhibits 2C9, moderately inhibits 2C19 a

1995b; Nemeroff et al, 1996a; Shen, 1995).

d) In a controlled study of performance of 90 healthy volunteers, the effects of fluoxetine, amitriptyline, c Volunteers received one of six treatment combinations, and were given performance tests including a cri search task, memory test, and vigilance test. Fluoxetine alone did not affect performance, but when fluox significant increase in the divided attention tracking error and significant impairment on the vigilance test coadministration with diazepam, significant impairment was observed. On most tests, the combination of effects. The authors concluded that the combination of diazepam and an antidepressant may increase a performing other complex tasks (Moskowitz & Burns, 1988).

e) A case was reported in which an 83-year old man developed delirium after the addition of fluoxetine a furosemide, potassium, digoxin, and acetaminophen. The patient was given fluoxetine 20 mg per day an for symptoms of depression, anxiety, and insomnia. The patient then developed symptoms of drug deliriu irrational speaking. The patient also developed an increased international normalized ratio (INR), after w presented to the hospital with left-sided weakness and later died from complications of a large interparer the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and and loss of anticoagulant control (Dent & Orrock, 1997a).

3.5.1.BT Dibenzepin

1) Interaction Effect: tricyclic antidepressant toxicity (dry mouth, urinary retention, sedation) and an increase de pointes, cardiac arrest)

2) Summary: Tricyclic antidepressants (TCAs) and fluoxetine have been shown to prolong the QTc interval a Prozac(R), 2001h; Marshall & Forker, 1982). Even though no formal drug interaction studies have been done coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as fluox 1999). In addition, concurrent use of fluoxetine and TCAs such as desipramine, nortriptyline, and imipramine concentrations (Preskorn et al, 1994a; Preskorn et al, 1994a; Aranow et al, 1989a; Downs et al, 1989a; Gooc

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of fluoxetine and a tricyclic antidepressant is not recc

7) Probable Mechanism: decreased tricyclic antidepressant metabolism; additive effects on QT prolongation

8) Literature Reports

a) Fluoxetine increased the level of tricyclic antidepressants (nortriptyline, imipramine, desipramine) in 4 ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients develope constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels (Aranow et al,

b) Fluoxetine statistically and clinically significantly increased desipramine concentrations in 18 healthy added to desipramine (50 mg daily), the mean maximum concentration of desipramine increased by 278 curve increased by 342%. Desipramine trough concentrations continued to be 198% above baseline thre same study compared pharmacokinetics of desipramine when combined with sertraline. The impact of se short-term increases in desipramine plasma concentrations (Preskorn et al, 1994).

c) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations w levels ranged from 109 to 150 ng/mL with oral doses of 300 mg at bedtime prior to fluoxetine therapy. Fc to the regimen, the desipramine serum level increased to 212 ng/mL within five days. The fluoxetine dos and the desipramine serum level was 419 ng/mL after four days. A worsening of depression and severe desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose to 200 mg dai ng/mL within two weeks (Bell & Cole, 1988).

d) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with a 40 mg daily and desipramine 150 mg daily for five weeks; fluoxetine was discontinued and the blood leve ng/mL with resolution of clinical symptoms (Goodnick, 1989).

e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant the patient's measured levels of desipramine had ranged from 148 to 160 ng/mL on a regimen of 300 mg 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a desipramine level of to 200 mg/day; eleven days later, the level was 244 ng/mL; the patient reported decreased energy, impa speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced t days. Eight days later, the desipramine level was 122 ng/mL (Downs et al, 1989).

f) Concomitant administration of fluoxetine and desipramine was reported to result in an increased desip year-old male within 10 days of the addition of fluoxetine to the patient's regimen (Preskorn et al, 1990).

3.5.1.BU Diclofenac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.BV Dicumarol

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2
(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax
threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig
taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wi
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b
warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to
protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl
patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi
mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p
SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients
treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4
corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively.
treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only
bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI
dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding
exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model

c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee
hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b
subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690
for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva
gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca
a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations.
week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril,
acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv
mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa
was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally
was discontinued. The next day the patient presented to the hospital with left-sided weakness and later c
interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim
warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.BW Diflunisal

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L
CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar

hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.BX Digitoxin

1) Interaction Effect: an increased risk of digitoxin toxicity (nausea, vomiting, arrhythmias)
2) Summary: The administration of fluoxetine to a patient taking digitoxin, also tightly bound to plasma protei
digitoxin (Prod Info Prozac(R), 1999c).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Patients receiving fluoxetine and digitoxin therapy concomitantly should be monitor
signs and symptoms of digitoxin toxicity.
7) Probable Mechanism: unknown

3.5.1.BY Digoxin

1) Interaction Effect: an increased risk of digoxin toxicity (nausea, vomiting, arrhythmias)
2) Summary: One case report describes a 93-year-old female stabilized on digoxin who experienced toxic le
her regimen for depression. Rechallenge with fluoxetine again caused her digoxin levels to increase dramatic
not clear, it could be related to displacement of digoxin from binding sites or reduced clearance of digoxin (Le
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Patients receiving fluoxetine and digoxin therapy concomitantly should be monitore
signs and symptoms of digoxin toxicity, including anorexia.
7) Probable Mechanism: unknown
8) Literature Reports
a) Digoxin 0.125 mg daily was being administered to a 93-year-old female for congestive heart failure ar
ranged from 1.0 to 1.4 nmol/L during the two months preceding the initiation of fluoxetine 10 mg daily. W
anorexia. Her digoxin level measured 4.2 nmol/L, while renal function and potassium levels remained un
discontinued, and her digoxin level returned to normal in five days with resolution of the anorexia. During
ranged from 0.9 nmol/L to 1.4 nmol/L. Because the symptoms of depression persisted, fluoxetine was ag
serum level was closely monitored. After two days of fluoxetine therapy, the digoxin level increased to 2.
Renal function remained unchanged, as did serum electrolytes. The patient again experienced anorexia,
(Leibovitz et al, 1998).

3.5.1.BZ Dihydroergotamine

1) Interaction Effect: an increased risk of ergotism (nausea, vomiting, vasospastic ischemia)
2) Summary: Because of the potential for serious toxicity including vasospasm that can occur with increased
concurrent use of fluoxetine and ergot derivatives is contraindicated. Fluoxetine and ergot derivatives are bot
enzymes, and the competition for metabolism could result in an increased plasma concentration of the ergot
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent use of fluoxetine and ergot derivatives is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A4- mediated ergot metabolism by fluoxetine

3.5.1.CA Dipyridamole

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events
hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008;
release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for
oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 200
7) Probable Mechanism: unknown

3.5.1.CB Dipyrone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L

CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.CC Disopyramide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class prolong the QTc interval is not recommended (Prod Info Quinaglute Dura-tabs(R), 1999). Fluoxetine has dem (Prod Info Prozac(R), 2001z).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class Ia antiarrhythmic agents and agents that pro recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CD Dofetilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class prolong the QTc interval is not recommended (Allen et al, 2002; Prod Info Tikosyn(TM) dofetilide capsules, 1 been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that pro recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CE Dolasetron

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Though citing no data, the manufacturer of dolasetron recommends caution if dolasetron is adr the QTc interval (Prod Info Anzemet(R), 1997). Fluoxetine has been shown to prolong the QTc interval at the Prozac(R), 2001y).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and dolasetron is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CF Doxepin

1) Interaction Effect: tricyclic antidepressant toxicity (dry mouth, urinary retention, sedation) and an increase de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and fluoxetine have been shown to prolong the QTc interval a Prozac(R), 2001h; Marshall & Forker, 1982). Even though no formal drug interaction studies have been done coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as fluox 1999). In addition, concurrent use of fluoxetine and TCAs such as desipramine, nortriptyline, and imipramine concentrations (Preskorn et al, 1994a; Preskorn et al, 1994a; Aranow et al, 1989a; Downs et al, 1989a; Gooc
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and a tricyclic antidepressant is not rec
7) Probable Mechanism: decreased tricyclic antidepressant metabolism; additive effects on QT prolongation
8) Literature Reports
a) Fluoxetine increased the level of tricyclic antidepressants (nortriptyline, imipramine, desipramine) in 4 ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients develope constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels (Aranow et al,

b) Fluoxetine statistically and clinically significantly increased desipramine concentrations in 18 healthy added to desipramine (50 mg daily), the mean maximum concentration of desipramine increased by 278 curve increased by 342%. Desipramine trough concentrations continued to be 198% above baseline thre same study compared pharmacokinetics of desipramine when combined with sertraline. The impact of s short-term increases in desipramine plasma concentrations (Preskorn et al, 1994).
c) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations w levels ranged from 109 to 150 ng/mL with oral doses of 300 mg at bedtime prior to fluoxetine therapy. Fo to the regimen, the desipramine serum level increased to 212 ng/mL within five days. The fluoxetine dos and the desipramine serum level was 419 ng/mL after four days. A worsening of depression and severe desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose to 200 mg dai ng/mL within two weeks (Bell & Cole, 1988).
d) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with a 40 mg daily and desipramine 150 mg daily for five weeks; fluoxetine was discontinued and the blood leve ng/mL with resolution of clinical symptoms (Goodnick, 1989).
e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant the patient's measured levels of desipramine had ranged from 148 to 160 ng/mL on a regimen of 300 mg 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a desipramine level of to 200 mg/day; eleven days later, the level was 244 ng/mL; the patient reported decreased energy, impa speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced t days. Eight days later, the desipramine level was 122 ng/mL (Downs et al, 1989).
f) Concomitant administration of fluoxetine and desipramine was reported to result in an increased desip year-old male within 10 days of the addition of fluoxetine to the patient's regimen (Preskorn et al, 1990).

3.5.1.CG Droperidol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Droperidol has been shown to prolong the QTc interval at the recommended therapeutic dose. have been done, the coadministration of droperidol and other drugs known to prolong the QTc interval, includ Inapsine(TM), 2001; Prod Info Prozac(R), 2001ab).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of droperidol and fluoxetine is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.CH Droxicam

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.CI Duloxetine

1) Interaction Effect: increased duloxetine and fluoxetine serum concentrations and an increased risk of sero
2) Summary: Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI). The concom is not recommended due to the potential for serotonin syndrome. In addition, the coadministration of duloxeti bioavailability of either drug, increasing the risk of serious adverse events. Duloxetine and fluoxetine are both of CYP2D6. Coadministration of duloxetine 40 mg once daily with another SSRI (the potent CYP2D6 inhibitor increase in the serum concentration of duloxetine (Prod Info CYMBALTA(R) delayed-release oral capsules, 2
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concomitant use of duloxetine and fluoxetine is not recommended due to the p Additionally, concomitant use has resulted in increased duloxetine and fluoxetine serum levels (Prod Info CY 2008).

7) Probable Mechanism: fluoxetine inhibition of CYP2D6-mediated duloxetine metabolism; additive serotone

3.5.1.CJ Eletriptan

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concon 1 (5HT-1) agonist, and a serotonin specific reuptake inhibitor (SSRI) (Prod Info Imitrex(R) Nasal Spray, 2003) similar interaction between SSRIs and eletriptan may occur (Prod Info Relpax(R), 2003). Concurrent use of a syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, halluci rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and c may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different syndrome with patients who are prescribed this combination and monitor them closely for symptoms of seroto Administration, 2006).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Coadministration of a triptan, such as eletriptan, and an SSRI may result in a life-th Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be pr are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms hyperthermia, hyperreflexia, incoordination).

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

3.5.1.CK Enflurane

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

2) Summary: Even though no formal drug interaction studies have been done, enflurane should be coadmini known to prolong the QTc interval, including fluoxetine (Owens, 2001c; Prod Info Prozac(R), 2001n).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of enflurane with other agents that can prolong the Q recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CL Enoxaparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2 (R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model

c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally was discontinued. The next day the patient presented to the hospital with left-sided weakness and later c interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.CM Epoprostenol

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 200
7) Probable Mechanism: unknown

3.5.1.CN Eptifibatide

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 200
7) Probable Mechanism: unknown

3.5.1.CO Ergoloid Mesylates

1) Interaction Effect: an increased risk of ergotism (nausea, vomiting, vasospastic ischemia)
2) Summary: Because of the potential for serious toxicity including vasospasm that can occur with increased concurrent use of fluoxetine and ergot derivatives is contraindicated. Fluoxetine and ergot derivatives are bot enzymes, and the competition for metabolism could result in an increased plasma concentration of the ergot
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent use of fluoxetine and ergot derivatives is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A4- mediated ergot metabolism by fluoxetine

3.5.1.CP Ergonovine

1) Interaction Effect: an increased risk of ergotism (nausea, vomiting, vasospastic ischemia)
2) Summary: Because of the potential for serious toxicity including vasospasm that can occur with increased concurrent use of fluoxetine and ergot derivatives is contraindicated. Fluoxetine and ergot derivatives are bot enzymes, and the competition for metabolism could result in an increased plasma concentration of the ergot
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent use of fluoxetine and ergot derivatives is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A4- mediated ergot metabolism by fluoxetine

3.5.1.CQ Ergotamine

1) Interaction Effect: an increased risk of ergotism (nausea, vomiting, vasospastic ischemia)
2) Summary: Because of the potential for serious toxicity including vasospasm that can occur with increased concurrent use of fluoxetine and ergot derivatives is contraindicated. Fluoxetine and ergot derivatives are bot enzymes, and the competition for metabolism could result in an increased plasma concentration of the ergot
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent use of fluoxetine and ergot derivatives is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A4- mediated ergot metabolism by fluoxetine

3.5.1.CR Erythromycin

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

2) Summary: Erythromycin significantly increased the mean QTc interval versus baseline in a retrospective s Erythromycin has demonstrated QTc prolongation in combination with other drugs that prolong the QT interva associated with QT prolongation (Prod Info Prozac(R), 2003a). Caution is advised with coadministration of dr

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Caution is advised if erythromycin and fluoxetine are used concomitantly. Monitor Q treatment.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) Erythromycin significantly increased the QTc interval compared with baseline in a retrospective study milligrams or 1 gram four times daily, with a mean of 15 doses received. Patients (n equal to 9) who rece increases in QT interval of 15% or greater. For all patients, the mean QTc interval increased from 432 m less than 0.01). In patients with delayed repolarization at baseline (n equal to 9), the QTc interval increas 0.01). In patients with heart disease (n equal to 30), all experienced an increase in QTc interval (mean o patients without heart disease (p less than 0.05). In 5 patients (10%), the QTc interval was severely prol pointes attributed to erythromycin. Of 16 patients receiving cotrimoxazole concomitantly, 8 developed QT Bauman, 1995).

3.5.1.CS Eszopiclone

1) Interaction Effect: decreased psychomotor function

2) Summary: Coadministration of 3 mg eszopiclone and 10 mg olanzapine resulted in the pharmacodynamic Substitution Test scores, a measurement of psychomotor function. No pharmacokinetic interactions were obs psychomotor function (Prod Info LUNESTA(TM), 2004).

3) Severity: minor

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Monitor patients for decreased psychomotor function. Adjust dose accordingly or co

7) Probable Mechanism: unknown

3.5.1.CT Etodolac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of up than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.CU Etofenamate

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of up

than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.CV Etoricoxib

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L
CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.CW Felbinac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L
CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.CX Fenbufen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L
CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.CY Fenfluramine

1) Interaction Effect: serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Fenfluramine is a nonspecific serotonin agonist that both enhances the release of serotonin an therapy with fenfluramine and another selective serotonin reuptake inhibitor, such as fluoxetine, has the pote Mahowald, 1996a). Serotonin syndrome is a hyperserotonergic state characterized by symptoms such as res hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Sternba fenfluramine should not be used in combination with fluoxetine.
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of fenfluramine and fluoxetine may result in an additive increase in and could result in serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes). Fe with fluoxetine or other serotonin specific reuptake inhibitors.
7) Probable Mechanism: additive serotonergic effects

3.5.1.CZ Fenoprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.DA Fentiazac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.DB Flecainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class prolong the QTc interval is not recommended (Prod Info Tambocor(R) flecainide acetate, 1998). Fluoxetine h recommended therapeutic dose (Prod Info Prozac(R), 2001w).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class I antiarrhythmic agents and agents that prolc recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.DC Floctafenine

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.DD Fluconazole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Case reports have described QT prolongation and torsades de pointes associated with flucona 1999). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod In drug interaction studies have been done, caution is advised if drugs known to prolong the QT interval are use
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if fluconazole and fluoxetine are used concomitantly.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.DE Flufenamic Acid

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.DF Fluphenazine

1) Interaction Effect: an increased risk of developing acute parkinsonism
2) Summary: The development of acute, severe parkinsonism has been observed in a patient receiving fluph for depression. Upon discontinuation of fluoxetine, the parkinsonism resolved. A similar interaction has been combination with paroxetine or sertraline (Kurlan, 1998a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients receiving concurrent therapy with fluphenazine and fluoxetine for t Therapy with fluoxetine may need to be discontinued.
7) Probable Mechanism: inhibition of cytochrome P450-mediated fluphenazine metabolism by fluoxetine
8) Literature Reports
a) A 63-year-old female with chronic, multiple motor and vocal tics was successfully treated with fluphen

for depression failed, the patient was started on fluoxetine 20 mg daily. After two weeks, she developed
resting tremor, rigidity, bradykinesia, postural imbalance, and stooped posture. The parkinsonism resolve
fluphenazine and the fluoxetine, but the tics reappeared (Kurlan, 1998).

3.5.1.DG Flurbiprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L
CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.DH Fluvoxamine

1) Interaction Effect: an increased risk of olanzapine adverse effects

2) Summary: Fluvoxamine inhibits cytochrome P450 1A2 enzymes and may inhibit olanzapine elimination (P
significance of this interaction is unknown since olanzapine is metabolized by multiple enzyme systems.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients for excessive olanzapine adverse effects (orthostatic hypotension,

7) Probable Mechanism: inhibition of olanzapine elimination

8) Literature Reports

a) A patient experienced elevated olanzapine plasma levels during coadministration of fluvoxamine. The
for several months for schizophrenia and secondary depression. She appeared to move rigidly, had a sli
Olanzapine concentration was 120 mcg/L and fluvoxamine concentration was 70 mcg/L. Olanzapine was
mg/day. Fourteen days after the last decrease in dose, olanzapine plasma levels were 38 mcg/L. Tremor
persisted. Fluvoxamine was replaced by paroxetine which resulted in paroxetine concentration of 0.027 r
(de Jong et al, 2001).

b) Addition of fluvoxamine to olanzapine therapy may result in olanzapine-induced side effects or intoxic
being treated for not less than 3 months with 10-20 mg/day of olanzapine. The dose of olanzapine was u
study and remained stable throughout the study period. Fluvoxamine 100 mg/day was added to olanzapi
and continued for 8 weeks. Olanzapine concentrations increased during fluvoxamine treatment 1.58-fold
week 4, and 1.81-fold from week 0 to week 8. Percentage change from week 0 to week 8 ranged from 1
demethylated metabolite were not significantly changed. Even though all eight patients had higher olanz
than on week 1, the ratio of increase of olanzapine blood serum concentrations from week 0 to week 8 d
serum levels (p greater than 0.05). This study confirmed that the addition of fluvoxamine to a stable dose
concentrations in the blood serum. Combined olanzapine and fluvoxamine should be used cautiously an
monitoring to avoid olanzapine-induced side effects or intoxication (Hiemke et al, 2002).

3.5.1.DI Fondaparinux

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2
(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax
threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig
taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b

warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally was discontinued. The next day the patient presented to the hospital with left-sided weakness and later c interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.DJ Foscarnet

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Foscarnet can prolong the QT interval in some patients, which may result in ventricular tachyca pointes. Because fluoxetine may also prolong the QT interval and increase the risk of arrhythmias, the concu not recommended (Prod Info Prozac(R), 2001t; Prod Info Foscavir(R), 1998).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of foscarnet and fluoxetine is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.DK Fosphenytoin

1) Interaction Effect: an increased risk of phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremor)
2) Summary: Fosphenytoin is a prodrug of phenytoin and the same interactions that occur with phenytoin are Cerebyx(R), 1999). Several case reports indicate that concurrent use of fluoxetine and phenytoin can result in leading to toxicity (FDA, 1994c; Jalil, 1992c; Woods et al, 1994a). Alternatively, patients who are stabilized on experience subtherapeutic concentrations of phenytoin and loss of seizure control when fluoxetine is disconti
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Monitor phenytoin serum levels with the addition of fluoxetine and periodically there dosage may be required with concomitant therapy. Serum levels of phenytoin should be monitored following because of the long half-life of fluoxetine, decreases in phenytoin levels may not be clinically significant for a
7) Probable Mechanism: decreased phenytoin metabolism
8) Literature Reports
a) Twenty-three reported cases of fluoxetine-phenytoin interactions that resulted in large increases in se phenytoin toxicity were evaluated. On the average, the adverse effects began within 2 weeks after fluoxe The average increase in plasma levels in 9 evaluable cases was 161% (range 75 to 309%) and the maxi evaluable cases ranged from 22 to 53.5 mcg/mL (therapeutic level, 10 to 20 mcg/mL) (FDA, 1994b).
b) An 84-year-old woman was stabilized on phenytoin 300 mg daily; after two months of treatment, fluox increased to 40 mg daily after 10 days (Jalil, 1992b). Within five days of starting fluoxetine, she develope mental status; her phenytoin serum level had increased from 15 to 35 mcg/mL. Both phenytoin and fluox symptoms of toxicity abated. Four weeks later she was rechallenged with the same dose of fluoxetine wi
c) In another case, a 57-year-old woman who had been stabilized on phenytoin 400 mg/d for a year (se mg/d (Jalil, 1992b). Ten days later she developed vomiting, vertigo, trunk ataxia, limb dysmetria, and mu serum level was 47 mcg/mL. Fluoxetine was discontinued and all signs and symptoms of toxicity disappe fluoxetine, the phenytoin serum level was 20 mcg/mL.
d) A 42-year-old male with a history of grand mal seizures and aggressive behavior was receiving pheny daily without resolution of his problems. His phenytoin level was 2.0 ng/mL and his dose was subsequen

daily was added for aggression, and the patient experienced resolution of his behavioral problems and a level ranged between 10.9 ng/mL and 15.7 ng/mL during fluoxetine therapy. However, the patient discon experienced a recurrence of problems. Phenytoin concentration was measured at 6.6 ng/mL six weeks a change in his phenytoin dose. This case report illustrates the need for close monitoring of phenytoin leve since subtherapeutic levels of phenytoin may result if doses of phenytoin are not readjusted following the 1999b).

3.5.1.DL Frovatriptan

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concon 1 (5HT-1) agonist, and a serotonin specific reuptake inhibitor (SSRI) (Prod Info Imitrex(R) Nasal Spray, 2003) similar interaction between SSRIs and frovatriptan may occur (Prod Info Frova(R), 2004). Concurrent use of f syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, halluci rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and d may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different syndrome with patients who are prescribed this combination and monitor them closely for symptoms of seroto Administration, 2006).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Coadministration of a triptan, such as frovatriptan, and an SSRI may result in a life- Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be pr are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms hyperthermia, hyperreflexia, incoordination).

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

3.5.1.DM Furazolidone

1) Interaction Effect: weakness, hyperreflexia, and incoordination

2) Summary: Although not its primary mechanism of action, furazolidone has monoamine oxidase inhibitor a reactions have been reported in patients receiving selective serotonin reuptake inhibitors (SSRI) in combinati Hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mer progressing to delirium and coma have been reported. Furazolidone should not be used in combination with a discontinuing therapy with a MAOI (Prod Info Furoxone(R), 1999).

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: If concurrent therapy with furazolidone and a selective serotonin reuptake inhibitor (monitor the patient for signs of serotonergic excess (mental status changes, diaphoresis, fever, weakness, hy

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

3.5.1.DN Galantamine

1) Interaction Effect: increased galantamine plasma concentrations

2) Summary: Based upon in vitro studies, the major enzymes involved in galantamine metabolism are CYP3 of CYP2D6. In a population pharmacokinetic analysis using a database of 852 Alzheimer's disease patients, fluoxetine (N=48), demonstrated a 25-33% decrease in galantamine clearance. The resulting plasma concen caution when it is coadministered with fluoxetine. Monitor for galantamine toxicity including anorexia, nausea, gastrointestinal bleeding (Prod Info RAZADYNE(R) ER extended release oral capsules, oral tablets, oral solu

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Increased galantamine plasma concentrations may result from fluoxetine inhibition (Monitor for galantamine toxicity including anorexia, nausea, vomiting, dizziness, arrhythmias, or gastrointestin extended release oral capsules, oral tablets, oral solution, 2007).

7) Probable Mechanism: inhibition of cytochrome CYP2D6-mediated galantamine metabolism

3.5.1.DO Gemifloxacin

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

2) Summary: Gemifloxacin should be avoided in patients receiving fluoxetine. Gemifloxacin has the potential (Prod Info Factive(R), 2003). Additive effects on QT prolongation may occur with the concomitant use of fluox

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of two drugs that prolong the QT interval, such as ge

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.DP Ginkgo

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

2) Summary: The addition of Ginkgo biloba and/or St. John's Wort to therapy with buspirone and fluoxetine r

case report (Spinella & Eaton, 2002a). It is unclear if Ginkgo or St. John's Wort, the combination of both, or o
Theoretically, Ginkgo may increase the risk of serotonin syndrome when taken with selective serotonin reupta
especially when ginkgo is taken to counteract sexual dysfunction associated with SSRIs. Ginkgo may inhibit
al, 1996), and has demonstrated serotonergic activity in animals (Ramassamy et al, 1992) which might increa
is combined with SSRIs. The potential MAO inhibitory activity of ginkgo is questionable. A human study did n
consumption (Fowler et al, 2000). Ginkgo biloba extract inhibited MAO-A/MAO-B in the rat brain in vitro (Slole
human platelets in vitro (White et al, 1996). No significant MAO inhibition was found in mice following oral cor

3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients closely for symptoms of serotonin syndrome if ginkgo is combined
(SSRIs).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) A 42-year-old female experienced symptoms consistent with a mixed hypomanic episode following co
biloba, and St. John's Wort. The symptoms resolved following discontinuation of Ginkgo and St. John's W
depression following a mild traumatic brain injury with fluoxetine 20 milligrams (mg) twice daily and busp
presentation, buspirone was increased to 20 mg twice daily for persistent anxiety and the patient began
Wort in unspecified doses. Melatonin was considered unlikely to have contributed to her symptoms. Gink
possible contributors since they may potentiate antidepressants, and considering the temporal relationsh
symptoms and discontinuation of the herbs and resolution of symptoms. However, the brain injury was c
Eaton, 2002).

3.5.1.DQ Halofantrine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Halofantrine can prolong the QT interval in some patients, which may result in ventricular tachy
pointes. Because fluoxetine has demonstrated QT prolongation at therapeutic doses and may increase the ri
of halofantrine with fluoxetine is not recommended (Prod Info Prozac(R), 2001i; Prod Info Halfan(R), 1998).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of halofantrine and fluoxetine is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.DR Haloperidol

1) Interaction Effect: an increased risk of parkinsonism (cogwheeling rigidity, unstable gait)
2) Summary: A patient receiving haloperidol experienced extreme parkinsonism following the addition of olar
pharmacokinetic interaction between olanzapine, a weak cytochrome P450 2D6 (CYP2D6) inhibitor, and halo
Pharmacodynamically, the small amount of dopamine (D2) blockade from olanzapine may have been enough
(Gomberg, 1999a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Patients should be closely monitored for signs and symptoms of increased parkinso
to haloperidol therapy. Doses of haloperidol may need to be decreased.
7) Probable Mechanism: competitive inhibition of cytochrome P450 2D6-mediated haloperidol metabolism; ir
8) Literature Reports
a) A 67-year-old hospitalized male with bipolar disorder who had stopped taking his medications was re
1 mg nightly, and valproate 750 mg twice daily. He had been experiencing some mild parkinsonian symp
worsen when haloperidol was reinstituted. Following stabilization on this regimen, it was decided to chan
minimize any parkinsonism that was a result of his medications. While tapering the haloperidol and initiat
parkinsonism that resulted in an inability to walk. His mental status remained unchanged. Haloperidol wa
and two days later the patient's parkinsonism side effects had resolved back to baseline. Benztropine wa
symptoms did not reoccur while on olanzapine (Gomberg, 1999).

3.5.1.DS Haloperidol

1) Interaction Effect: haloperidol toxicity (pseudoparkinsonism, akathisia, tongue stiffness) and an increased
de pointes, cardiac arrest)
2) Summary: Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Balk, 20
been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001x).
drugs that potentially prolong the QTc interval. In addition, several case reports describe development of extr
haloperidol were taken together, possibly due to inhibition of haloperidol metabolism (Benazzi, 1996a; Goff et
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and haloperidol is not recommended.
7) Probable Mechanism: inhibition of haloperidol metabolism by fluoxetine; theoretical additive effects on QT
8) Literature Reports

a) Fluoxetine increased plasma concentrations of haloperidol in 8 outpatients. Patients received fluoxeti doses of haloperidol (average dose, 14 mg per day). After ten days, mean plasma concentrations of halo symptom scores did not change appreciably after the addition of fluoxetine although one patient develop tremors. Extrapyramidal symptoms were expected to increase because of indirect inhibition of dopamine
b) A 39-year-old male experienced tardive dyskinesia with concomitant fluoxetine and haloperidol thera months, then haloperidol 2 mg twice daily was started and later lowered to 1 mg per day. Five months la dyskinesia was diagnosed. The suggested mechanism was the down-regulation of dopamine activity (St
c) A 39-year-old female developed tardive dyskinesia associated with concomitant fluoxetine and halope to 5 mg a day for two years (both with and without benztropine) with occasional mild, reversible extrapyra haloperidol, she started taking fluoxetine, which was increased over several days to 40 mg twice a day. A 5 mg each on two consecutive days (along with continuation of fluoxetine). She then experienced severe Both fluoxetine and haloperidol were withdrawn. During the next seven days her extrapyramidal symptor
d) A 40-year-old male developed urinary retention while taking fluoxetine and haloperidol. During a recu with fluoxetine 20 mg per day, alprazolam 1.5 mg per day, and haloperidol 1 mg per day. The patient ha without incident. Approximately one week after beginning therapy, the patient developed difficulty in void restlessness, hand tremors, and insomnia. After discontinuation of haloperidol and alprazolam, side effe postulated that the interaction was due to fluoxetine inhibition of cytochrome CYP2D6, which metabolizes

3.5.1.DT Halothane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, halothane should be administ known to prolong the QTc interval, including fluoxetine (Owens, 2001; Prod Info Prozac(R), 2001).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of halothane with other agents that can prolong the Q recommended.
7) Probable Mechanism: additive effect on QT interval

3.5.1.DU Heparin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2 (R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv

mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa
was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally
was discontinued. The next day the patient presented to the hospital with left-sided weakness and later c
interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim
warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.DV Hydroquinidine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class
prolong the QTc interval is not recommended (Prod Info Quinaglute Dura-tabs(R), 1999). Fluoxetine has dem
(Prod Info Prozac(R), 2001z).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class Ia antiarrhythmic agents and agents that pro
recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.DW Hydroxytryptophan

1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, ment
2) Summary: Hydroxytryptophan (5-HTP) may potentiate the serotonergic effect of selective serotonin reupta
Since 5-HTP increases serotonin levels, when combined with an SSRI, the serotonin level may be increased
Caution is advised with 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 syndrome resulting from this combinatio
HTP) and a selective serotonin reuptake inhibitor (SSRI) are used concomitantly. Monitor the patient for early
confusion, and disorientation.
7) Probable Mechanism: additive serotonergic effect
8) Literature Reports
a) Hydroxytryptophan (5-HTP) (200 milligrams (mg) orally) as a single dose increased plasma cortisol a
unmedicated patients with major depression or obsessive compulsive disorder (OCD). These responses
fluoxetine (n = 16) (p less than 0.0001). Mean fluoxetine dose for depressed patients was 44 mg/day,and
prolactin (PRL) levels in patients taking 5-HTP with tricyclic antidepressants (n = 14) or those receiving n
different from each other. A measurement of serotonergic effects of antidepressants can be evaluated by
(HPA) axis or PRL response. No clinical manifestations of serotonin syndrome were reported in patients
(Meltzer et al, 1997).

3.5.1.DX Ibuprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L
CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.DY Ibutilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class
prolong the QTc interval is not recommended (Allen et al, 2002; Prod Info Tikosyn(TM) dofetilide capsules, 1
been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that pro recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.DZ Iloperidone
1) Interaction Effect: increased plasma concentrations of iloperidone
2) Summary: Coadministration of iloperidone and fluoxetine results in increased plasma levels of iloperidone iloperidone (Prod Info FANAPT(TM) oral tablets, 2009).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: established
6) Clinical Management: If administered with fluoxetine, reduce iloperidone doses by one-half. Upon withdra resume the previous iloperidone dose (Prod Info FANAPT(TM) oral tablets, 2009).
7) Probable Mechanism: inhibition of the CYP2D6-mediated metabolism of iloperidone
8) Literature Reports
a) Coadministration of fluoxetine 20 mg twice daily for 21 days and iloperidone 3 mg (single doses) in 2 classified as CYP2D6 extensive metabolizers, increased the AUC of iloperidone and the P88 metabolite P95 metabolite by one-half (Prod Info FANAPT(TM) oral tablets, 2009).

3.5.1.EA Iloprost
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 200
7) Probable Mechanism: unknown

3.5.1.EB Imipramine
1) Interaction Effect: tricyclic antidepressant toxicity (dry mouth, urinary retention, sedation) and an increase de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and fluoxetine have been shown to prolong the QTc interval a Prozac(R), 2001h; Marshall & Forker, 1982). Even though no formal drug interaction studies have been done coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as fluox 1999). In addition, concurrent use of fluoxetine and TCAs such as desipramine, nortriptyline, and imipramine concentrations (Preskorn et al, 1994a; Preskorn et al, 1994a; Aranow et al, 1989a; Downs et al, 1989a; Gooc
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and a tricyclic antidepressant is not rec
7) Probable Mechanism: decreased tricyclic antidepressant metabolism; additive effects on QT prolongation
8) Literature Reports
a) Fluoxetine increased the level of tricyclic antidepressants (nortriptyline, imipramine, desipramine) in 4 ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients develope constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels (Aranow et al,
b) Fluoxetine statistically and clinically significantly increased desipramine concentrations in 18 healthy added to desipramine (50 mg daily), the mean maximum concentration of desipramine increased by 278 curve increased by 342%. Desipramine trough concentrations continued to be 198% above baseline thre same study compared pharmacokinetics of desipramine when combined with sertraline. The impact of s short-term increases in desipramine plasma concentrations (Preskorn et al, 1994).
c) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations w levels ranged from 109 to 150 ng/mL with oral doses of 300 mg at bedtime prior to fluoxetine therapy. Fo to the regimen, the desipramine serum level increased to 212 ng/mL within five days. The fluoxetine dos and the desipramine serum level was 419 ng/mL after four days. A worsening of depression and severe desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose to 200 mg dai ng/mL within two weeks (Bell & Cole, 1988).
d) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with a 40 mg daily and desipramine 150 mg daily for five weeks; fluoxetine was discontinued and the blood leve ng/mL with resolution of clinical symptoms (Goodnick, 1989).
e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant the patient's measured levels of desipramine had ranged from 148 to 160 ng/mL on a regimen of 300 mg 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a desipramine level of to 200 mg/day; eleven days later, the level was 244 ng/mL; the patient reported decreased energy, impa speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced t

days. Eight days later, the desipramine level was 122 ng/mL (Downs et al, 1989).
f) Concomitant administration of fluoxetine and desipramine was reported to result in an increased desip year-old male within 10 days of the addition of fluoxetine to the patient's regimen (Preskorn et al, 1990).

3.5.1.EC Indomethacin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of up than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.ED Indoprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of up than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.EE Insulin Aspart, Recombinant
1) Interaction Effect: hypoglycemia
2) Summary: Fluoxetine may increase the blood glucose-lowering effect of insulin and the susceptibility to hy powder inhaler, 2006; Prod Info NOVOLOG(R), 2005; Prod Info LEVEMIR(R) injection, 2005; Prod Info LANT Apidra(TM), 2004).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Blood glucose levels should be closely monitored when fluoxetine is added or disco doses of insulin may be required with concomitant therapy.
7) Probable Mechanism: additive hypoglycemia

3.5.1.EF Insulin Detemir
1) Interaction Effect: hypoglycemia
2) Summary: Fluoxetine may increase the blood glucose-lowering effect of insulin and the susceptibility to hy powder inhaler, 2006; Prod Info NOVOLOG(R), 2005; Prod Info LEVEMIR(R) injection, 2005; Prod Info LANT Apidra(TM), 2004).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Blood glucose levels should be closely monitored when fluoxetine is added or disco doses of insulin may be required with concomitant therapy.

7) Probable Mechanism: additive hypoglycemia

3.5.1.EG Insulin Glargine, Recombinant

1) Interaction Effect: hypoglycemia
2) Summary: Fluoxetine may increase the blood glucose-lowering effect of insulin and the susceptibility to hy powder inhaler, 2006; Prod Info NOVOLOG(R), 2005; Prod Info LEVEMIR(R) injection, 2005; Prod Info LANT Apidra(TM), 2004).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Blood glucose levels should be closely monitored when fluoxetine is added or discc doses of insulin may be required with concomitant therapy.
7) Probable Mechanism: additive hypoglycemia

3.5.1.EH Insulin Glulisine

1) Interaction Effect: hypoglycemia
2) Summary: Fluoxetine may increase the blood glucose-lowering effect of insulin and the susceptibility to hy powder inhaler, 2006; Prod Info NOVOLOG(R), 2005; Prod Info LEVEMIR(R) injection, 2005; Prod Info LANT Apidra(TM), 2004).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Blood glucose levels should be closely monitored when fluoxetine is added or discc doses of insulin may be required with concomitant therapy.
7) Probable Mechanism: additive hypoglycemia

3.5.1.EI Insulin Human Inhaled

1) Interaction Effect: hypoglycemia
2) Summary: Fluoxetine may increase the blood glucose-lowering effect of insulin and the susceptibility to hy powder inhaler, 2006; Prod Info NOVOLOG(R), 2005; Prod Info LEVEMIR(R) injection, 2005; Prod Info LANT Apidra(TM), 2004).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Blood glucose levels should be closely monitored when fluoxetine is added or discc doses of insulin may be required with concomitant therapy.
7) Probable Mechanism: additive hypoglycemia

3.5.1.EJ Iproniazid

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with fluoxetine and a monoamine oxidase (M serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Prod Info Prozac(R), 1 1993i; Feighner et al, 1990i; Kline et al, 1989i; Suchowersky & de Vries, 1990i). Concomitant use is contrainc
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of fluoxetine and iproniazid is contraindicated. Wait at least two wee initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before initiating
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod syndrome (Sternbach, 1991j). Serotonin syndrome is a condition of serotonergic hyperstimulation and m mental status, hyperreflexia, diaphoresis, shivering, and tremor (Sternbach, 1991j). If the syndrome is nc result.

b) It has been suggested that fluoxetine therapy be discontinued for at least five weeks before beginning 28-year old woman discontinued fluoxetine for six weeks before starting therapy with tranylcypromine. O fever, paresthesias, confusion, abdominal cramping, and various other CNS symptoms. Upon discontinu began to resolve. Blood samples taken three days after discontinuation of tranylcypromine revealed no p level was 84 ng/mL (Coplan & Gorman, 1993h).

c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylc restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressur one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, ar adverse reactions.

d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Klir insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours

e) Two cases suggestive of an interaction between fluoxetine and selegiline have been reported. One ca

observed approximately one month after adding selegiline to fluoxetine therapy. The patient improved tw
and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanc
temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued, with relatively qu
fluoxetine alone occurred without incident (Suchowersky & de Vries, 1990h).

3.5.1.EK Isocarboxazid

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with fluoxetine and a monoamine oxidase (M
serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus
diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Prod Info Prozac(R), 1
1993o; Feighner et al, 1990o; Kline et al, 1989o; Suchowersky & de Vries, 1990o). Concomitant use is contra
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of fluoxetine and a MAO inhibitor is contraindicated. Wait at least tw
before initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before in
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod
syndrome (Sternbach, 1991p). Serotonin syndrome is a condition of serotonergic hyperstimulation and n
mental status, hyperreflexia, diaphoresis, shivering, and tremor (Sternbach, 1991p). If the syndrome is n
result.

b) It has been suggested that fluoxetine therapy be discontinued for five weeks before beginning therap
one case report describes a 28-year old woman who had discontinued a 2-year fluoxetine regimen for si
tranylcypromine. Over the next few days the patient developed fever, paresthesias, confusion, abdomina
Upon discontinuation of tranylcypromine, the patient's symptoms began to resolve. Blood samples taken
tranylcypromine revealed no presence of fluoxetine; however, the norfluoxetine level was 84 ng/mL (Cop

c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylc
restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressur
one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, ar
adverse reactions.

d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Klir
insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added
rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours

e) Interactions between fluoxetine and selegiline were suggested in two case reports (Suchowersky & d
episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy.
drugs were discontinued, and no further details were provided. The second case involved diaphoresis, v
occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinuec
Rechallenge with fluoxetine alone occurred without incident.

3.5.1.EL Isoflurane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, isoflurane should be administ
known to prolong the QTc interval, including fluoxetine (Owens, 2001a; Prod Info Prozac(R), 2001k).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of isoflurane with other agents that can prolong the Q
recommended.
7) Probable Mechanism: additive effect on QT interval

3.5.1.EM Isoxicam

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L
CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of

upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.EN Isradipine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Isradipine can prolong the QT interval in some patients, which may result in ventricular tachyca
pointes. Because fluoxetine may also prolong the QT interval and increase the risk of arrhythmias, the concu
not recommended (Prod Info DynaCirc(R), 2000).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of isradipine and fluoxetine is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.EO Ketoprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L
CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.EP Ketorolac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L
CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.EQ Lamifiban

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events
hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008;
release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for
oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 200

7) Probable Mechanism: unknown

3.5.1.ER Levodopa
1) Interaction Effect: decreased levodopa effectiveness
2) Summary: Concurrent use of olanzapine may antagonize the pharmacological effects of levodopa (Prod I
of this interaction is unknown.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Monitor patients for levodopa efficacy.
7) Probable Mechanism: pharmacological antagonism

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

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

3.5.1.EU Lexipafant
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events
hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008;
release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for
oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 200
7) Probable Mechanism: unknown

3.5.1.EV Lidoflazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Lidoflazine and fluoxetine have been shown to prolong the QTc interval at the recommended th
Hanley & Hampton, 1983). Even though no formal drug interaction studies have been done, the coadministra
not recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of lidoflazine and fluoxetine is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.EW Linezolid
1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental s
2) Summary: Linezolid is a reversible, nonselective monoamine oxidase inhibitor (MAOI). Concurrent admini
and a MAOI may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by sy
changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions hav
reports of serotonin syndrome associated with concomitant use of linezolid and serotonergic agents, includin
Morin, 2007; Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension, 2008; Prod Info PROZAC(R) ora
are used concomitantly, monitor for serotonin syndrome effects, including confusion, delirium, restlessness, t
If symptoms occur, consider discontinuation of either one or both of the agents (Prod Info ZYVOX(R) IV injec
washout period of 2 weeks is usually recommended following discontinuation of an MAOI and initiation of fluo

washout period of 5 weeks is usually recommended prior to initiation of an MAOI (Prod Info PROZAC(R) oral
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Unless carefully monitored for serotonin syndrome, linezolid should not be administ
ZYVOX(R) IV injection, oral tablets, oral suspension, 2008). A washout period of 2 weeks is usually recomme
initiation of fluoxetine. Following discontinuation of fluoxetine, a washout period of 5 weeks is usually recomm
PROZAC(R) oral capsules, oral solution, 2006). If fluoxetine and linezolid are used concomitantly, monitor clo
as neuromuscular abnormalities (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hyperton
(including tachycardia, mydriasis, diaphoresis, and diarrhea), and mental status changes (including agitation
threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care a
Shannon, 2005).
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) A 4-year-old female patient, weighing 12.8 kg, experienced serotonin syndrome-like symptoms follow
Eleven days after receiving fluoxetine 5 mg daily for acute stress disorder in response to a burn injury, th
hours. Two days later, she was premedicated with oral fentanyl 200 mcg prior to a wound debridement p
agitated and had myoclonus in her arms and legs. She also had mydriasis, was unable to visually track a
lower left quadrant. Discontinuation of fluoxetine and initiation of oral diphenhydramine 25 mg led to part
linezolid was discontinued and replaced with an alternate antibiotic. Symptoms of agitation, myoclonic m
2 days (Thomas et al, 2004).
b) The concomitant administration of fluoxetine and linezolid was associated with mild symptoms of sero
described in a case report. The patient, who had recently achieved complete remission of acute myeloge
maintenance chemotherapy, routinely received treatment with oral fluoxetine 60 mg once daily, oral meth
mg twice daily, transdermal nicotine patch 21 mg (changed daily), oral lorazepam 2 mg twice daily (with
quetiapine 200 mg every evening. On day 9 of admission, the fluoxetine dose was increased to 80 mg da
every 12 hours was initiated on day 43. Within 12 hours of initiating linezolid, the patient experienced phy
(described as feeling like a "runner's cramp" and making it "difficult to breathe"). The discomfort continue
next day. On day 47, linezolid was discontinued, after a total of 6 linezolid doses, and the pain and other
linezolid therapy, vital signs and laboratory results were unremarkable, except for chemotherapy-induced
(Steinberg & Morin, 2007).
c) A retrospective chart review identified one highly probable case of serotonin syndrome in a patient wh
and venlafaxine, followed by citalopram. Charts of 72 inpatients who received linezolid and an SSRI or v
reviewed for a diagnosis of serotonin syndrome (SS) using the Sternbach and the Hunter Serotonin Toxi
treated concomitantly with linezolid and an SSRI or venlafaxine. Four patients met the criteria for having
one case involved an 81-year-old woman who was diagnosed with a high probability of having SS after r
followed by citalopram. Linezolid was given for a vancomycin-resistant Enterococcus urinary tract infecti
eat, was confused as to time and place, and began shouting. Although she appeared to have met 6 of th
for SS, a diagnosis of SS was not documented in her chart. Her blood pressure was 180 mm Hg with a h
of 50 breaths/min. The following day, she barely spoke and could not be aroused; additional symptoms i
eyes rolled back in her head, and labored breathing. Linezolid was discontinued, and she was sedated a
symptoms and 2 days after linezolid was stopped, she was extubated and had returned to baseline ment
et al, 2006).
d) In one case report, a 39-year-old female experienced symptoms of serotonin syndrome after concom
was admitted to the emergency room after being found unresponsive at home. This patient had a history
dependency. Before admission, her medications consisted of disulfiram, fluoxetine, buspirone, cyclobenz
discontinued upon admission. The patient was given two doses of physostigmine for anticholinergic sym
cyclobenzaprine overdose. Two days after admission, the patient became sedated, developed tachycard
alcohol withdrawal. She was given lorazepam and haloperidol for the alcohol withdrawal and agitation. C
depression thought to be from either pneumonia or respiratory suppression from lorazepam. The patient
staphylococcus aureus (sputum) and on day thirteen, was extubated and her mental status improved. O
linezolid. Immediate changes in her mental status were apparent. She experienced convulsions, tremors
linezolid, the patient had a temperature of 98 degrees, blood pressure of 140/90, a heart rate of 170, and
and the vancomycin regimen restarted. The patient was diagnosed with benzodiazepine withdrawal, neu
serotonin syndrome. Serotonin syndrome was diagnosed as a likely drug interaction between linezolid a

3.5.1.EX Lithium

1) Interaction Effect: weakness, dyskinesias, increased extrapyramidal symptoms, encephalopathy, and brai
2) Summary: An encephalopathic syndrome followed by irreversible brain damage has occurred in a few pat
antagonist, particularly haloperidol. A causal relationship between these events and the concomitant adminis
has not been established (Prod Info LITHOBID(R) slow-release oral tablets, 2005). Coadministration of lithiur
caused a wide variety of encephalopathic symptoms, brain damage, extrapyramidal symptoms, and dyskines
effects have occurred with therapeutic lithium levels (Amdisen, 1982; Prakash, 1982; Addonizio et al, 1988a)
using such combinations with no severe adverse consequences (Goldney & Spence, 1986). The mechanism
treatment decreases neostriatal dopaminergic activity, probably through a direct action on the G protein and t
stimulate adenyl cyclase (Carli et al, 1994). Hyperglycemic reactions have also occurred during combined ph
3) Severity: major
4) Onset: delayed

5) Substantiation: probable
6) Clinical Management: Monitor patients closely for any signs of toxicity or extrapyramidal symptoms, espec particularly haloperidol, and lithium are used. Serum lithium levels should be monitored periodically. Some cli therapeutic range.
7) Probable Mechanism: unknown
8) Literature Reports
a) Concomitant haloperidol and lithium therapy has resulted in symptoms of encephalopathy, confusion, patients with mania (Cohen & Cohen, 1974; Loudon & Waring, 1976; Thomas, 1979). Irreversible neurol Hurwitz, 1983; Keitner & Rahman, 1984).
b) Seizures, encephalopathy, delirium, and abnormal EEG occurred in four patients during combined lith Serum lithium levels were below 1 mEq/L at the time of the toxic reaction in all cases. All patients had pr another phenothiazine. Three of these patients developed symptoms within eight days of initiating combi
c) The addition of lithium to neuroleptic therapy exacerbated extrapyramidal symptoms (EPS) in a small received at least five days of treatment with either oral thiothixene, haloperidol, or fluphenazine in mean to initiation of the lithium and were experiencing drug-induced extrapyramidal symptoms. Oral lithium wa doses to achieve a therapeutic serum concentration. The maximum levels attained were 0.65 to 1.27 mE patients following the addition of lithium. However, only three patients developed marked symptoms and Significantly increased symptoms included gait, shoulder shaking, elbow rigidity, and tremor.
d) Ten patients treated with clozapine and lithium were studied (Blake et al, 1992). Of the ten patients, f including jerking of limbs, facial spasms and tics, tremor of hands and arms, tongue twitching, and stumb delirium. These effects reversed when lithium was discontinued or given at a lower dose. On rechallenge symptoms. By keeping serum lithium no greater than 0.5 mEq/L, clozapine could be safely coadministere
e) Chlorpromazine serum levels can be significantly reduced in the presence of lithium treatment. If use result in rebound elevation of chlorpromazine levels, resulting in chlorpromazine toxicity. In patients on a withdrawal of the lithium may precipitate chlorpromazine cardiotoxicity. In this report, such toxicity was m associated with prolongation of the QTc interval. Hypotension and EPS are also possible in this situation
f) However, other data do not support that such adverse events are frequent or indeed causally related dopamine antagonist antipsychotic drugs and lithium have been used successfully in many patients with that the interaction may only become significant with very high doses of one or both drugs or with failure symptoms (Miller & Menninger, 1987).
g) A 69-year-old patient with oxygen-dependent chronic obstructive pulmonary disorder and a 25-year h risperidone 3 mg for the treatment of new-onset auditory and visual hallucinations. She had also been m for more than 10 years. In addition, she was given amantadine (100 mg twice daily) for tremor. Three we experienced a decline in mental status in addition to dizziness, worsening tremors, nausea and vomiting, hallucinations. She was then admitted to the hospital for delirium. Her lithium serum level was 1.36 mEq/ were discontinued. Although her lithium level decreased to 0.41 mEq/L, she continued to experience pro hallucinations for almost one week. After she started to respond to commands, she was restarted on lithi mild hypomania. Five days later, she was discharged with a regimen of lithium and low-dose lorazepam delirium could have been caused by the concurrent use of lithium and risperidone. Other factors could al serum lithium level and the underlying pulmonary pathology. In addition, amantadine, which facilitates th mild anticholinergic effect, may have contributed (Chen & Cardasis, 1996).

3.5.1.EY Lithium
1) Interaction Effect: possible increased lithium concentrations and/or an increased risk of SSRI-related sero myoclonus, mental status changes)
2) Summary: Concomitant use of lithium and various SSRIs has been associated with enhanced side effects elevated lithium levels. The combination has resulted in neurotoxicity and increased lithium levels in one case symptoms of lithium toxicity and serotonin syndrome have also been reported in patients who demonstrated t concurrent fluoxetine and lithium (Muly et al, 1993a; Noveske et al, 1989a). Two studies have failed to identif and citalopram (Gram et al, 1993a; Baumann et al, 1996a). Combined administration of citalopram (40 mg da days) had no significant effect on the pharmacokinetics of citalopram or lithium. However, plasma lithium leve adjustment to the lithium dose in accordance with standard clinical practice. Lithium may enhance the serotor should be exercised when citalopram and lithium are coadministered (Prod Info Celexa(R), 2004). Concurren reports of increased lithium levels and neurotoxicity, serotonin syndrome, somnolence, and mania (Salama & Evans & Marwick, 1990; Burrai et al, 1991a). No pharmacokinetic interference was apparent during a multiple paroxetine (Prod Info Paxil CR(TM), 2003). If these two agents are to be given concomitantly, the manufactur clinical experience is available. Drug interactions leading to lithium toxicity have been reported when lithium w fluvoxamine (both in the same pharmacological class as paroxetine, eg, selective serotonin reuptake inhibitor 1989a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Monitor patients on concurrent lithium and selective serotonin reuptake inhibitor the lithium. In addition, monitor patients for signs and symptoms associated with serotonin syndrome (hypertensi changes).
7) Probable Mechanism: unknown
8) Literature Reports
a) Concomitant administration of oral lithium carbonate and oral fluoxetine resulted in increased lithium s

woman with a bipolar affective disorder (Salama & Shafey, 1989). Fluoxetine 20 mg daily was added to a patient complaints of weakness, tiredness, decreased concentration, and early morning awakening. Lithi range of 0.75 to 1.15 mEq/L prior to fluoxetine. Fluoxetine was discontinued and the dose of lithium decr serum level within 48 hours to 1.2 mEq/L. The neurologic symptoms subsided within seven days as the l contribution of fluoxetine to lithium toxicity in this patient was obscured by the fact that the lithium was re

b) A 53-year old woman who had been taking fluoxetine 20 mg daily and lorazepam 0.5 mg four times d 900 mg per day added to her regimen in order to augment her response to fluoxetine. Within 48 hours, th developed a coarse tremor in her right arm. Vital signs showed a rectal temperature of 101 degrees F, ar elevated leukocyte count and slightly elevated bilirubin level. After discontinuation of lithium and fluoxetir four days. At no point did the lithium levels reach a toxic level, suggesting that the patient's symptoms we and lithium (Noveske et al, 1989).

c) Serotonin syndrome was precipitated when lithium 300 mg twice daily was added to a three-month re later, the patient's lithium level was measured at 0.65 mEq/L and the dose was increased to 300 mg thre change, the patient experienced akathisia, myoclonus, hyperreflexia, shivering, tremor, diarrhea, and inc initiation of cyproheptadine therapy, the patient's symptoms began to improve. The patient was discharg without further symptoms of serotonin syndrome (Muly et al, 1993).

d) Eight healthy male volunteers completed three phases of an interaction study to determine the effects subjects were extensive metabolizers of sparteine, indicating normal cytochrome P450 2D6 enzyme acti oxidation, citalopram metabolites are excreted by the kidney, as is lithium. Each subject received citalopr days, lithium 30 mmol (1980 mg) alone daily for five days, and lithium coadministered with citalopram on treatment phase. Results showed that the concurrent administration of citalopram and lithium did not sig (Gram et al, 1993).

e) Twenty-four patients experiencing depression (DSM III criteria) were randomized under double-blind daily) and lithium carbonate (800 mg daily) or placebo. All of the subjects had failed to respond to four w coadministered on days 29 to 42. No evidence of a pharmacokinetic interaction between lithium and cita tolerated (Baumann et al, 1996).

f) Serotonin syndrome was described in a 53-year-old patient who was stabilized on lithium 1400 mg da fluvoxamine 50 mg daily. Over a 10-day period the fluvoxamine dose was increased to 200 mg daily; trer developed. After two weeks, tremor, impaired motor function coordination, marked bilateral hyperreflexia ankles were seen. After 12 weeks of continued therapy, during which time no further deterioration occurr fluvoxamine, and the neuromuscular symptoms abated over a 2-week period. After four weeks the patier Spigset, 1993).

g) Three cases of mania were reported in patients who were treated with lithium and fluvoxamine. The r weeks, respectively, after cotherapy was begun. Fluvoxamine was discontinued and, in two of the three treatment of depression occurred with lithium alone. The third patient improved, but depression reappear (Burrai et al, 1991).

h) In an open-labeled, placebo-controlled study, lithium 600 mg was administered to 16 subjects orally t the morning on day nine. In addition, oral sertraline 100 mg or placebo was given twice, ten hours and tw steady-state lithium level was only decreased by 1.4% (0.01 mEq/L) and the lithium renal clearance incre coadministered. Seven subjects experienced side effects, mainly tremors, after receiving lithium and sert placebo and lithium experienced side effects (Wilner et al, 1991).

3.5.1.EZ Lorcainide

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

2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class prolong the QTc interval is not recommended (Prod Info Tambocor(R) flecainide acetate, 1998). Fluoxetine h recommended therapeutic dose (Prod Info Prozac(R), 2001w).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of class I antiarrhythmic agents and agents that prolo recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.FA Lornoxicam

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar

hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.FB Meclofenamate

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L
CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.FC Mefenamic Acid

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L
CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.FD Mefloquine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose
formal drug interaction studies have been done, caution is advised if mefloquine is used with other drugs whi
(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and mefloquine is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.FE Meloxicam

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L
CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified

5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.FF Meperidine

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: A 43-year-old male on fluoxetine every other day experienced serotonin syndrome immediatel (Tissot, 2003). If fluoxetine and meperidine are used concomitantly, monitor closely for symptoms of serotoni threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care a Shannon, 2005).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: A case of serotonin syndrome was reported with coadministration of fluoxetine and discouraged (Tissot, 2003). If fluoxetine and meperidine are used concomitantly, monitor closely for symptom abnormalities (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including a be life-threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive Shannon, 2005).
7) Probable Mechanism: additive pharmacologic effects
8) Literature Reports
a) A 43-year-old male on fluoxetine every other day experienced serotonin syndrome immediately after other medications were rosiglitazone and fenofibrate. His medical history includes type 2 diabetes, dysli Prior to this adverse event he received meperidine and midazolam, while not on fluoxetine, without any s administered intravenous midazolam and 50 mg of intravenous meperidine. He immediately became agi verbal commands because of confusion. Blood pressure (180/100 mm Hg) and heart rate (130 bpm) inc He had diaphoresis and dilated pupils. Within 10 minutes his blood pressure started to decrease. He hac minutes, his agitation subsided, he remained sleepy and confused, and blood pressure and heart contin 98.4 degrees Farenheit. After 60 to 90 minutes his sensorium appeared to clear and diaphoresis resolve signs over the next 24 hours. He was treated with hydromorphone for abdominal pain without any adver fentanyl, midazolam, and propofol pre-endoscopy without any event, but had not taken fluoxetine for 2 w

3.5.1.FG Mesoridazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose data, the manufacturer of mesoridazine states that concomitant use with other drugs which prolong the QT in 2000).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and mesoridazine is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.FH Methylergonovine

1) Interaction Effect: an increased risk of ergotism (nausea, vomiting, vasospastic ischemia)
2) Summary: Because of the potential for serious toxicity including vasospasm that can occur with increased concurrent use of fluoxetine and ergot derivatives is contraindicated. Fluoxetine and ergot derivatives are bot enzymes, and the competition for metabolism could result in an increased plasma concentration of the ergot
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent use of fluoxetine and ergot derivatives is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A4- mediated ergot metabolism by fluoxetine

3.5.1.FI Methylphenidate

1) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations
2) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metab (SSRIs). Downward dose adjustments of the SSRI may be necessary when it is used concurrently with meth discontinuing methylphenidate, the SSRI dose may need to be adjusted as needed (Prod Info METADATE C

3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing methylphenidate to patients who take an selective se use of methylphenidate and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease coadministered. Additionally, consider adjusting the SSRI dose if necessary when initiating or discontinuing n CD(R) extended-release oral capsules, 2007).
7) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by methylphenidate

3.5.1.FJ Methysergide
1) Interaction Effect: an increased risk of ergotism (nausea, vomiting, vasospastic ischemia)
2) Summary: Because of the potential for serious toxicity including vasospasm that can occur with increased concurrent use of fluoxetine and ergot derivatives is contraindicated. Fluoxetine and ergot derivatives are bot enzymes, and the competition for metabolism could result in an increased plasma concentration of the ergot
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent use of fluoxetine and ergot derivatives is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A4- mediated ergot metabolism by fluoxetine

3.5.1.FK Metoprolol
1) Interaction Effect: an increased risk of metoprolol adverse effects (shortness of breath, bradycardia, hypot
2) Summary: To date, little information is available related to the effects of combined fluoxetine and metopro between metoprolol and fluoxetine resulting in bradycardia (Walley et al, 1993a). Fluoxetine is a potent inhibi isoenzyme that catalyzes metoprolol metabolism (DeVane, 1994). Additional research is needed to further as pharmacokinetics.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Atenolol should be considered for fluoxetine-treated patients who require a beta blo coadministered, monitor patients for metoprolol adverse effects. A reduction in the metoprolol dose may be n
7) Probable Mechanism: inhibition of hepatic metabolism of metoprolol
8) Literature Reports
a) A case report described a possible interaction between metoprolol and fluoxetine resulting in bradyca with metoprolol 100 mg daily developed lethargy and bradycardia within two days after fluoxetine 20 mg was discontinued and metoprolol was replaced with sotalol 80 mg twice daily. A week later fluoxetine wa bradycardia. Fluoxetine is known to inhibit hepatic metabolism. Metoprolol is extensively metabolized via and possibly CYP3A). Sotalol does not undergo significant hepatic metabolism (Walley et al, 1993).

3.5.1.FL Milnacipran
1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental s
2) Summary: Concurrent use of milnacipran and an SSRI may result in hypertension, coronary artery vasocc life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordinat pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea (Prod Info SAV
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of milnacipran and an SSRI may result in hypertension and coron serotonergic effects. If these agents are used together, discuss the risks of serotonin syndrome with the patie syndrome (restlessness, hyperthermia, hyperreflexia, incoordination), especially during treatment initiation an tablets, 2009).
7) Probable Mechanism: additive serotonergic effect

3.5.1.FM Mirtazapine
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Concurrent use of olanzapine with mirtazapine and tramadol in a 53-year-old male resulted in s Fetchko, 2002). If olanzapine is used concomitantly with mirtazapine and/or tramadol, monitor closely for sym syndrome can be life-threatening. If serotonin syndrome develops, discontinue the offending agents and prov necessary (Boyer & Shannon, 2005).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: A case of serotonin syndrome was reported with coadministration of olanzapine, mi 2002). If 2 or more of these drugs are are used concomitantly, monitor closely for symptoms of serotonin syn (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic h diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation an threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care a Shannon, 2005).

7) Probable Mechanism: additive serotonergic pharmacologic effects
8) Literature Reports
a) A 53-year-old male on mirtazapine and tramadol experienced serotonin syndrome 8 days after olanza
mirtazapine 45 mg/day for depression and tramadol 150 mg/day for chronic back pain. Olanzapine 10 m
was admitted 8 days later after being found by the police wandering the streets in inappropriate dress an
afebrile, tachycardic (120 bpm), and had flushing, twitching of his face, tremors, myoclonus, hyperreflexi
agitated. He spoke with a stutter. He had marked derailment, appeared perplexed, had prominent percep
hallucinations. The creatine phosphokinase was normal. All medications were discontinued and within 12
Fetchko, 2002).

3.5.1.FN Mirtazapine
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Concurrent use of fluoxetine and mirtazapine resulted in serotonin syndrome in a 75-year-old v
nausea, dry mouth, intense anxiety and agitation with suicidal ideas. Other symptoms were difficulty walking,
insomnia (Benazzi, 1998). If fluoxetine and mirtazapine are used together, monitor closely for symptoms of se
life-threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive car
Shannon, 2005).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: A case of serotonin syndrome was reported with concomitant use of fluoxetine and
discouraged (Benazzi, 1998). If fluoxetine and mirtazapine are used together, monitor closely for symptoms c
abnormalities (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering
mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including a
be life-threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive
Shannon, 2005).
7) Probable Mechanism: potentially additive pharmacologic effects
8) Literature Reports
a) Within a few hours of starting mirtazapine and shortly after stopping fluoxetine, a 75-year-old woman
syndrome. Besides fluoxetine 20 mg/day, she was on chlorpromazine 75 mg/day, and lorazepam 2.5 mg
fluoxetine was discontinued and soon afterward mirtazapine 30 mg/day was started and the dose of chlo
a few hours of starting mirtazapine, she experience dizziness, headache, nausea, dry mouth, intense an
symptoms were difficulty walking, marked resting tremor of the hands, and insomnia. Over the next 3 day
discontinued on day 5. Her symptoms improved the following day. Fluoxetine 20 mg/day was restarted o
nausea, headache, and agitation resolution over the following days. Over the next 10 days, tremor, anxie
improved (Benazzi, 1998).

3.5.1.FO Moclobemide
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with fluoxetine and a monoamine oxidase (M
serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus
diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Prod Info Prozac(R), 1
1993r; Feighner et al, 1990r; Kline et al, 1989s; Suchowersky & de Vries, 1990s). Although not reported spec
similar interaction may occur. Concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of fluoxetine and a MAO inhibitor is contraindicated. Wait at least tw
before initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before in
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod
syndrome (Sternbach, 1991t). Serotonin syndrome is a condition of serotonergic hyperstimulation and m
mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and c
b) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Klin
insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added
rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours
c) Two cases suggestive of an interaction between fluoxetine and selegiline, a selective monoamine oxi
(Suchowersky & de Vries, 1990r). One case involved a first episode of mania being observed approxima
fluoxetine therapy. The patient improved two months after both drugs were discontinued, and no further
diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to
were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occur
d) In three of five cases of serotonin syndrome following overdoses, the drug combination that induced t
selective monoamine oxidase inhibitor, and citalopram. Of these three patients, moclobemide blood conc
therapeutic level, and citalopram concentrations ranged from normal to 5 times the therapeutic level (Ne
e) Moclobemide is a selective and reversible inhibitor of monoamine oxidase A (MAO-A). Based on anim
and MAO-B are essential for the development of serotonin syndrome. In an effort to assess the safety ar
fluoxetine and moclobemide, 18 healthy subjects participated in a randomized, placebo-controlled, parall

dose of moclobemide 300 mg on days 1 and 24, fluoxetine 40 mg on days 2 through 8, and fluoxetine 20
were randomized to receive either placebo or moclobemide on an ascending dose schedule. Doses of m
increased to 200 mg on day 17, 300 mg on day 18, and 600 mg on days 19 through 23. Steady-state flu
achieved when moclobemide therapy was initiated, and did not change with the addition or increasing do
serotonin syndrome or any kind of a pharmacodynamic interaction between these two agents. Additional
platelets almost completely as expected, but moclobemide had no effect on serotonin uptake during sing
suggest that a long wash-out period between treatment with moclobemide and fluoxetine is not necessar
f) An 82-year-old woman developed various serotonin syndrome symptoms after changing from fluoxeti
period in between. She experienced agitation, confusion, and tremor, progressing to inability to answer q
After treatment with 4 mg cyproheptadine, her condition improved significantly (Chan et al, 1998a).

3.5.1.FP Morniflumate

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L
CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.FQ Nabumetone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L
CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.FR Nadroparin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2
(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax
threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig
taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally was discontinued. The next day the patient presented to the hospital with left-sided weakness and later c interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.FS Naproxen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of up than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.FT Naratriptan

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Rare incidences of weakness, hyperreflexia, and incoordination have been reported with the co inhibitor (SSRI) and a 5-hydroxytryptamine-1 (5HT-1) agonist (Prod Info Amerge(TM), 2002). Concurrent use syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, halluci rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and c may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different syndrome with patients who are prescribed this combination and monitor them closely for symptoms of seroto Administration, 2006).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as naratriptan, and an SSRI may result in a life-t Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be pr are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms hyperthermia, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.FU Nebivolol

1) Interaction Effect: increased nebivolol exposure and plasma levels

2) Summary: Nebivolol is partially metabolized by the CYP2D6 isozyme. Coadministration of a single 10 mg receiving fluoxetine, a CYP2D6 inhibitor, at a dose of 20 mg/day for 21 days led to 8- and 3-fold increases in (pharmacologically active isomer). Closely monitor blood pressure in patients receiving fluoxetine and nebivo of nebivolol may be necessary (Prod Info BYSTOLIC(TM) oral tablets, 2007).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Coadministration of fluoxetine, a CYP2D6 inhibitor, and nebivolol led to increased e nebivolol, the pharmacologically active isomer. In patients receiving these agents concomitantly, closely mon may be necessary (Prod Info BYSTOLIC(TM) oral tablets, 2007).

7) Probable Mechanism: inhibition of CYP2D6-mediated nebivolol metabolism

3.5.1.FV Nialamide

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta

2) Summary: Concurrent administration or overlapping therapy with fluoxetine and a monoamine oxidase (M serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Prod Info Prozac(R), 1 1993g; Feighner et al, 1990g; Kline et al, 1989g; Suchowersky & de Vries, 1990g). Concomitant use is contra

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of fluoxetine and nialamide is contraindicated. Wait at least two we initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before initiating

7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase

8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod syndrome (Sternbach, 1991h). Serotonin syndrome is a condition of serotonergic hyperstimulation and m mental status, hyperreflexia, diaphoresis, shivering, and tremor (Sternbach, 1991h). If the syndrome is n result.

b) It has been suggested that fluoxetine therapy be discontinued for at least five weeks before beginning 28-year old woman discontinued fluoxetine for six weeks before starting therapy with tranylcypromine. O fever, paresthesias, confusion, abdominal cramping, and various other CNS symptoms. Upon discontinu began to resolve. Blood samples taken three days after discontinuation of tranylcypromine revealed no p level was 84 ng/mL (Coplan & Gorman, 1993f).

c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylc restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressur one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, ar adverse reactions.

d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Klin insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours

e) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. drugs were discontinued, and no further details were provided. The second case involved diaphoresis, v occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued Rechallenge with fluoxetine alone occurred without incident.

3.5.1.FW Niflumic Acid

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.FX Nimesulide

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.FY Nortriptyline

1) Interaction Effect: tricyclic antidepressant toxicity (dry mouth, urinary retention, sedation) and an increase de pointes, cardiac arrest)

2) Summary: Tricyclic antidepressants (TCAs) and fluoxetine have been shown to prolong the QTc interval a Prozac(R), 2001h; Marshall & Forker, 1982). Even though no formal drug interaction studies have been done coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as fluox 1999). In addition, concurrent use of fluoxetine and TCAs such as desipramine, nortriptyline, and imipramine concentrations (Preskorn et al, 1994a; Preskorn et al, 1994a; Aranow et al, 1989a; Downs et al, 1989a; Gooc

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of fluoxetine and a tricyclic antidepressant is not rec

7) Probable Mechanism: decreased tricyclic antidepressant metabolism; additive effects on QT prolongation

8) Literature Reports

a) Fluoxetine increased the level of tricyclic antidepressants (nortriptyline, imipramine, desipramine) in 4 ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients develope constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels (Aranow et al,

b) Fluoxetine statistically and clinically significantly increased desipramine concentrations in 18 healthy added to desipramine (50 mg daily), the mean maximum concentration of desipramine increased by 278 curve increased by 342%. Desipramine trough concentrations continued to be 198% above baseline thre same study compared pharmacokinetics of desipramine when combined with sertraline. The impact of s short-term increases in desipramine plasma concentrations (Preskorn et al, 1994).

c) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations w levels ranged from 109 to 150 ng/mL with oral doses of 300 mg at bedtime prior to fluoxetine therapy. Fo to the regimen, the desipramine serum level increased to 212 ng/mL within five days. The fluoxetine dos and the desipramine serum level was 419 ng/mL after four days. A worsening of depression and severe desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose to 200 mg dai ng/mL within two weeks (Bell & Cole, 1988).

d) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with a 40 mg daily and desipramine 150 mg daily for five weeks; fluoxetine was discontinued and the blood leve ng/mL with resolution of clinical symptoms (Goodnick, 1989).

e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant the patient's measured levels of desipramine had ranged from 148 to 160 ng/mL on a regimen of 300 mg 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a desipramine level of to 200 mg/day; eleven days later, the level was 244 ng/mL; the patient reported decreased energy, impa speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced t days. Eight days later, the desipramine level was 122 ng/mL (Downs et al, 1989).

f) Concomitant administration of fluoxetine and desipramine was reported to result in an increased desi year-old male within 10 days of the addition of fluoxetine to the patient's regimen (Preskorn et al, 1990).

3.5.1.FZ Octreotide

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

2) Summary: Octreotide and fluoxetine have been shown to prolong the QTc interval at the recommended th Prod Info Sandostatin(R), 1999). Even though no formal drug interaction studies have been done, the coadm

interval is not recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of octreotide and fluoxetine is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.GA Oxaprozin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.GB Parecoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.GC Pargyline
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental st
2) Summary: Concurrent administration or overlapping therapy with fluoxetine and a monoamine oxidase (M serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Prod Info Prozac(R), 1 1993m; Feighner et al, 1990m; Kline et al, 1989m; Suchowersky & de Vries, 1990m). Concomitant use is cor
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of fluoxetine and pargyline is contraindicated. Wait at least two wee initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before initiating
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod syndrome (Sternbach, 1991n). Serotonin syndrome is a condition of serotonergic hyperstimulation and n mental status, hyperreflexia, diaphoresis, shivering, and tremor (Sternbach, 1991n). If the syndrome is n result.
b) It has been suggested that fluoxetine therapy be discontinued for at least five weeks before beginning 28-year old woman discontinued fluoxetine for six weeks before starting therapy with tranylcypromine. O

fever, paresthesias, confusion, abdominal cramping, and various other CNS symptoms. Upon discontinu began to resolve. Blood samples taken three days after discontinuation of tranylcypromine revealed no p level was 84 ng/mL (Coplan & Gorman, 1993l).

c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylc restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressur one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, ar adverse reactions.

d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Klir insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours

e) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. drugs were discontinued, and no further details were provided. The second case involved diaphoresis, v occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinuec Rechallenge with fluoxetine alone occurred without incident.

3.5.1.GD Parnaparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2 (R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wl (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model

c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh cas a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally was discontinued. The next day the patient presented to the hospital with left-sided weakness and later d interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.GE Paroxetine

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

2) Summary: Coadministration of paroxetine with drugs that are metabolized by cytochrome P450 2D6 (CYP with caution (Prod Info Paxil CR(TM), 2002).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When paroxetine is coadministered with fluoxetine monitor patients for signs and sy sedation, urinary retention, blurred vision). Fluoxetine doses may need to be reduced.
7) Probable Mechanism: decreased cytochrome P450 2D6-mediated fluoxetine metabolism

3.5.1.GF Pentamidine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Pentamidine and fluoxetine have been shown to prolong the QTc interval at the recommended Lindsay et al, 1990). Even though no formal drug interaction studies have been done, the coadministration of recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pentamidine and fluoxetine is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.GG Pentazocine
1) Interaction Effect: hypertension, diaphoresis, ataxia, flushing, nausea, dizziness, and anxiety
2) Summary: A case of neurologic effects associated with concomitant use of fluoxetine and pentazocine has 1990a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Until more data are available, concomitant use of fluoxetine and pentazocine should
7) Probable Mechanism: unknown
8) Literature Reports
a) One study reported a case in which coadministration of fluoxetine and pentazocine was associated w male taking fluoxetine 40 mg daily was administered oral pentazocine 50 mg for a severe headache. App pentazocine, the patient became hypertensive, diaphoretic, flushed, ataxic, paresthetic, nauseated, lightl between fluoxetine and pentazocine may have occurred, a hypersensitivity to pentazocine alone was not
b) Fluoxetine administered seven days before surgery had no effect on kappa-opiate pentazocine analg produced by morphine (p less than 0.05), a mu-opiate. The duration of action of morphine analgesia was authors point out that the effect of chronic fluoxetine administration on mu-opiate analgesia is not clear a 1994).

3.5.1.GH Pentosan Polysulfate Sodium
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2((R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca
a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations.
week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril,
acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv
mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa
was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally
was discontinued. The next day the patient presented to the hospital with left-sided weakness and later c
interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim
warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.GI Phenelzine

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with fluoxetine and a monoamine oxidase (M
serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus
diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Prod Info Prozac(R), 1
1993e; Feighner et al, 1990e; Kline et al, 1989e; Suchowersky & de Vries, 1990e). Concomitant use of phene
least five weeks between discontinuation of fluoxetine and initiation of phenelzine and at least 10 days betwe
fluoxetine, or other serotoninergic agents (Prod Info Nardil(R), 1995).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of fluoxetine and phenelzine is contraindicated. Wait at least 14 day
fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before initiating therapy v
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod
syndrome (Sternbach, 1991f). Serotonin syndrome is a condition of serotonergic hyperstimulation and m
mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and c
b) It has been suggested that fluoxetine therapy be discontinued for five weeks before beginning therap
one case report describes a 28-year old woman who had discontinued a 2-year fluoxetine regimen for si
tranylcypromine. Over the next few days the patient developed fever, paresthesias, confusion, abdomina
Upon discontinuation of tranylcypromine, the patient's symptoms began to resolve. Blood samples taken
tranylcypromine revealed no presence of fluoxetine; however, the norfluoxetine level was 84 ng/mL (Cop
c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylc
restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressur
one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, ar
adverse reactions.
d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Klin
insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added
rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours
e) Two cases suggestive of an interaction between fluoxetine and selegiline were reported (Suchowersk
episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy.
drugs were discontinued, and no further details were provided. The second case involved diaphoresis, v
occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued
Rechallenge with fluoxetine alone occurred without incident.

3.5.1.GJ Phenindione

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2
(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax
threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig
taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b
warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to
protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl
patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi
mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p

SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients
treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4
corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively.
treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only
bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI
dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding
exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee
hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b
subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690
for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva
gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca
a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations.
week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril,
acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv
mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa
was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally
was discontinued. The next day the patient presented to the hospital with left-sided weakness and later d
interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim
warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.GK Phenprocoumon

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2
(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax
threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig
taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b
warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to
protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl
patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi
mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p
SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients
treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4
corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively.
treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only
bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI
dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding
exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee
hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b
subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690
for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva
gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca
a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations.
week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril,
acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv
mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa
was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally
was discontinued. The next day the patient presented to the hospital with left-sided weakness and later d
interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim
warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.GL Phenylalanine

1) Interaction Effect: increased incidence of tardive dyskinesia

2) Summary: Taking phenylalanine concomitantly with certain neuroleptic drugs may exacerbate tardive dysk phenylalanine metabolism in certain patients may lead to phenylalanine accumulation in the brain and in turn amino acids. This may interfere with the synthesis of catecholamines (Gardos et al, 1992a).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Caution is advised if phenylalanine is administered with a neuroleptic agent. Monito dyskinesia.

7) Probable Mechanism: reduced brain availability of other large neutral amino acids and interference with ca

8) Literature Reports

a) Phenylalanine tended to increase the incidence of tardive dyskinesia in patients taking neuroleptics ir studied: (1) patients with unipolar depression with tardive dyskinesia (n=11), (2) patients with no tardive greater than or equal to 100 milligrams (mg) of a chlorpromazine equivalent for at least 3 months (n=10), previously exposed to a neuroleptic drug (n=10). Neuroleptic agents were taken during the study by 6 pa Patients received powdered phenylalanine 100 mg/kilogram dissolved in orange juice after an overnight phenylalanine administration and 2 hours after administration. Three patients in group 1 (with tardive dys phenylalanine plasma levels, this group as a whole had higher (though nonsignificant) mean phenylalani dyskinesia score (measured using the Abnormal Involuntary Movements Scale (AIMS)) nonsignificantly i level and postloading AIMS scores were significantly positively correlated in group 1 (rs=0.347, p less tha p less than 0.05). Postloading phenylalanine level and baseline AIMS scores demonstrated a trend towa correlation coefficient 0.679, p less than 0.05). In all patients, phenylalanine loading increased plasma ph plasma tyrosine increased 2.5 times as a result of conversion of phenylalanine to tyrosine. Plasma levels tryptophan decreased slightly (Gardos et al, 1992).

3.5.1.GM Phenylbutazone

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of up than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.GN Phenytoin

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

2) Summary: Several case reports indicate that concurrent use of fluoxetine and phenytoin can result in sign leading to toxicity (FDA, 1994a; Jalil, 1992a; Woods et al, 1994). Alternatively, patients who are stabilized on experience subtherapeutic concentrations of phenytoin and loss of seizure control when fluoxetine is disconti vitro study, the inhibitory effects of fluoxetine on cytochrome P450 2C9 were evaluated using p-hydroxylation reflecting CYP2C9 activity. In vivo, p-hydroxylation of phenytoin depends on the formation of 5-(p-hydroxy-ph specifically the R-component of the racemic fluoxetine mixture, impaired the formation of HPPH, which can le levels (Schmider et al, 1997).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor phenytoin serum levels with the addition of fluoxetine and periodically there may be required with concomitant therapy. Serum levels of phenytoin should be monitored following the disc the long half-life of fluoxetine, decreases in phenytoin levels may not be clinically significant for a few weeks.

7) Probable Mechanism: decreased phenytoin metabolism

8) Literature Reports

a) Twenty-three reported cases of fluoxetine-phenytoin interactions have resulted in large increases in s phenytoin toxicity. On the average, the adverse effects began within two weeks after fluoxetine was adde increase in plasma levels in nine evaluable cases was 161% (range 75 to 309%) and the maximum pher

ranged from 22 to 53.5 mcg/mL (therapeutic level, 10 to 20 mcg/mL) (FDA, 1994).
b) An 84-year-old woman was stabilized on phenytoin 300 mg daily. After two months of treatment, fluox
increased to 40 mg daily after 10 days (Jalil, 1992). Within five days of starting fluoxetine, she developec
status; her phenytoin serum level had increased from 15 to 35 mcg/mL. Both phenytoin and fluoxetine w
symptoms of toxicity abated. Four weeks later she was rechallenged with the same dose of fluoxetine wi
c) In another case, a 57-year-old woman who had been stabilized on phenytoin 400 mg daily for a year
20 mg daily (Jalil, 1992). Ten days later she developed vomiting, vertigo, trunk ataxia, limb dysmetria, an
serum level was 47 mcg/mL. Fluoxetine was discontinued and all signs and symptoms of toxicity disappe
post-fluoxetine, the phenytoin serum level was 20 mcg/mL.
d) A 42-year-old male with a history of grand mal seizures and aggressive behavior was receiving pheny
daily without resolution of his problems. His phenytoin level was 2.0 ng/mL and his dose was subsequen
daily was added for aggression, and the patient experienced resolution of his behavioral problems and a
level ranged between 10.9 ng/mL and 15.7 ng/mL during fluoxetine therapy. However, the patient discon
experienced a recurrence of problems. Phenytoin concentration was measured at 6.6 ng/mL six weeks a
change in his phenytoin dose. This case report illustrates the need for close monitoring of phenytoin leve
since subtherapeutic levels of phenytoin may result if doses of phenytoin are not readjusted following the
1999).

3.5.1.GO Pimozide

1) Interaction Effect: bradycardia, somnolence, and potentially increased risk of cardiotoxicity (QT prolongati
2) Summary: One case of bradycardia and somnolence resulting from concomitant fluoxetine and pimozide t
Although a specific interaction study has not been conducted with these agents, due to the potential for additi
of fluoxetine and pimozide is contraindicated (Prod Info PROZAC(R) oral capsule, oral pulvule, oral solution,
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Due to the possibility of additive effects on the QT interval, the concurrent administr
contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) One case has been reported in which concurrent use of pimozide 5 mg daily and fluoxetine 20 mg da
bradycardia and somnolence. The pulse rate gradually returned to normal after discontinuation of pimozi
a higher fluoxetine dose also resulted in bradycardia (Ahmed et al, 1993).

3.5.1.GP Pirazolac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl
petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L
CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.GQ Pirmenol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class
prolong the QTc interval is not recommended (Prod Info Quinaglute Dura-tabs(R), 1999). Fluoxetine has dem
(Prod Info Prozac(R), 2001z).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class Ia antiarrhythmic agents and agents that pro
recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.GR Piroxicam

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.GS Pirprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.GT Prajmaline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class prolong the QTc interval is not recommended (Prod Info Quinaglute Dura-tabs(R), 1999). Fluoxetine has dem (Prod Info Prozac(R), 2001z).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class Ia antiarrhythmic agents and agents that pro recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.GU Probucol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Fluoxetine and probucol have been shown to prolong the QTc interval at the recommended the Gohn & Simmons, 1992; Prod Info Lorelco(R), 1991). Even though no formal drug interaction studies have be prolong the QTc interval is not recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and probucol is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.GV Procainamide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class prolong the QTc interval is not recommended (Prod Info Quinaglute Dura-tabs(R), 1999). Fluoxetine has dem

(Prod Info Prozac(R), 2001z).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class Ia antiarrhythmic agents and agents that pro recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.GW Procarbazine
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with fluoxetine and a monoamine oxidase (M serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Prod Info Prozac(R), 1 1993a; Feighner et al, 1990a; Kline et al, 1989a; Suchowersky & de Vries, 1990a). Concomitant use is contra
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: established
6) Clinical Management: Concurrent use of fluoxetine and procarbazine is contraindicated. Wait at least two initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before initiating
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod syndrome (Sternbach, 1991a). Serotonin syndrome is a condition of serotonergic hyperstimulation and m mental status, hyperreflexia, diaphoresis, shivering, and tremor (Sternbach, 1991a). If the syndrome is n result.
b) It has been suggested that fluoxetine therapy be discontinued for at least five weeks before beginning 28-year old woman discontinued fluoxetine for six weeks before starting therapy with tranylcypromine. O fever, paresthesias, confusion, abdominal cramping, and various other CNS symptoms. Upon discontinu began to resolve. Blood samples taken three days after discontinuation of tranylcypromine revealed no p level was 84 ng/mL (Coplan & Gorman, 1993).
c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylc restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressur one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, ar adverse reactions.
d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Klir insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours
e) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. drugs were discontinued, and no further details were provided. The second case involved diaphoresis, v occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued Rechallenge with fluoxetine alone occurred without incident.

3.5.1.GX Prochlorperazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturers of some phenothiazines state that concomitant use not recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Inf 2002; Prod Info Thorazine(R), 2002) . Other phenothiazines may have similar effects, though no reports are a the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and a phenothiazine is not recommende
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.GY Propafenone
1) Interaction Effect: increased serum propafenone concentrations and an increased risk of cardiotoxicity (QT arrest)
2) Summary: Propafenone has been shown to prolong the QTc interval (Larochelle et al, 1984). Fluoxetine h recommended therapeutic dose (Prod Info Prozac(R), 2001e). Even though no formal drug interaction studies known to prolong the QT interval are used concomitantly. In addition, fluoxetine may inhibit cytochrome P450 propafenone (Cai et al, 1999a).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Caution is advised if fluoxetine and propafenone are used concomitantly.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated propafenone metabolism; theoretical a
8) Literature Reports

a) The metabolism of propafenone enantiomers was altered after fluoxetine treatment in 9 healthy Chine CYP2D6 metabolizers. Subjects received a single oral dose of propafenone 400 mg both before and afte clearance of both S- and P- enantiomers of propafenone decreased from approximately 75 L/hr to 50 L/h Compared to baseline, the elimination half life, peak concentration, and area under the curve for both en significantly increased (Cai et al, 1999).

3.5.1.GZ Propranolol

1) Interaction Effect: an increased risk of complete heart block
2) Summary: Metabolism of propranolol occurs in the liver and is thought to involve cytochrome P450IID6 (C CYP2D6 (DeVane, 1994a). It is theoretically possible that coadministered fluoxetine could inhibit propranolol concentrations of this beta blocker and possible toxicity. One case report describes a man who developed co was added to propranolol therapy (Drake & Gordon, 1994a).
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Fluoxetine should be prescribed cautiously to patients on propranolol therapy. A ba prior to the initiation of fluoxetine.
7) Probable Mechanism: impaired atrioventricular conduction
8) Literature Reports
a) A 53-year-old male experienced a loss of consciousness two weeks after fluoxetine 20 mg daily was included propranolol 40 mg twice daily for anxiety. He had no previous cardiac history. An electrocardiog fluoxetine and propranolol were both discontinued. Two days later, the patient reverted to sinus rhythm v heart block was attributed to the fluoxetine-propranolol combination, since sinus rhythm returned two day patient had no previous complications from propranolol therapy. Because 5-hydroxytryptamine (5-HT) re fluoxetine may have potentiated the action of 5-HT, causing impaired atrioventricular conduction (Drake

3.5.1.HA Propyphenazone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.HB Proquazone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.HC Quetiapine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs known fluoxetine, is not recommended. Several antipsychotic agents have demonstrated QT prolongation including quetiapine (Owens, 2001b), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), and zotepine (Swe
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and antipsychotics is not recommended
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.HD Quinidine

1) Interaction Effect: an increased risk of fluoxetine and quinidine toxicity and an increased risk of cardiotoxic cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class drugs known to prolong the QTc interval is not recommended (Prod Info Quinaglute Dura-tabs(R), 1999a). Fl therapeutic doses (Prod Info Prozac(R), 2001af). In addition, quinidine inhibits CYP2D6 which may reduce flu 1993b) and fluoxetine inhibits CYP3A4, which may reduce quinidine metabolism (Nemeroff et al, 1996).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of Class Ia antiarrhythmic agents, such as quinidine, fluoxetine, is not recommended.
7) Probable Mechanism: altered fluoxetine or quinidine metabolism; additive effects on QT prolongation
8) Literature Reports
a) In vitro studies found that quinidine, a potent inhibitor of CYP2D6, inhibited fluoxetine N-demethylatio indicating that fluoxetine is, in part, metabolized by CYP2D6, this study showed that much of fluoxetine n

3.5.1.HE Rasagiline

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with selective serotonin reuptake inhibitors, in the selective MAO-B inhibitor selegiline, has been reported to cause serious, sometimes fatal reactions. Sign myoclonus, autonomic instability with rapid vital sign fluctuations, and mental status changes progressing to e reactions have been reported with serotonin-norepinephrine reuptake inhibitors (SNRIs) and non-selective M not allow concomitant use of fluoxetine; the combination of rasagiline and fluoxetine should be avoided. Wait before initiating fluoxetine therapy. Wait at least five weeks or more, especially if fluoxetine has been used ch fluoxetine before initiating therapy with rasagiline (Prod Info AZILECT(R) oral tablets, 2006).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concurrent use of fluoxetine and rasagiline should be avoided. Wait at least two we fluoxetine therapy. Wait at least five weeks or more, especially if fluoxetine has been used chronically and/or before initiating therapy with rasagiline.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod syndrome (Sternbach, 1991l). Serotonin syndrome is a condition of serotonergic hyperstimulation and m mental status, hyperreflexia, diaphoresis, shivering, and tremor (Sternbach, 1991l). If the syndrome is nc result.

3.5.1.HF Reviparin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2 (R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to

protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally was discontinued. The next day the patient presented to the hospital with left-sided weakness and later c interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.HG Risperidone

1) Interaction Effect: increased plasma concentrations of risperidone
2) Summary: Concomitant use of fluoxetine (CYP2D6 inhibitor) and risperidone (CYP2D6 substrate) has res concentrations and an increased risk of risperidone adverse effects such as serotonin syndrome, QT prolong mechanism of action is inhibition of CYP2D6-mediated metabolism of risperidone by fluoxetine. One study de patients treated concurrently with fluoxetine and risperidone (Prod Info RISPERDAL(R) oral tablets, oral solut al, 2002). Monitoring the patient for increased risperidone plasma levels side effects may be necessary (Spin reevaluated if fluoxetine is initiated or discontinued (Prod Info RISPERDAL(R) oral tablets, oral solution, orally 2002a).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concomitant use of fluoxetine and risperidone has resulted in increased risperidone risperidone side effects (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegrating tablets, 200 plasma risperidone levels and side effects (serotonin syndrome, extrapyramidal symptoms, and cardiotoxicity risperidone (Spina et al, 2002). Reevaluate the dose of risperidone when concomitant fluoxetine is initiated or tablets, oral solution, orally disintegrating tablets, 2008).
7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of risperidone
8) Literature Reports
a) Fluoxetine (a CYP2D6 inhibitor) 20 mg/day has been shown to increase the plasma concentration of fold. Fluoxetine did not affect the concentration of 9-hydroxyrisperidone. The dosage of risperidone shou discontinued (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegrating tablets, 2008).
b) Fluoxetine, an inhibitor of cytochrome CYP2D6, may impair the elimination of risperidone, primarily b hydroxylation and, to a lesser extent, by simultaneously affecting the further metabolism of 9-hydroxyrisp risperidone biotransformation. In an open, 4-week, pharmacokinetic study including 9 patients with schiz type, risperidone concentrations increased when fluoxetine was coadministered with risperidone. Patient to 6 mg/day for at least four weeks and received adjunctive fluoxetine therapy 20 mg/day for the manage risperidone concentrations increased from 12 ng/mL at baseline to 49 nanograms (ng)/mL (p less than 0 at week 4. Plasma concentrations of 9-hydroxyrisperidone (9-OH-risperidone) showed no significant incr weeks of concurrent therapy, the active moiety (risperidone plus 9-OH-risperidone) was increased by 75 compared with baseline. The mean plasma risperidone to 9-OH-risperidone ratio also increased significa symptoms during week 2 of concomitant therapy and were treated with anticholinergic medication. The a risperidone levels may be warranted in patients receiving concomitant fluoxetine and risperidone treatme

3.5.1.HH Ritonavir

1) Interaction Effect: reduced olanzapine effectiveness
2) Summary: An open-label study involving 14 healthy volunteers revealed a significant alteration in pharma exposure of olanzapine when administered in the presence of ritonavir. Baseline blood samples were drawn 10 mg tablet. Venous blood samples were then obtained at specified times. After a 14-day washout period, s then 400 mg BID for 4 days, then 500 mg BID for 4 days. Blood samples were again drawn at specified times

were as follows: Statistically significant reductions in the mean olanzapine area under the plasma concentrati 235 (ng)hr/mL) (p less than 0.001); the half-life by 50% (from 32 hr to 16 hr) (p less than 0.00001) and the pe to 9 ng/mL) (p less than 0.002). The oral clearance of olanzapine increased by 115% (from 20 L/hr to 43 L/hr usually well-tolerated and a clear relationship between plasma concentrations and toxicity has not been defin needs further study (Penzak et al, 2002).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor patients for olanzapine efficacy. Doses of olanzapine may need to be adjus Patients stabilized on olanzapine and ritonavir, who have their ritonavir discontinued, should have be monitor increased systemic exposure to olanzapine.
7) Probable Mechanism: induction or CYP1A2- and glucuronosyl transferase-mediated metabolism of olanza

3.5.1.HI Ritonavir
1) Interaction Effect: alterations in cardiac and/or neurologic function
2) Summary: Coadministration of fluoxetine 30 mg twice daily for eight days and ritonavir 600 mg as a single in the area under the concentration-time curve (AUC) of ritonavir but no changes in the ritonavir maximum co experience has revealed reports of cardiac and neurologic events when ritonavir and fluoxetine have been co
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Monitor the patient for changes in cardiac and/or neurologic function.
7) Probable Mechanism: unknown

3.5.1.HJ Rizatriptan
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concon 1 (5HT-1) agonist, and a serotonin specific reuptake inhibitor (SSRI) (Prod Info Imitrex(R), 1998). Because ri similar interaction between SSRIs and rizatriptan may occur (Prod Info Maxalt(R), 1998a). Concurrent use of syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, halluci rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and c may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different syndrome with patients who are prescribed this combination and monitor them closely for symptoms of seroto Administration, 2006).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as rizatriptan, and an SSRI may result in a life-th Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be pr are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms hyperthermia, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) Twelve healthy volunteers received paroxetine 20 mg daily for two weeks and a single dose of rizatrip were not altered by the administration of paroxetine (Prod Info Maxalt(R), 1998).

3.5.1.HK Rofecoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.HL Selegiline

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with fluoxetine and selegiline may result in Cl hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental sta tremor. Serious, even fatal, reactions have been reported (Prod Info Prozac(R), 1999g; Sternbach, 1991m; C Kline et al, 1989k; Suchowersky & de Vries, 1990k). Concomitant use is contraindicated. A minimum of 14 da before initiating therapy with fluoxetine. At least five weeks should elapse after discontinuing fluoxetine prior t EMSAM(R) transdermal patch, 2006).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of fluoxetine and selegiline is contraindicated. Wait at least two wee fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before initiating therapy v
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod syndrome (Sternbach, 1991l). Serotonin syndrome is a condition of serotonergic hyperstimulation and m mental status, hyperreflexia, diaphoresis, shivering, and tremor (Sternbach, 1991l). If the syndrome is nc result.
b) It has been suggested that fluoxetine therapy be discontinued for five weeks before beginning therap one case report describes a 28-year old woman who had discontinued a 2-year fluoxetine regimen for si tranylcypromine. Over the next few days the patient developed fever, paresthesias, confusion, abdomina Upon discontinuation of tranylcypromine, the patient's symptoms began to resolve. Blood samples taken tranylcypromine revealed no presence of fluoxetine; however, the norfluoxetine level was 84 ng/mL (Cop
c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylc restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressur one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, ar adverse reactions.
d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Klin insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours
e) Two cases suggestive of an interaction between fluoxetine and selegiline were reported (Suchowersk episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. drugs were discontinued, and no further details were provided. The second case involved diaphoresis, v occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinued Rechallenge with fluoxetine alone occurred without incident.

3.5.1.HM Sematilide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class prolong the QTc interval is not recommended (Allen et al, 2002; Prod Info Tikosyn(TM) dofetilide capsules, 19 been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that pro recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.HN Sertindole
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs know fluoxetine, is not recommended. Several antipsychotic agents have demonstrated QT prolongation including quetiapine (Owens, 2001b), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), and zotepine (Sw
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and antipsychotics is not recommended
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.HO Sibrafiban
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified

5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 200
7) Probable Mechanism: unknown

3.5.1.HP Sibutramine
1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, ment
2) Summary: Sibutramine inhibits the reuptake of norepinephrine, dopamine, and serotonin. In addition, the t M2, also inhibit the reuptake of these neurotransmitters. A hyperserotonergic state, termed serotonin syndror concurrently with a selective serotonin reuptake inhibitor. Coadministration of sibutramine and selective serot (Prod Info Meridia(R), 1997).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Sibutramine should not be administered with serotonergic agents, including selectiv increased risk of serotonin syndrome.
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, m hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated

3.5.1.HQ Sotalol
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class prolong the QTc interval is not recommended (Allen et al, 2002; Prod Info Tikosyn(TM) dofetilide capsules, 1 been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that pro recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.HR Spiramycin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Spiramycin and fluoxetine have been shown to prolong the QTc interval at the recommended t Stramba-Badiale et al, 1997). Even though no formal drug interaction studies have been done, the coadminis interval is not recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of spiramycin and fluoxetine is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.HS St John's Wort
1) Interaction Effect: reduced olanzapine efficacy
2) Summary: This interaction is based on in vitro information that St. John's Wort induced CYP1A2 enzymes reduced blood theophylline concentrations and loss of efficacy (Nebel et al, 1999). Since olanzapine is metab olanzapine may be similarly affected. If St. John's Wort and olanzapine are taken together, their dosages sho that increased dosages of olanzapine may be required. Discontinuation of St. John's Wort should be done ca increase and dose reduction may be required.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of olanzapine with St. John's Wort. If patients elect to remai consistent dosing. Olanzapine dosage may need to be increased. Patients should not discontinue St. John's downward adjustments in olanzapine dose may be necessary as well as monitoring for increased side effects constipation, dry mouth, asthenia).
7) Probable Mechanism: induction of cytochrome P450 1A2 enzymes by St. John's Wort

3.5.1.HT St John's Wort
1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, ment
2) Summary: Case reports describe the onset of serotonin syndrome-like symptoms, mania, and hypomania sertraline, fluoxetine, and paroxetine therapy (Spinella & Eaton, 2002c; Barbanel et al, 2000a; Waksman et a a syndrome resembling sedative/hypnotic intoxication after adding St. John's Wort to paroxetine therapy (Go serotonin reuptake and may have mild monoamine oxidase inhibitory activity (Singer et al, 1999; Thiede & W serotonin reuptake inhibitors may result in serotonin syndrome.
3) Severity: major

4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Patients should be advised to wait two weeks after stopping St. John's Wort before therapy. If a patient plans to replace selective serotonin reuptake inhibitor (SSRI) therapy with St. John's Wor taken into consideration, waiting at least 5 half-lives for the SSRI to be metabolized out of the body.
7) Probable Mechanism: additive serotonergic effect
8) Literature Reports

a) Five cases have been reported of serotonin syndrome in the elderly after combining prescription antic developed dizziness, nausea, vomiting and a headache 4 days after starting St. John's Wort 300 milligra sertraline 50 mg daily. Her symptoms resolved 2 to 3 days after stopping all medications. Case 2 develo after starting St. John's Wort 300 mg twice daily combined with sertraline 75 mg daily. His symptoms res medications, and he resumed sertraline use without complications. The third case developed nausea, vo starting St. John's Wort 300 mg twice daily combined with sertraline 50 mg daily. His symptoms improve and taking cyproheptadine 4 mg three times daily. Case 4 developed nausea, anxiety, restless, and irrita three times daily combined with sertraline 50 mg daily. Cyproheptadine 4 mg twice daily was administere 1 week after stopping the medication. Cases 1 through 4 resumed their prescriptive sertraline after symp Case 5 developed nausea, vomiting and restlessness 3 days after starting St. John's Wort 300 mg three twice daily. She continued to take St. John's Wort but discontinued the nefazodone and over 1 week her therapy with nefazodone, but continued therapy with St. John's Wort and mild to moderate symptoms of 1999).

b) A 50-year-old female taking St. John's Wort 600 mg daily experienced symptoms of sedative intoxica paroxetine 20 mg. She was incoherent, groggy, slow-moving, and complained of nausea and weakness. receiving paroxetine 40 mg daily for eight months without adverse effects. After a night of sleep, she retu 1998).

c) A 61-year-old female experienced restlessness and involuntary movements of her extremities after b after discontinuing St. John's Wort 600 mg daily. The patient reported agitation and akathisia 8 hours aft presented with diaphoresis and involuntary movement of all extremities with hyperreflexia and rigidity. Bl normal. After admission, blood pressure increased to 200/116 mmHg and heart rate increased to 145 be 212 units/liter (U/L) initially to 1024 U/L. The patient was managed with supportive care and lorazepam a 2000).

d) A 28-year-old male developed a manic syndrome following comedication with St. John's Wort and se replacement therapy following bilateral orchidectomy 2 years earlier, but testosterone levels were subthe 50 milligrams daily for depression following a 2 week trial of St. John's Wort per patient preference (dose patient was instructed to discontinue St. John'sWort, but continued it despite this advice. The patient exp physician, believing that he did not need further treatment. Over 2 months, the patient had elated mood, could not afford, and was ultimately arrested for stealing fuel for the car. On arrest, he was referred to ps disinhibition. He was observed to be over-aroused, distractible, have flight of ideas, and grandiose delus The authors state the possibility of the manic state resulting from sertraline therapy alone, and that St. Jo result of monoamine oxidase inhibition. Since the patient's testosterone level was subnormal, the possibi considered low. However, the patient had elevated gonadotropin levels (luteinizing hormone and follicle- predisposed the patient to mania (Barbanel et al, 2000).

e) A 42-year-old female experienced symptoms consistent with a mixed hypomanic episode following co biloba, and St. John's Wort. The symptoms resolved following discontinuation of Ginkgo and St. John's V depression following a mild traumatic brain injury with fluoxetine 20 milligrams (mg) twice daily and busp presentation, buspirone was increased to 20 mg twice daily for persistent anxiety and the patient began t Wort in unspecified doses. Melatonin was considered unlikely to have contributed to her symptoms. Gink possible contributors since they may potentiate antidepressants, and considering the temporal relationsh symptoms and discontinuation of the herbs and resolution of symptoms. However, the brain injury was c Eaton, 2002b).

3.5.1.HU Sulfamethoxazole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cotrimoxazole and fluoxetine have been shown to prolong the QTc interval at the recommende 2001ah; Lopez et al, 1987). Even though no formal drug interaction studies have been done, the coadministra is not recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of cotrimoxazole and fluoxetine is not recommended
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.HV Sulfinpyrazone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; release capsules, solution, 2008).
3) Severity: major

4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 200
7) Probable Mechanism: unknown

3.5.1.HW Sulindac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.HX Sulodexide
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 200
7) Probable Mechanism: unknown

3.5.1.HY Sultopride
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs know fluoxetine, is not recommended. Several antipsychotic agents have demonstrated QT prolongation including quetiapine (Owens, 2001b), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), and zotepine (Sw
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and antipsychotics is not recommended
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.HZ Sumatriptan
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concon reuptake inhibitor (SSRI) (Prod Info Imitrex(R), 2002). Concurrent use of a triptan and an SSRI may result in threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be awa intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the ri prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Dr
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as sumatriptan, and an SSRI, such as fluoxetine serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan o physician. If these agents are used together, discuss the risks of serotonin syndrome with the patient and mo (restlessness, hyperthermia, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

8) Literature Reports
a) In the Canadian post-marketing surveillance program of fluoxetine, six cases of suspected drug intera these cases, two are strongly suggestive of a drug interaction. Patients demonstrated symptoms consist 1997).

3.5.1.IA Suprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.IB Tamoxifen
1) Interaction Effect: decreased tamoxifen efficacy
2) Summary: A retrospective analysis revealed a 1.9-fold higher breast cancer recurrence rate in patients re tamoxifen than those receiving tamoxifen alone (Aubert, Stanek, and Yao, 2009). Coadministration of tamoxi fluoxetine, may inhibit the CYP2D6-mediated metabolism of tamoxifen to the active metabolite, endoxifen. M concomitantly with tamoxifen closely for loss of tamoxifen efficacy.
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of fluoxetine and tamoxifen may result in decreased concentratior thereby decreasing tamoxifen efficacy. If administered concurrently, monitor closely for decreased tamoxifen
7) Probable Mechanism: inhibition of CYP2D6-mediated tamoxifen metabolism to endoxifen (active metaboli
8) Literature Reports
a) A retrospective analysis of breast cancer patients revealed a 1.9-fold higher 2-year recurrence rate of therapy with tamoxifen and a CYP2D6 inhibitor compared with those receiving tamoxifen therapy alone. 1928 patients who were new to tamoxifen therapy in a 30-month period and who had follow-up data for a Among these patients, 353 (median age, 53 years) received tamoxifen concurrently with a CYP2D6 inhib tamoxifen alone. Disease recurrence was identified by diagnosis and insurance billing codes for mastect radiation therapy, occurring at least 6 months after initiation of tamoxifen therapy. The 2-year breast can receiving concomitant tamoxifen and CYP2D6 inhibitor therapy compared with 7.5% in women receiving hazard ratio, 1.92). Intervention procedures in the tamoxifen/CYP2D6 inhibitor group to treat breast canc (36%), and radiation therapy (47%); corresponding intervention rates in the tamoxifen only group were 5 and Yao, 2009).

3.5.1.IC Tamsulosin
1) Interaction Effect: an increase in tamsulosin plasma exposure
2) Summary: In vitro data have shown that tamsulosin is primarily metabolized by CYP2D6 and CYP3A4 hep a mild inhibitor of CYP450 enzymes, resulted in moderate increases in tamsulosin plasma exposure. Althoug conducted with moderate or strong CYP2D6 inhibitors, such as fluoxetine, use caution if these agents are co tamsulosin doses exceeding 0.4 mg (Prod Info FLOMAX(R) oral capsules, 2007). Patients should be monitor as postural hypotension, dizziness, and syncope.
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for increased tamsulosin plasma exposures, use caution when fluoxetine, are coadministered with tamsulosin, particularly at tamsulosin doses higher than 0.4 mg (Prod Info patients for increased tamsulosin adverse effects (postural hypotension, dizziness, and episodes of syncope)
7) Probable Mechanism: potential inhibition of CYP2D6-mediated tamsulosin metabolism

3.5.1.ID Tapentadol
1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental s
2) Summary: Concurrent use of tapentadol and a selective serotonin reuptake inhibitor (SSRI) may result in

threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea (Prod Info tapentadol imm
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of tapentadol and an SSRI may result in a life-threatening conditic used together, monitor the patient closely for symptoms of serotonin syndrome (restlessness, hyperthermia, l treatment initiation and dose increases (Prod Info tapentadol immediate release oral tablets, 2008).
7) Probable Mechanism: additive serotonergic effect

3.5.1.IE Tedisamil
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class prolong the QTc interval is not recommended (Allen et al, 2002; Prod Info Tikosyn(TM) dofetilide capsules, 19 been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that pro recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.IF Telithromycin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, telithromycin should be coadn also known to prolong the QTc interval, including fluoxetine (Owens, 2001d; Prod Info Prozac(R), 2001o).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of telithromycin with other agents that can prolong th recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.IG Tenidap
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of up than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.IH Tenoxicam
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar

hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.II Terfenadine

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although 2 cases have been reported in which concomitant terfenadine and fluoxetine resulted
heart disease, a study of 12 healthy males demonstrated no significant pharmacokinetic or pharmacodynami
(Swims, 1993a; Marchiando & Cook, 1995a; Bergstrom et al, 1997a). Terfenadine and fluoxetine have been
doses. The administration of terfenadine with any other medication that may prolong the QT interval is contra
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The concomitant administration of fluoxetine and terfenadine is contraindicated.
7) Probable Mechanism: decreased terfenadine metabolism
8) Literature Reports
a) In a study of 12 healthy male volunteers, fluoxetine did not inhibit the metabolism of terfenadine. Fluo
Terfenadine 60 mg was given alone and after eight days of the nine-day fluoxetine regimen. A high dose
interaction rigorously. Subject were monitored for changes in terfenadine pharmacokinetics and adverse
slight decrease in terfenadine plasma concentration. In addition, the area under the plasma concentratio
decreased by fluoxetine. No change in blood pressure, heart rate, or cardiac electrographic tracings (EK
dizziness after taking terfenadine alone and one subject had an abnormal EKG at baseline and during al
1997).
b) A 39-year old woman experienced cardiac toxicity due to a possible interaction of terfenadine and flu
patient's medications included acyclovir, beclomethasone, pseudoephedrine, and ibuprofen. During hosp
program, the patient was started on fluoxetine 40 mg daily, terfenadine 60 mg twice daily, and disulfiram
patient underwent a routine electrocardiogram (ECG) study that revealed a prolonged QT interval of 550
had no prior history of heart disease. Terfenadine was discontinued, and an ECG taken one week later r
c) A case report describes a possible interaction with terfenadine and fluoxetine in a 41-year-old male w
beats, and shortness of breath a month after institution of fluoxetine 20 mg daily; he had no previous hist
fluoxetine, terfenadine 60 mg twice daily, ibuprofen 800 mg three times daily, misoprostol 100 mcg four t
dichloralphenazone 100 mg, isometheptene mucate 65 mg) as needed, and ranitidine 150 mg twice daily
frequent sinus tachycardia, three isolated atrial premature contractions, and three couplets. Terfenadine
symptoms did not reoccur. Fluoxetine is a known enzyme inhibitor and may have inhibited terfenadine m
seen in this patient (Swims, 1993).

3.5.1.IJ Tetrabenazine

1) Interaction Effect: increased risk of QT interval prolongation, neuroleptic malignant syndrome, extrapyram
2) Summary: Tetrabenazine causes a small increase in the correct QT interval. As the degree of prolongatio
torsade de pointes-type VT. The concomitant use of tetrabenazine with other drugs known for QT prolongatic
randomized, double-blind, placebo controlled crossover study of healthy subjects, the effect of a single 25 mg
interval was studied with moxifloxacin as a positive control. The 50 mg dose of tetrabenazine caused an appr
(Prod Info XENAZINE(R) oral tablets, 2008). In addition to QT prolongation, tetrabenazine may also cause ac
syndrome and extrapyramidal disorders, which may be exaggerated when coadministered with neuroleptic dr
oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of tetrabenazine with olanzapine or other neuroleptic drugs may ir
as QT interval prolongation and increased risk of torsade de pointes. Other adverse reactions, such as neuro
disorders may be enhanced when given with a dopamine agonist such as olanzapine (Prod Info XENAZINE(I
7) Probable Mechanism: increased dopamine levels; additive effects on QT interval prolongation

3.5.1.IK Tetrabenazine

1) Interaction Effect: increased exposure to tetrabenazine
2) Summary: Caution should be used when administering a strong CYP2D6 inhibitor (eg, fluoxetine, paroxet
substrate), and the daily dose of tetrabenazine should be halved if fluoxetine and tetrabenazine are used con
tetrabenazine given after 10 days of daily administration of paroxetine 20 mg, an increase in tetrabenazine ex
When compared with tetrabenazine alone, coadministration with paroxetine caused an approximately 30% in
of the alpha-HTBZ metabolite of tetrabenazine. Subjects given paroxetine prior to tetrabenazine alone experi
increase in the AUC of the beta-HTBZ metabolite of tetrabenazine. The elimination half-life for both metabolit
tetrabenazine was coadministered with paroxetine (Prod Info XENAZINE(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable

6) Clinical Management: Use caution when prescribing fluoxetine to patients who take tetrabenazine. Patient tetrabenazine should have their daily dose of tetrabenazine decreased by half if coadministration with fluoxet and tetrabenazine may cause elevated tetrabenazine levels. Monitor for increased tetrabenazine side effects depression, anxiety, akathisia, and nausea (Prod Info XENAZINE(R) oral tablets, 2008).
7) Probable Mechanism: inhibition of CYP2D6-mediated tetrabenazine metabolism by fluoxetine

3.5.1.IL Thioridazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Fluoxetine inhibits the metabolism of thioridazine through inhibition of CYP2D6. The resulting e prolongation (Prod Info Mellaril(R), 2000). Fluoxetine has been shown to prolong the QTc interval at the reco 2001ae). Although citing no data, the manufacturer of thioridazine states that concomitant use with other drug contraindicated (Prod Info Mellaril(R), 2000).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and thioridazine is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated thioridazine metabolism; additive effec

3.5.1.IM Tiaprofenic Acid
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of up than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.IN Ticlopidine
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 200
7) Probable Mechanism: unknown

3.5.1.IO Tinzaparin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2 (R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b

warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally was discontinued. The next day the patient presented to the hospital with left-sided weakness and later c interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.IP Tipranavir
1) Interaction Effect: increased fluoxetine plasma concentrations
2) Summary: Although the drug interaction between fluoxetine and tipranavir/ritonavir has not been studied, tipranavir/ritonavir may result in increased fluoxetine plasma concentrations. Fluoxetine doses may need to b initiated (Prod Info APTIVUS(R) oral capsules, solution, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of fluoxetine and tipranavir/ritonavir may increase fluoxet these agents are coadministered and consider adjusting the fluoxetine dose as needed upon initiation of tipra capsules, solution, 2008).
7) Probable Mechanism: unknown

3.5.1.IQ Tirofiban
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008; release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 200
7) Probable Mechanism: unknown

3.5.1.IR Tolmetin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent

Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.IS Toloxatone

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental st
2) Summary: Concurrent administration or overlapping therapy with fluoxetine and a monoamine oxidase (M serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Prod Info Prozac(R), 1 1993c; Feighner et al, 1990c; Kline et al, 1989c; Suchowersky & de Vries, 1990c). As a reversible and selecti not potentiate the effects of selective serotonin reuptake inhibitors to the same frequency, extent, and duratio further studies confirm the safety and efficacy of this combined therapy, concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of fluoxetine and toloxatone is contraindicated. Wait at least two we initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before initiating
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod syndrome (Sternbach, 1991c). Serotonin syndrome is a condition of serotonergic hyperstimulation and m mental status, hyperreflexia, diaphoresis, shivering, and tremor (Sternbach, 1991c). If the syndrome is n result.
b) It has been suggested that fluoxetine therapy be discontinued for at least five weeks before beginnin 28-year old woman discontinued fluoxetine for six weeks before starting therapy with tranylcypromine. O fever, paresthesias, confusion, abdominal cramping, and various other CNS symptoms. Upon discontinu began to resolve. Blood samples taken three days after discontinuation of tranylcypromine revealed no p level was 84 ng/mL (Coplan & Gorman, 1993b).
c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylc restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressur one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, ar adverse reactions.
d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Klir insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours
e) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. drugs were discontinued, and no further details were provided. The second case involved diaphoresis, v occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinuec Rechallenge with fluoxetine alone occurred without incident.

3.5.1.IT Tramadol

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Concurrent use of olanzapine with mirtazapine and tramadol in a 53-year-old male resulted in s Fetchko, 2002). If olanzapine is used concomitantly with mirtazapine and/or tramadol, monitor closely for sym syndrome can be life-threatening. If serotonin syndrome develops, discontinue the offending agents and prov necessary (Boyer & Shannon, 2005).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: A case of serotonin syndrome was reported with coadministration of olanzapine, mi 2002). If 2 or more of these drugs are are used concomitantly, monitor closely for symptoms of serotonin syn (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic h diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation an threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care a Shannon, 2005).
7) Probable Mechanism: additive serotonergic pharmacologic effects
8) Literature Reports
a) A 53-year-old male on mirtazapine and tramadol experienced serotonin syndrome 8 days after olanz mirtazapine 45 mg/day for depression and tramadol 150 mg/day for chronic back pain. Olanzapine 10 m was admitted 8 days later after being found by the police wandering the streets in inappropriate dress an afebrile, tachycardic (120 bpm), and had flushing, twitching of his face, tremors, myoclonus, hyperreflexi agitated. He spoke with a stutter. He had marked derailment, appeared perplexed, had prominent percep hallucinations. The creatine phosphokinase was normal. All medications were discontinued and within 1

Fetchko, 2002).

3.5.1.IU Tramadol

1) Interaction Effect: an increased risk of seizures and serotonin syndrome (hypertension, hyperthermia, myo concentrations of tramadol and decreased concentrations of tramadol active metabolite, M1

2) Summary: Seizures and serotonin syndrome have been reported in patients using tramadol. Some medic the seizure threshold. The risk of seizures and serotonin syndrome may be enhanced when fluoxetine and tra (R), 2001). Fluoxetine is also an inhibitor of CYP2D6, and concomitant administration with tramadol may resu decreases in active metabolite, M1, concentrations. This may cause an increase in side effects or a reductior ULTRAM(R)ER extended-release oral tablets, 2005).

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Caution should be used if tramadol is to be administered to patients receiving conc combination, especially in patients with underlying conditions that might predispose to seizures. Observe the serotonin syndrome. Also, monitor patients for signs and symptoms of narcotic toxicity (extreme sedation, res analgesic effect of tramadol.

7) Probable Mechanism: increased concentration of serotonin in the nervous system and periphery; inhibitio active metabolite by quinidine

8) Literature Reports

a) The combination of tramadol and fluoxetine may result in serotonin syndrome and mania. A 72-year-o treated with fluoxetine for the past 10 years. She was prescribed tramadol 150 mg daily for articular pain began to feel nervous, had a temperature of 37.2 C, piloerection, and muscular contractions. She discon symptoms disappeared. She was still agitated, euphoric, hyperactive, had rapid speech, paranoid ideatic hospitalized and haloperidol treatment was initiated, however, her symptoms continued. She was readm olanzapine was initiated. Two weeks later she became euthymic and continued olanzapine therapy after for inducing mania and serotonergic syndrome when using tramadol combined with SSRIs must be cons

3.5.1.IV Tranylcypromine

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta

2) Summary: Concurrent administration or overlapping therapy with fluoxetine and a monoamine oxidase (M serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Prod Info Prozac(R), 1 1993q; Feighner et al, 1990q; Kline et al, 1989q; Suchowersky & de Vries, 1990q; Sternbach, 1988a). Conco

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of fluoxetine and tranylcypromine is contraindicated. Wait at least tw before initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before in

7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase

8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod syndrome (Sternbach, 1991r). Serotonin syndrome is a condition of serotonergic hyperstimulation and m mental status, hyperreflexia, diaphoresis, shivering, and tremor (Sternbach, 1991r). If the syndrome is nc result.

b) It has been suggested that fluoxetine therapy be discontinued for five weeks before beginning therap one case report describes a 28-year old woman who had discontinued a 2-year fluoxetine regimen for si tranylcypromine. Over the next few days the patient developed fever, paresthesias, confusion, abdomina Upon discontinuation of tranylcypromine, the patient's symptoms began to resolve. Blood samples taken tranylcypromine revealed no presence of fluoxetine; however, the norfluoxetine level was 84 ng/mL (Cop

c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylc restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressur one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, ar adverse reactions.

d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Klir insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours

e) Two cases suggestive of an interaction between fluoxetine and selegiline were reported (Suchowersk episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. drugs were discontinued, and no further details were provided. The second case involved diaphoresis, v occurred in close temporal relationship to adding fluoxetine and selegiline. Both drugs were discontinuec Rechallenge with fluoxetine alone occurred without incident.

f) A 31-year-old female received fluoxetine 20 mg daily for 14 days, and was subsequently discontinued 1988). The administration of tranylcypromine 10 mg daily commenced two days following the discontinua increased tranylcypromine to 20 mg daily and developed a serotonin-like syndrome two to three hours la tranylcypromine, all signs and symptoms resolved within 24 hours.

3.5.1.IW Trazodone

1) Interaction Effect: trazodone toxicity (sedation, dry mouth, urinary retention) or serotonin syndrome (hyper changes)
2) Summary: When given concurrently, trazodone and fluoxetine have been reported to be therapeutically ef Shader, 1990; Swerdlow & Andia, 1989; Neirenberg et al, 1992; Maes et al, 1997a). Coadministration of traz in speech dysfunction in a 43-year old man following traumatic brain injury (Patterson et al, 1997a). There ha syndrome due to interactions between selective serotonin reuptake inhibitors and antidepressants (George & Alderman & Lee, 1996). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstim hyperthermia, myoclonus and changes in mental status (Sternbach, 1991y). Further clinical studies are nece of serotonin syndrome associated with this drug combination.
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Due to the potential for impairment in trazodone metabolism, patients should be mo Occasional dosage reductions of trazodone may be required. Serotonin syndrome, characterized by hyperter status changes, may also occur during concomitant therapy.
7) Probable Mechanism: decreased trazodone clearance
8) Literature Reports
a) Five cases of elevated antidepressant levels, four involving tricyclic antidepressants (nortriptyline, imi trazodone, have been reported. After the addition of fluoxetine, the ratio of antidepressant level to dose i tricyclics and by 31% in the patient on trazodone. The trazodone-treated patient developed sedation and
b) A 44-year-old man developed symptoms characteristic of serotonin syndrome due to a possible inter patient had been taking fluoxetine 40 mg daily and trazodone 100 mg daily for approximately two months experienced disorientation, tremor, diaphoresis, and anxiety, followed by uncontrollable shaking and loss with cyproheptadine 4 mg orally, symptoms resolved over the next 30 minutes. Trazodone was discontin 40 mg daily without further complications (George & Godleski, 1996).
c) Serotonin syndrome was also reported in a 29-year-old woman taking trazodone and paroxetine. The at bedtime for approximately three months for depression and insomnia. The patient's depressive sympt trazodone was subsequently decreased to 50 mg daily at bedtime for two weeks before paroxetine 20 m after the first dose of paroxetine, the patient became agitated, confused, shaky, and diaphoretic. Upon e concentration, intermittent myoclonus in all extremities, hyperreflexia, tremor, and diaphoresis. After disc patient's symptoms resolved (Reeves & Bullen, 1995).
d) A 43-year-old male with traumatic brain injury developed speech dysfunction during therapy with fluo treated with trazodone 150 mg at bedtime for chronic pain as a result of a fall. After undergoing a compre rehabilitation, fluoxetine 20 mg every morning was added to the patient's regimen for treatment of sympt therapy with fluoxetine, the patient began to slur his speech and later exhibited a slow rate of speech, inc phonemes, and word-finding difficulties. After discontinuation of fluoxetine and tapering of trazodone the speech difficulty and returned to normal over the next week (Patterson et al, 1997).
e) The pharmacokinetic effect of trazodone and fluoxetine cotherapy was studied in 27 inpatients with a trazodone 100 mg daily, followed one week later with the addition of fluoxetine 20 mg daily, pindolol 7.5 placebo had no significant effect on the plasma concentrations of trazodone or its active metabolite, met when fluoxetine was combined with trazodone, levels of mCPP increased from a mean baseline value of increase was also associated with an improvement in the clinical response to the antidepressants (Maes

3.5.1.IX Trifluoperazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Although citing no data, the manufacturers of some phenothiazines state that concomitant use not recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Inf 2002; Prod Info Thorazine(R), 2002) . Other phenothiazines may have similar effects, though no reports are a the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and a phenothiazine is not recommende
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.IY Trimethoprim
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Cotrimoxazole and fluoxetine have been shown to prolong the QTc interval at the recommende 2001ah; Lopez et al, 1987). Even though no formal drug interaction studies have been done, the coadministra is not recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of cotrimoxazole and fluoxetine is not recommended
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.IZ Trimipramine
1) Interaction Effect: tricyclic antidepressant toxicity (dry mouth, urinary retention, sedation) and an increase

de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and fluoxetine have been shown to prolong the QTc interval a Prozac(R), 2001h; Marshall & Forker, 1982). Even though no formal drug interaction studies have been done coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as fluox 1999). In addition, concurrent use of fluoxetine and TCAs such as desipramine, nortriptyline, and imipramine concentrations (Preskorn et al, 1994a; Preskorn et al, 1994a; Aranow et al, 1989a; Downs et al, 1989a; Gooc
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and a tricyclic antidepressant is not recc
7) Probable Mechanism: decreased tricyclic antidepressant metabolism; additive effects on QT prolongation
8) Literature Reports
a) Fluoxetine increased the level of tricyclic antidepressants (nortriptyline, imipramine, desipramine) in 4 ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients develope constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels (Aranow et al,
b) Fluoxetine statistically and clinically significantly increased desipramine concentrations in 18 healthy added to desipramine (50 mg daily), the mean maximum concentration of desipramine increased by 278 curve increased by 342%. Desipramine trough concentrations continued to be 198% above baseline thre same study compared pharmacokinetics of desipramine when combined with sertraline. The impact of se short-term increases in desipramine plasma concentrations (Preskorn et al, 1994).
c) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations w levels ranged from 109 to 150 ng/mL with oral doses of 300 mg at bedtime prior to fluoxetine therapy. Fo to the regimen, the desipramine serum level increased to 212 ng/mL within five days. The fluoxetine dos and the desipramine serum level was 419 ng/mL after four days. A worsening of depression and severe desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose to 200 mg dai ng/mL within two weeks (Bell & Cole, 1988).
d) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with a 40 mg daily and desipramine 150 mg daily for five weeks; fluoxetine was discontinued and the blood leve ng/mL with resolution of clinical symptoms (Goodnick, 1989).
e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant the patient's measured levels of desipramine had ranged from 148 to 160 ng/mL on a regimen of 300 mg 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a desipramine level of to 200 mg/day; eleven days later, the level was 244 ng/mL; the patient reported decreased energy, impa speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced to days. Eight days later, the desipramine level was 122 ng/mL (Downs et al, 1989).
f) Concomitant administration of fluoxetine and desipramine was reported to result in an increased desip year-old male within 10 days of the addition of fluoxetine to the patient's regimen (Preskorn et al, 1990).

3.5.1.JA Tryptophan
1) Interaction Effect: serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Tryptophan is metabolized to serotonin, and fluoxetine, a selective serotonin reuptake inhibitor & Fontaine, 1986a; Boyer & Blumhardt, 1992). It is possible that combining these agents may result in excess "serotonin syndrome".
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: If tryptophan and fluoxetine are coadministered, monitor patients for signs of seroto myoclonus, mental status changes). It may be necessary to reduce doses of one or both agents or to discont
7) Probable Mechanism: additive adverse effects
8) Literature Reports
a) In a case series, the concurrent use of fluoxetine 50 to 100 mg daily and L-tryptophan 1 to 4 g daily re nervous system toxicity (agitation, poor concentration, nausea, diarrhea, paresthesias, palpitations, chills insomnia) within a few days. Tryptophan was discontinued and the symptoms disappeared (Steiner & Fo
b) Concurrent paroxetine (another SSRI) and tryptophan have been linked to headache, nausea, sweati tryptophan administration increases serotonin concentration in the central nervous system and paroxetin receive potent serotonin reuptake inhibitors should be advised not to take L-tryptophan.

3.5.1.JB Valdecoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown

8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar
hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of u
than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose
confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of
upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with
TORADOL(R) oral tablets, 2007).

3.5.1.JC Vasopressin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Fluoxetine and vasopressin have been shown to prolong the QTc interval at the recommended
Jacoby & Wiegman, 1990). Even though no formal drug interaction studies have been done, the coadministra
is not recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and vasopressin is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.JD Venlafaxine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
(hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Venlafaxine and fluoxetine have been shown to prolong the QTc interval at the recommended
Prod Info Effexor(R) XR, 2000). Even though no formal drug interaction studies have been done, the coadmi
interval is not recommended. In addition, the concurrent use of venlafaxine and fluoxetine may result in serot
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of venlafaxine and fluoxetine is not recommended.
7) Probable Mechanism: additive effects on QT prolongation; additive serotonergic effect

3.5.1.JE Warfarin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2
(R) oral capsules, delayed-release capsules, solution, 2008). Bleeding events reported have included epistax
threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported wi
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for sig
taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, wh
(Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme b
warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to
protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl
patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks followi
mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected p
SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients
treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4
corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively.
treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only
bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI
dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding
exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model
c) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal blee
hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal b
subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690
for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interva
gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekam
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh ca

a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations.
week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril,
acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was giv
mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin wa
was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally
was discontinued. The next day the patient presented to the hospital with left-sided weakness and later c
interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regim
warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.JF Xemilofiban

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events
hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008;
release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for
oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 200
7) Probable Mechanism: unknown

3.5.1.JG Ziprasidone

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coa
known to prolong the QTc interval, including fluoxetine (Prod Info Geodon(TM), 2002; Prod Info Prozac(R), 2
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the
recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fata
prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or in
ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) a
QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine
less than that observed with thioridazine (Prod Info Geodon(R), 2002).

3.5.1.JH Zolmitriptan

1) Interaction Effect: an increased risk of serotonin syndrome and an increased risk of cardiotoxicity (QT prol
2) Summary: Zolmitriptan and fluoxetine have been shown to prolong the QTc interval at the recommended t
Prod Info Zomig(R), 2001). Even though no formal drug interaction studies have been done, the coadministra
is not recommended. Additionally, concurrent use of a triptan and an SSRI may result in serotonin syndrome
serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid chan
temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans r
either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndr
combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administratio
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of a triptan, such as zolmitriptan, and an SSRI, such as fluoxetine
serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan o
physician. If these agents are used together, discuss the risks of serotonin syndrome with the patient and mo
(restlessness, hyperthermia, hyperreflexia, incoordination). Additionally, concurrent administration of zolmitrip
risk of cardiotoxicity due to additive QT prolongation effects.
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation; addit
8) Literature Reports
a) The pharmacokinetics of zolmitriptan were unaffected by 4 weeks of pretreatment with fluoxetine 20 r

3.5.1.JI Zolpidem

1) Interaction Effect: an increased risk of hallucinations
2) Summary: Short-term combined therapy with fluoxetine and zolpidem was determined to be safe by a stu
dose of zolpidem followed by one washout day, the subjects were given a daily dose of fluoxetine on days thr
evening on days 28 through 32. There were no significant changes in either fluoxetine or zolpidem plasma co
tolerated well, either individually or combined (Allard et al, 1998a). However, the publication of five case repo
elucidates potential interactions between zolpidem and various antidepressant medications. Five patients rep

zolpidem and antidepressant medication. The hallucination episodes all lasted longer than one hour, but resc
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Observe patients for hallucinatory activity. Alternative anti-insomnia medication may
7) Probable Mechanism: unknown
8) Literature Reports
a) A study conducted by Lorex Pharmaceuticals and Boston Research and Science Consulting demonst therapy with fluoxetine and zolpidem. In this study, 29 healthy female volunteers were given a single eve washout day. This was followed by a daily morning dose of fluoxetine 20 mg on days 3 through 27. On d zolpidem was added. Steady state plasma concentrations of fluoxetine and norfluoxetine were reached c serial venous blood sampling. There were no significant differences in area under concentration curve (A reach peak concentration (Tmax) after one or five consecutive doses of zolpidem in conjunction with fluo pharmacokinetic mean parameters were observed for zolpidem: AUC 917.04 ng/hr/mL on day 28, 978.7 day 28, 175.91 ng/mL on day 32, Tmax 1.67 hr on day 28, 1.54 hr on day 32. For fluoxetine the following 2879.63 ng/hr/mL on day 32, Cmax 133.48 ng/mL on day 27, 142.23 ng/mL on day 32, Tmax 8.28 hr on significant difference was a higher half-life value for zolpidem on day 32, the fifth consecutive dose of zol 1998).
b) The Washington Poison Center reports that they received five different calls from patients experienci zolpidem and antidepressant medication. Four of the five reports came from patients taking serotonin reu antidepressant medications being taken were desipramine, fluoxetine, sertraline, venlafaxine, and bupro lasted longer than one hour, but the patients' symptoms resolved without further sequelae. The authors c might cause hallucinations has not been firmly established (Elko et al, 1998).

3.5.1.JJ Zomepirac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have incl petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info L CELEXA (R) oral tablet, solution, 2005).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressar hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of up than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin inc
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with TORADOL(R) oral tablets, 2007).

3.5.1.JK Zotepine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs known fluoxetine, is not recommended. Several antipsychotic agents have demonstrated QT prolongation including quetiapine (Owens, 2001b), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), and zotepine (Swe
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and antipsychotics is not recommended
7) Probable Mechanism: additive effects on QT prolongation

3.5.2 Drug-Food Combinations

3.5.2.A Ethanol

1) Interaction Effect: excessive central nervous system depression
2) Summary: Coadministration of olanzapine and ethanol will potentiate the orthostatic hypotension observed of ethanol (45 mg/70 kg) had no effect on olanzapine pharmacokinetics, these drugs should not be taken con depressive effects of both drugs (Prod Info Zyprexa(R), 1999d).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of olanzapine and ethanol should be avoided if at all possible. If the

caution should be used.
7) Probable Mechanism: additive central nervous system depression

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters

A) Therapeutic

1) Physical Findings

a) Signs of improvement in bipolar symptoms.

1) Positive symptoms (distortion of normal function) include hallucinations, irritability, delusions, incoher

2) Negative symptoms (loss or diminution of function) include blunted affect, emotional or social withdra

b) Improvement in target symptoms associated with depression (depressed mood, suicidal thoughts or inten sleep patterns, lack of pleasure/interest in usual activities, feeling of excessive guilt/worthlessness, psychomo thinking/concentration/memory).

B) Toxic

1) Laboratory Parameters

a) Fasting blood glucose levels should be assessed in any patient who exhibits symptoms of hyperglycemia. treatment and regularly thereafter in patients with diabetes mellitus, with borderline increased blood glucose l 200 mg/dL), or with risk factors for diabetes mellitus (i.e., obesity, family history of diabetes) (Prod Info SYME

b) Lipid profile evaluations should be done at the beginning of treatment and periodically during therapy to m triglycerides, LDL, and HDL (Prod Info SYMBYAX(R) oral capsule, 2009)

c) ECG at baseline and periodically during treatment (Pacher & Kecskemeti, 2004)

d) Serum sodium levels should be monitored (levels lower than 110 mmol/L have been reported). There is a the syndrome of inappropriate antidiuretic hormone secretion) in patients receiving concomitant diuretics, pat hyponatremia is confirmed, fluoxetine/olanzapine should be discontinued and medical management may be r

2) Physical Findings

a) Abnormal bleeding should be monitored for ecchymoses, hematomas, epistaxis and petechiae especially NSAIDs, warfarin or other anticoagulants.

b) Allergic reactions including anaphylaxis and rash should be monitored. Systemic reactions possibly relate If an etiology for these reactions cannot be identified, fluoxetine/olanzapine therapy should be discontinued (F

c) Body temperature dysregulation should be monitored for signs of dehydration, excessive or lack of sweati able to produce urine. Activities such as exercising strenuously, extreme heat exposure, concomitant anticho body temperature.

d) Body weight should be monitored regularly during treatment (Prod Info SYMBYAX(R) oral capsule, 2009).

e) Hyperglycemia symptoms should be monitored regularly in all patients for signs of polydipsia, polyuria, po symptoms of hyperglycemia during atypical antipsychotic treatment should undergo fasting blood glucose tes resolved when the atypical antipsychotic was stopped; however, some patient required ongoing anti- diabetic (Prod Info SYMBYAX(R) oral capsule, 2009).

f) Hyponatremia (as a result of SIADH) should be monitored including symptoms of headache, difficulty conc weakness, and unsteadiness. More severe symptoms include hallucination, syncope, seizure, coma, and res increased risk of hyponatremia in patients receiving concomitant diuretics, patients who are volume depleted, fluoxetine/olanzapine therapy should be discontinued and medical management may be necessary.

g) If intolerable withdrawal symptoms occur following a decrease in dose or when therapy is being discontinu previously prescribed dose and taper the dose at a more gradual rate. Symptoms may include dysphoric moo disturbances, anxiety, confusion , headache, lethargy, emotional lability, insomnia, and hypomania (Prod Info

h) Involuntary, dyskinetic movements should be monitored periodically. There is an increased incidence of ta females with some irreversible cases. Risk benefit of continued treatment should be assessed if symptoms d 2009).

i) Mania/hypomania may be activated in patients with undiagnosed bipolar disorder. Monitoring is recommen (Prod Info SYMBYAX(R) oral capsule, 2009).

j) Orthostatic hypotension, including dizziness, tachycardia, bradycardia, and syncope should be monitored e patients with cardiovascular or cerebrovascular disease, or conditions which might predispose patients to hyp

concomitant antihypertensive drugs) (Prod Info SYMBYAX(R) oral capsule, 2009)
k) Monitor patients receiving antidepressants for worsening of depression, suicidality, or unusual changes in 2009) especially at the initiation of therapy or during dose adjustment. Such monitoring should include at leas their family members or caregivers during the initial 4 weeks of treatment, then visits every other week for the clinically indicated beyond 12 weeks. Families and caregivers should be advised of the need for close observ communication with the prescriber (US Food and Drug Administration, 2004).
l) Patients who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggre mania may be at an increased risk for worsening depression or suicidality. If these symptoms are observed, t necessary to discontinue medications when symptoms are severe, sudden in onset, or were not part of the pa Administration, 2004).
m) Seizures should be monitored, especially in patients with a history of seizure disorder or with comorbiditie
n) Serotonin syndrome or neuroleptic malignant syndrome-like reactions should be monitored including men (tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (muscle rigidity, hyperreflexia, symptoms. There may be an increased risk of this reaction with concomitant use of serotonergic drugs (inclu serotonin, or antipsychotics or dopamine antagonists, all of which are not recommended during fluoxetine/ola discontinued if serotonin syndrome or neuroleptic malignant syndrome-like reactions occur (Prod Info SYMBY

4.2 Patient Instructions

A) Olanzapine/Fluoxetine (By mouth)

Fluoxetine Hydrochloride/Olanzapine

Treats depression that is a part of bipolar disorder or that does not respond to other antidepressants. This medicir inhibitor (SSRI) antidepressant.

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to olanzapine (Zyprexa®) or fluoxetine (Proz have used an MAO inhibitor (MAOI) such as Eldepryl®, Marplan®, Nardil®, or Parnate® within the past 14 days. for at least 5 weeks after you stop using Symbyax®. You should not use this medicine if you are using pimozide (

How to Use This Medicine:
Capsule
Your doctor will tell you how much of this medicine to use and how often. Do not use more medicine or use it This medicine should come with a Medication Guide. Read and follow these instructions carefully. Ask your d Ask your pharmacist for the Medication Guide if you do not have one. Your doctor might ask you to sign some information.
You may take this medicine with or without food.

If a Dose is Missed:
If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next d the missed dose. Do not use extra medicine to make up for a missed dose.

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

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, a
Make sure your doctor knows if you are using digitoxin, linezolid (Zyvox®), omeprazole (Prilosec®), rifampin (Imitrex®), tramadol (Ultram®), tryptophan, or vinblastine. Tell your doctor if you are using a blood thinner (su for mental illness (such as clozapine, fluvoxamine, haloperidol, lithium, tryptophan, Clozaril®, Haldol®, or Luv levodopa, Sinemet®, or Stalevo®), phenothiazine medicine (such as prochlorperazine, Compazine®, Mellaril medicine for heart rhythm problems (such as flecainide, propafenone, Rythmol®, or Tambocor®).
Make sure your doctor knows if you are also using a pain or arthritis medicine (such as aspirin, diclofenac, ibu Daypro®, Motrin®, Orudis®, Relafen®, or Voltaren®), medicine for seizures (such as carbamazepine, pheny depression (such as amitriptyline, desipramine, imipramine, nortriptyline, Aventyl®, Elavil®, Norpramin®, Par as alprazolam, diazepam, Librium®, Valium®, or Xanax®), or blood pressure medicine (such as atenolol, hyd Cozaar®, Diovan®, Lotrel®, Norvasc®, Prinivil®, Toprol®, or Zestril®).
Do not drink alcohol while you are using this medicine.
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and a sedatives.
Tell your doctor if you are also using any other medicine that contains olanzapine or fluoxetine. Some other b Prozac®, Prozac Weekly™, or Sarafem®.

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant, or if you have diabetes, seizures, bleeding problems, liver glaucoma, trouble swallowing, or a history of neuroleptic malignant syndrome (NMS), breast cancer, or sever

have any kind of heart or circulation problems, including heart disease, low blood pressure, high blood pressu
history of heart attack or stroke.
Do not breastfeed while you are using this medicine.
For some children, teenagers, and young adults, this medicine can increase thoughts of suicide. Tell your do
your child start to feel more depressed and have thoughts about hurting yourselves. Report any unusual thou
especially if they are new or are getting worse quickly. Make sure the doctor knows if you or your child have t
increase in energy, or start to act reckless. Also tell the doctor if you or your child have sudden or strong feeli
violent, or scared. Let the doctor know if you, your child, or anyone in your family has bipolar disorder (manic-
This medicine may raise or lower your blood sugar, or it may cover up symptoms of very low blood sugar (hy
Your doctor will need to check your blood at regular visits while you are using this medicine. Be sure to keep
This medicine may increase your cholesterol and fats in the blood. If this condition occurs, your doctor may g
amount of cholesterol and fats in the blood.
This medicine may increase your weight. Your doctor may need to check your weight regularly during treatme
If you develop new hives or a skin rash, even a mild one, stop using this medicine and call your doctor right a
This medicine may cause a serious condition called serotonin syndrome when it is taken with certain medicin
other medicines.
Tardive dyskinesia (a movement disorder) may occur and may not go away after you stop using the medicine
your child have any of the following symptoms while taking this medicine: lip smacking or puckering, puffing c
the tongue, uncontrolled chewing movements, or uncontrolled movements of the arms and legs.
You might get overheated while using this medicine. Drink plenty of water during hot weather, while exercisin
gets too hot, you might feel dizzy, weak, tired, or confused. You might have an upset stomach or vomit. Call y
away from the heat does not cool you down.
Some side effects are more likely to happen in elderly people who have memory problems or other reduced r
person who will be using this medicine has forgetfulness or confusion related to aging (such as Alzheimer's d
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that cou
also feel lightheaded when getting up suddenly from a lying or sitting position, so stand up slowly.
Do not stop using this medicine suddenly without asking your doctor. You may need to slowly decrease your
If your symptoms do not improve or if they get worse, call your doctor.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, c
Bloody or black, tarry stools.
Change in how much or how often you urinate.
Changes in behavior, or thoughts of hurting yourself or others.
Chest pain, shortness of breath, or coughing up blood.
Confusion, weakness, and muscle twitching.
Fast, slow, uneven, or pounding heartbeat.
Feeling very thirsty or hungry.
Fever, unusual sweating, or feeling too hot.
Lightheadedness or fainting.
Muscle pain, tenderness, or weakness.
Muscle stiffness, spasms, or other muscle movements you cannot control (especially in your face or mouth).
Pain in your lower leg (calf).
Seizures or tremors.
Severe stomach pain, or vomiting of blood or material that looks like coffee grounds.
Sudden or severe headache, problems with vision, speech, or walking.
Swelling in your hands, ankles, or feet.
Trouble breathing or swallowing.
Trouble sleeping, racing thoughts, feeling very nervous, energetic, or restless.
Unusual bleeding or bruising.
Yellowing of your skin or the whites of your eyes.

If you notice these less serious side effects, talk with your doctor:
Blurred vision.
Diarrhea.
Dry mouth, sore throat, or hoarseness.
Increase in appetite.
Joint pain or swelling.
Sleepiness or unusual drowsiness.
Tiredness.
Trouble concentrating.
Trouble having sex.
Weight gain.

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

4.3 Place In Therapy

A) Depression Associated with Bipolar I Disorder

1) The combination of olanzapine and fluoxetine is effective for the treatment of depressive episodes associated established guidelines for the length of time patients with bipolar disorder experiencing a major depressive episod chronic illness requiring chronic treatment. The use olanzapine/fluoxetine for extended periods should periodically continued therapy(Prod Info SYMBYAX(R) oral capsule, 2009).

B) Treatment-Resistent Depression

1) Combination olanzapine and fluoxetine is effective for the acute treatment of treatment-resistant major depress 2 separate previous trials of antidepressant therapy. There are no established guidelines for the length of time pat treated; however, it is considered a chronic illness requiring chronic treatment. The use olanzapine/fluoxetine for e reevaluated for benefits and risks of continued therapy (Prod Info SYMBYAX(R) oral capsule, 2009).

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) Although the exact mechanism of the combination of olanzapine and fluoxetine is unknown, the enhanced anti serotonin, norepinephrine, and dopamine activation. Increased norepinephrine and dopamine release in the prefr well as increases in serotonin, have been demonstrated in animal studies (Prod Info SYMBYAX(R) oral capsules,

2) Olanzapine is a psychotropic agent and fluoxetine is an antidepressant. Fluoxetine is an inhibitor of the seroto norepinephrine and dopamine transporters. The following list provides the binding affinity of olanzapine to neurotr capsules, 2007):

High affinity:
- serotonin 5HT2A/2C
- 5HT6
- dopamine D1-4
- histamine H-1
- adrenergic alpha-1

Moderate affinity
- serotonin 5HT3
- muscarinic M1-5

Weak affinity
- GABA-A
- benzodiazepine
- beta-adrenergic

3) The therapeutic and adverse effects of olanzapine may be due to its antagonism of certain receptors, such as M1-5 receptor antagonism, somnolence effects related to histamine H-1 receptor antagonism, and orthostatic hyp histamine H-1 receptor antagonism. Fluoxetine does not contribute to the above effects because of its relatively lo histamine H-1 receptors (Prod Info SYMBYAX(R) oral capsules, 2007).

4.5 Therapeutic Uses

Bipolar disorder, depressed phase

Major depressive disorder, Treatment resistant

4.5.A Bipolar disorder, depressed phase

FDA Labeled Indication

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Indicated in adults for the acute treatment of depressive episodes associated with bipolar I disorder (Pro Efficacy of olanzapine/fluoxetine was established in 2 identically designed, 8-week, randomized, double- Info Symbyax(TM), 2003).

3) Adult:

a) Both olanzapine monotherapy and olanzapine plus fluoxetine combination therapy were more effective tha In a randomized, double-blind, placebo-controlled, multi- center, international study, patients with bipolar I dis the Montgomery-Asberg Depression Rating Scale (MADRS) received olanzapine (n=370; 5 to 20 milligrams (olanzapine plus fluoxetine (n=86; 6 and 25 mg/day, 6 and 50 mg/day, or 12 and 50 mg/day; mean dose, 7.4 a weeks. The primary objective of the study compared olanzapine monotherapy versus placebo with regard to to 8 weeks. Throughout all 8 weeks of the study, treatments with both olanzapine and olanzapine-fluoxetine c reductions in depressive symptoms (as measured by the MADRS) as compared with placebo (p less than 0.0 improvement in the mean MADRS score at weeks 4, 6, and 8 were observed with olanzapine-fluoxetine com monotherapy (p=0.01, p=0.02, p=0.01, respectively). The rate of response (defined as at least a 50% improv

of at least 4 weeks of study) was significantly higher in olanzapine-treated patients as compared with placebo
Additionally, the response rate was significantly higher in the olanzapine-fluoxetine group as compared with b
p less than 0.001) and olanzapine groups (56.1% vs 39%, respectively; p=0.006). There were no statistically
regard to rates of treatment-emergent mania. Adverse events were similar between the combination therapy
olanzapine-fluoxetine group had a significantly higher rate of nausea and diarrhea (Tohen et al, 2003).

b) The efficacy of olanzapine/fluoxetine for the treatment of depressive episodes associated with bipolar disc
week, randomized, double-blind, controlled studies (n=403, n=385) of patients who met Diagnostic and Statis
Bipolar I Disorder, Depressed utilizing flexible dosing of olanzapine/fluoxetine (6/25, 6/50, or 12/50 mg/day), c
studies included patients (greater than or equal to 18 years of age) with or without psychotic symptoms and v
primary rating instrument used to assess depressive symptoms in these studies was the Montgomery-Asberg
clinician-rated scale with total scores ranging from 0 to 60. The primary outcome measure of these studies wa
MADRS total score. In both studies, SYMBYAX was statistically significantly superior to both olanzapine mon
MADRS total score (Prod Info Symbyax(TM), 2003).

4.5.B Major depressive disorder, Treatment resistant

FDA Labeled Indication

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Indicated for the acute treatment of treatment-resistant major depressive disorder in adults who experien
antidepressant therapy (Prod Info SYMBYAX(R) oral capsule, 2009).
Reduced symptoms of major depressive disorder in patients with non-treatment resistant and treatment-

3) Adult:

a) Combination therapy with olanzapine/fluoxetine resulted in significantly greater reductions in the mean tot
(MADRS) scores when compared with olanzapine or fluoxetine alone, according to 3 clinical trials of 579 adu
did not respond to 2 antidepressant therapies of adequate dose and duration, including a randomized, double
patients received olanzapine 6 to 18 milligrams (mg) plus fluoxetine 25 to 50 mg (Prod Info SYMBYAX(R) ora

b) Combination treatment with olanzapine and fluoxetine effectively reduced symptoms of major depressive
and treatment-resistant depression. In an open-label, multicenter, 76-week study, patients (n=560) with majo
resistant depression, received combination therapy with olanzapine and fluoxetine at mean doses of 7.5 milli
Efficacy was assessed by mean change from baseline in the Montgomery-Asberg Depression Rating Scale (
Impression-Severity of Illness scale (CGI-S) score. At 76 weeks, there was a 67.7% (21.8 points) mean reduc
mean score was reduced by 49.3% (2.2.points). Mean change scores for both the MADRS and CGI-S were s
points (p=0.0001). At endpoint, 61.6% of patients were considered responders (defined as at least a 50% dec
endpoint) and throughout the study period, 56.3% of patients achieved remission (defined as 2 consecutive M
However, 14.8% of patients who remitted, relapsed by endpoint. Patients with treatment-resistant depression
patients with non-treatment-resistant depression. Somnolence (47.7%), weight gain (39.8%), dry mouth (37.1
(22.3%), rhinitis (22.1%), asthenia (19.3%), and tremor (18.8%) were the most commonly reported adverse e
2003).

4.6 Comparative Efficacy / Evaluation With Other Therapies

Fluoxetine

Olanzapine

4.6.A Fluoxetine

4.6.A.1 Depression - Schizophrenia

a) Results of an 8-week, double-blind trial demonstrated that patients receiving both olanzapine and fluoxeti
improvement in Montgomery-Asberg Depression Rating Scale (MADRS) and Clinical Global Impression (CGI
medication alone. Twenty-eight patients with nonpsychotic treatment-refractory depression received olanzapi
to 60 milligrams/day). In addition, there were no significant differences in adverse events among the 3 differe

4.6.B Olanzapine

4.6.B.1 Depression - Schizophrenia

a) Results of an 8-week, double-blind trial demonstrated that patients receiving both olanzapine and fluoxeti
improvement in Montgomery-Asberg Depression Rating Scale (MADRS) and Clinical Global Impression (CGI
medication alone. Twenty-eight patients with nonpsychotic treatment-refractory depression received olanzapi
to 60 milligrams/day). In addition, there were no significant differences in adverse events among the 3 differe

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Last Modified: June 26, 2009

DRUGDEX® Consults

RECOMMENDATION, EVIDENCE AND EFFICACY RATINGS

RESPONSE

The Thomson Efficacy, Strength of Evidence and Strength of Recommendation definitions are outlined below:

Table 1. Strength Of Recommendation		
Class I	Recommended	The given test or treatment has been proven to be useful, and should be performed or administered.
Class IIa	Recommended, In Most Cases	The given test, or treatment is generally considered to be useful, and is indicated in most cases.
Class IIb	Recommended, In Some Cases	The given test, or treatment may be useful, and is indicated in some, but not most, cases.
Class III	Not Recommended	The given test, or treatment is not useful, and should be avoided.
Class Indeterminant	Evidence Inconclusive	

Table 2. Strength Of Evidence	
Category A	Category A evidence is based on data derived from: Meta-analyses of randomized controlled trials with homogeneity with regard to the directions and degrees of results between individual studies. Multiple, well-done randomized clinical trials involving large numbers of patients.
Category B	Category B evidence is based on data derived from: Meta-analyses of randomized controlled trials with conflicting conclusions with regard to the directions and degrees of results between individual studies. Randomized controlled trials that involved small numbers of patients or had significant methodological flaws (e.g., bias, drop-out rate, flawed analysis, etc.). Nonrandomized studies (e.g., cohort studies, case-control studies, observational studies).
Category C	Category C evidence is based on data derived from: Expert opinion or consensus, case reports or case series.
No Evidence	

Table 3. Efficacy		
Class I	Effective	Evidence and/or expert opinion suggests that a given drug treatment for a specific indication is effective
Class IIa	Evidence Favors Efficacy	Evidence and/or expert opinion is conflicting as to whether a given drug treatment for a specific indication is effective, but the weight of evidence and/or expert opinion favors efficacy.
Class IIb	Evidence is Inconclusive	Evidence and/or expert opinion is conflicting as to whether a given drug treatment for a specific indication is effective, but the weight of evidence and/or expert opinion argues against efficacy.
Class III	Ineffective	Evidence and/or expert opinion suggests that a given drug treatment for a specific indication is ineffective.

Subject: RE: Updated DRUGDEX Monographs
From: "Torgerson, James E." <JETORGERSON@stoel.com>
Date: Sun, 14 Mar 2010 09:02:49 -0700
To: "Jim Gottstein" <jim.gottstein@psychrights.org>

Hi Jim:

I will pass your request on to my client and get back to you with its response as soon as I have it.

Regards,

Jim

From: Jim Gottstein [mailto:jim.gottstein@psychrights.org]
Sent: Saturday, March 13, 2010 12:24 PM
To: Torgerson, James E.
Cc: Jim Gottstein
Subject: Updated DRUGDEX Monographs

Hi Jim,

I am working on a motion for a preliminary injunction I expect to file shortly after everyone's responses to the complaint are in and in working through that it has become apparent the most recent DRUGDEX® monographs are extremely relevant. For example, the FDA approved Seroquel and Zyprexa for limited pediatric uses on December 4, 2009, which is not reflected in the DRUGDEX monographs I have. The injunction which I will be seeking would, of course, not prohibit causing or presenting claims to Medicaid for those newly approved indications. Additions to medically accepted indications as a result of new FDA approval is easy enough for me to pick up, but DRUGDEX also updates its monographs pertaining to indications that have not received FDA approval.

It seems likely the judge would order your client to provide them in the context of the motion for preliminary injunction and I can certainly subpoena them to a hearing (subject to your possible objection), but I would prefer not to have to go to the court. Therefore, I am writing to ask if your client would voluntarily provide me with copies of the most recent monographs, and updates as they occur, for the drugs included in the Medically Accepted Indications Chart, plus the following drugs which I intend to add to the chart:

- alprazolam (Xanax®)
- Clonazepam (Klonopin®)
- clorazepate (Tranxene®)
- diazepam (Valium®)
- flurazepam (Dalmane®)
- lorzepam (Ativan®)

- temazepam (Restoril®)
- zaleplon (Sonata®)
- Zolpidem (Ambien®)

Granting me access to DRUGDEX would certainly be acceptable to me and presumably easier for your client, but I know your client closely guards access to DRUGDEX. Perhaps your client can grant me access to just the drugs of interest. Again, these would be the drugs included in the Medically Accepted Indications Chart as well as those listed above.

Please let me know.
--

James B. (Jim) Gottstein, Esq.
President/CEO

Law Project for Psychiatric Rights
406 G Street, Suite 206
Anchorage, Alaska 99501
USA
Phone: (907) 274-7686) Fax: (907) 274-9493
jim.gottstein[[at]]psychrights.org
http://psychrights.org/

PsychRights®
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The Law Project for Psychiatric Rights is a public interest law firm devoted to the defense of people facing the horrors of forced psychiatric drugging. We are further dedicated to exposing the truth about these drugs and the courts being misled into ordering people to be drugged and subjected to other brain and body damaging interventions against their will. Extensive information about this is available on our web site, http://psychrights.org/. Please donate generously. Our work is fueled with your IRS 501(c) tax deductible donations. Thank you for your ongoing help and support.